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Best Oral Presentations

1- S-061 -Association of 1p/19q Co-Polysomy and Prognosis In Glial Tumors
Ayşegül Çınar KUŞKUCU, Emre Can TÜYSÜZ, Sezin GÜRKAN, Kaan YALTIRIK, Ferda ÖZKAN, Ömer Faruk BAYRAK, Uğur TÜRE

2-S-014 - In Silico Analysis of 5'UTR Variants Creating UORF and Their Possible Pathogenicity-Related Features
Çağrı GÜLEÇ

3-S-083 - First Noonan Patient with Glomuvenous Malformations with GLMN Mutation
Filiz HAZAN

Best Poster Presentations

- P-019 - Integration of Global miRNA and MRNA Expression Profiles in Sporadic Colorectal Cancer
  Edibe Ece ABACI, Namood-E SAHAR, Nevin BELDER, Berna SAVAŞ, Arzu ENSARİ, Ayhan KUZU, Hilal ÖZDAĞ,

- P-043 - Clinical Findings of 16p13.11 Copy Number Variatıons
  Naz GÜLERAY, Sümeyra OĞUZ, Gizem ÜREL DEMİR, Pelin Özlem ŞİMŞEK KİPER, Gülen Eda UTİNE, Koray BODUROĞLU, Mehmet ALİKAŞİFOĞLU

- P-132 - Mutation Spectrum of the KMT2D Gene for the Kabuki Syndrome
  Gözde YEŞİL, Nilay GÜNEŞ, Ayça ASLANGER, Beyhan TÜYSÜZ

Invited Speakers Abstracts

Detection and Quantification of Mosaic Copy Number Alterations and Structural Chromosome Anomalies by Chromosomal Microarray Analysis

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Chromosomal mosaicism is defined as the presence of two or more chromosomally distinct cell lines in one individual. Mosaic structural chromosome abnormalities, including large copy number alterations that present in only a subset of cells, have been detected in 0.2–1.0% of patients ascertained for clinical genetic testing. Chromosomal mosaicism is often difficult to detect due to subtle phenotypic abnormalities, technical limitations, and tissue specificity. Standard chromosome analysis is labor intensive and 30 cells must be counted to exclude 10% mosaicism with 95% confidence. Compared with karyotyping, chromosomal microarray analysis offer a higher-resolution and higher-throughput assay in detection of mosaic cases. This study presents six cases with mosaic copy number alterations detected by single nucleotide polymorphism (SNP) based CMA. The first case, a prenatal case, showed a mosaic gain (about 2.6 copies) of the entire short arm of chromosome 18 (18p) and a non-mosaic gain (3 copies) of the entire long arm of chromosome 18 (18q) resulting in a mosaic complex trisomy 18. CMA revealed a mosaic Turner syndrome with a suggestive of 45,X/46,X,r(X) karyotype in the second case. About 25% mosaic 8 Mb deletion of 15q25.1q25.3 and about 50% mosaic 11.7 Mb gain of 16q23.1q24.2 were detected in the third and fourth cases, respectively. The fifth case showed an approximately 11.6 Mb mosaic gain of 7q11.21q11.23. This pericentromeric mosaic gain (about 80% mosaicism) may suggest a marker chromosome derived from chromosome 7 in this patient. The last case had mosaic trisomy 8 (about 40% mosaicism). In conclusion, these cases further underline the important role of detection of mosaic structural abnormalities and copy number alteration using high-resolution chromosomal microarray analysis.

Key Words: Mosaic Structural Anomalies, Mosaic Copy Number Alterations, Chromosomal Mosaicism, Chromosomal Microarray Analysis

Investitgating the Effects of TNFRSF11A Gene Variatıons on the Risk of the Breast Cancer Development on Patients Carrying BRCA1 and BRCA2 Mutations

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In our research, the aim was to investigate the effects of TNFRSF11A gene rs9646629, rs4485469, rs34739845, rs4941129, rs17069904, rs884205 single nucleotide polymorphisms on breast cancer development in BRCA1 or BRCA2 pathogenic variation carrier phenomenon with breast cancer. The research was conducted on 23 patients diagnosed with BRCA1 or BRCA2 pathogenic variation and 28 patients that didn't have any trace of BRCA1 or BRCA2 pathogenic variation, and 55 healthy people included as a control group. Genotypes were determined on patients and control group included in the research by isolating the DNA from peripheral venous blood, using the polymerases chain reaction system in accordance with the protocol of the kit used, and by allelic discrimination for single nucleotide polymorphisms. In the light of the analyses performed, no statistically significant differences were found between TNFRSF11A gene rs9646629, rs4485469, rs34739845, rs4941129, rs17069904, rs884205 single nucleotide polymorphisms and breast cancer patients carrying BRCA1 or BRCA2 pathogenic variation. The differences between the results of the genetic study can be caused by ethnic differences among the populations. In this context BRCA1 / 2 in the etiology of occurring breast cancer mutations reason that there may be a role for TNFRSF11 variations, increasing the number of samples to be held in different centers in Turkey, we öngörüsünd it should be supported by new studies.

Key Words: TNFRSF11A, Breast Cancer, BRCA1, BRCA2, Single Nucleotide Polymorphism

Non-invasive cancer diagnosis: Who should be done?

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Recent advances in oncology bring us closer to the goals of treatment, which is the use of treatment strategies that take account of the change between individuals. Cancers are tumors that occur due to the accumulation of molecular changes in genes that control cell viability, growth, proliferation and differentiation. At present, the molecular profile of cancers is typically evaluated using samples of the primary tumor or a single metastatic lesion. Therapeutic strategies are then defined according to this molecular profile. However, the molecular profile of tumors develops dynamically over time. Liquid biopsy is a term that refers to the sampling of non-solid biological tissue, most commonly blood, as well as saliva, urine, cerebrospinal fluid, and other body fluids. Non-invasive samples from cancer patients are used for the extraction of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and ultimately other tumor-derived materials (eg, exosomes). The possible uses for non-invasive cancer screening methods include detection of cancers in the high-risk group, minimal residual disease monitoring, determination of metastasis before radiological imaging, detection of response to treatment, identification of targeted agents, finding of new driver mutations. Careful assessment of potential mutations is important to avoid unnecessary treatment of patients and to ensure the development of drugs in the appropriate patient population. Some TP53 / KRAS mutations were also detected in some healthy individuals who did not develop cancer during follow-up. Lung cancer is usually captured in the advanced stage due to the lack of screening. Many cfDNA studies are aimed at early detection and monitoring of recurrence. The discrepancy between studies is often explained by the use of different technologies, small tumor size and unseen tumor regions. Many studies have demonstrated the usefulness of ctDNA in advanced NSCLC conditions. Tissue biopsy should be considered when ctDNA results are negative.

Key Words: Liquid Biopsy, Non invasive cancer

Algorithms, Guidelines and Genetic Consultation in Non-Invasive Cancer Genotyping (Liquid Biopsy, Plasma genotyping)

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Plasma genotyping is an important prognostic, diagnostic, and theranostic tool, which plays a critical role in the detection and management of tumors. Clinical applications include monitoring tumor burden, primary tumor diagnosis, assessment of treatment response, therapy monitoring, emergence of resistances to targeted therapies, detection of minimal residual disease, and evaluation of tumor heterogeneity. Mainly circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) are used. CTCs are clearly associated with poor prognosis in many cancers. ctDNA represents between <0.1–10% of the total cfDNA detectable in human blood. Due to limited capabilities of PCR-based methods, NGS is usually recommended in guidelines. Plasma is preferred over serum. Plasma genotyping can be considered at the time of initial diagnosis in all patients who need tumor molecular profiling, but it is particularly recommended when tumor tissue is scarce, unavailable, or a significant delay potentially greater than 2 weeks is expected in obtaining tumor tissue and also for detecting drug resistance mutations. Most of the guidelines do not recommend plasma genotyping in routine cancer management, except for lung cancers. The International Association for the Study of Lung Cancer (IASLC) recommends plasma genotyping for analyzing especially EGFR mutations but also ALK, ROS1, KRAS, RET, MET, BRAF, and ERBB2 (HER2). A positive result for EGFR T790M should be considered adequate to initiate osimertinib in the second-line setting after progression on therapy with a first- or second-generation EGFR TKI; however, a negative result requires confirmation with molecular analysis on a tissue biopsy. KRAS, NRAS, BRAF mutations, MET, ERBB2 and EGFR amplifications are also mechanisms of resistance to EGFR TKI. ALK and ROS1 fusions are associated with sensitivity to TKIs, and their mutations associated with kinase domain are responsible from resistance. The liquid biopsy report should include the platform used, variant allele fraction of a given mutation, all the findings of the molecular analysis and clinically relevant information. Testing may identify high-risk germline (hereditary) DNA variants, and it requires genetic counseling. Even tough plasma genotyping is very useful and easy to perform, there are still many questions and further studies are needed for the test to enter routine practice.

Key Words: Algorithm, Guideline, Liquid Biopsy, Plasma genotyping, EGFR

Environmental Risk Factors in Young Breast Cancer Patients

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Aim: A “risk factor” is anything that increases risk of developing breast cancer. Mainly there are two main risk categories, certain risk factors that are out of one's control and the ones which are under control. Uncontrollable risk factors for breast cancer are age, family history, and medical history. However, there are some risk factors that can be controlled, such as weight, physical activity, and alcohol consumption. Methods: Breast cancer patients that were categorized as "young" and selected for this study were those who were under 50. These were referred for genetic counseling according to NCCN age criteria. All the patients were categorized according to their individual habits like smoking and alcohol consumption, family and medical history, as well as hormonal status such as menarche, contraceptive usage history. The results were also categorized individually with their genetic backgrounds of BRCA status and other genes. Results: All the patients were 50 years of age and younger. Personal history of all were categorized. First all were asked where they were in 1986 and then, after the chernobyl disaster. Most of the patients were in Istanbul and northern parts of Turkey. The menarch age, pregnancy, breast-feeding status were not significantly aggregated to any category. Same results were obtained for smoking and alcohol consumption habits, hormon usage and hormonal risk factors such as PCOS. These were evaluated with genetic risks of carrying any mutation keading to hereditary cancer susceptibility. Conclusion:Many women faces breast cancer, the estimated ratio is one in eight. Although age is the main risk factor, this survey was done from younger patients. The question is "why me?" ... Although we know that some of these are due to hereditary predisposition, it is only the 10 to 15 percent of all tested. So there should be more. It seems that consequences of Chernobyl disaster is one of the main suspects in neighborhoods and the countries nearby like Turkey. Then comes the hormonal issues like contraceptive usage and history of assisted reproductive techniques. In conclusion, all these risk factors should be taken into account as well as genetic test results in a comprehensive genetic counseling session.

Key Word: Young Breast Cancer, Environmental Risk Factors

Colorectal Carcinoma Molecular Subtypes and Evolution of Therapy

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Colorectal carcinoma (CRC), constitutes about 10.2 % of all human cancers according to Globocan 2018. In Turkey, CRC ranks the 3rd in incidence in both sexes. About 20% of the cases are metastatic at the first presentation, besides about half of the early stage CRC patients recurrs, mostly as distant metastasis. From 1950s till 2000s, there was only 5-Fluorouracil on the hand and the median overall survival (OS) was about 12 months for metatstatic cases. In the early 2000s irinotecan, oxaliplatin, oral pro-drugs (as capecitabine) and various combinations were added to the armamentarium. After 2004, targeted therapies, antiangigogenic and anti-EGFR (epidermal growth factor receptor) were on the bench, mostly in combination with the chemotherapy backbone. With different protocols up to 30 months of median OS was achieved in metastatic (m) CRC. In the last decade, the role of immunotherapy is under investigation. For the treatment selection, molecular heterogeneity is important for mCRC. In other words, in mCRC RAS (KRAS/NRAS) mutated tumors are intrinsically resistant to EGFR monoclonal antibodies as targeted therapy or microsatellite instable (MSI) tumors are uniquely sensitive to immune checkpoint inhibitor treatment. This evidence lead to standard indications for anti-EGFR therapy (cetuximab/panitimumab) for RAS-wild only mCRC, and immunotherapy (pembrolizumab/nivolumab) for MSI tumors. Besides those validated predictive biomarkers, additional prognostic and/or predictive biomarkers such as braf mutations and HER2 amplifications are under investigation for the treatment planning. Possibility to use next-generation sequencing (NGS) assays to test multiple gene alterations has been thougt to guide drug development in the subtypes with targetable oncogenic drivers. Circulating tumor DNA (ctDNA), was reported to detect emerging new genomic alterations in patients progressing on anti-EGFR treatment and hoped to to guide new treatment strategies and drug development. CRC, was moleculary well characterized in the carcinogenesis as stepwise accumulation of genetic events for growth and progression. However, CRC is molecularly heterogenic and different subtypes were reported in terms of genomic, epigeomic, transcriptomic, stroma-tumor microenvironment, driver genes and even clinical as primary tumor location (proximal versus distal). Genomically chromosomal instable (CIN) subgroup constitutes about 85% of CRC, heterogeneous in terms of transcriptomic subtypes (CMS2-4), located mostly in the left colon, including rectum, whereas MSI tumors correlate with more hypermutation and hypermethylation and prone to locate in the right or proximal colon. Transcriptomic subtypes were recently identified into 4 consensus molecular subtypes (CMS): CMS1 (MSI immune) has a strong immune cell infiltration, CMS2 (canonical) shows WNT and EGFR signaling dependance, CMS3 (metabolic) has mutations in the MAPK pathway, CMS4 (mesenchymal) has a predominant TGFβ activation with bad prognosis. CMS subgroups has a prognostic impact in early-stage and advanced stage CRC. NGS,liquid biopsy and ctDNA, gene-expression classifiers and immune markers such as proteomics in tumor microenvironment are the prospects for clinical translation of molecular tests in CRC.

Key Words: Colorectal carcinoma, molecular subtypes

Investigation of Genetic Basis of Colorectal Cancers by Using Next Generation Sequencing

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Colorectal cancers, one of the common types of cancer in our country and all over the world, are cancers that can be seen as sporadic or hereditary, affecting the colon and the rectum. Hereditary colorectal cancers are rare and are classified as familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP) and hereditary non-polyposis colorectal cancer (HNPCC). Pathogenic variations in the APC gene cause autosomal dominant inherited FAP, whereas pathogenic variants in the MUTYH gene cause an autosomal recessive MAP phenotype. The HNPCC's are caused by defects in DNA mismatch repair genes (MMRG). In this study, we aimed to present the determined variations in cancer-related genes screened by Next Generation Sequencing Analysis in 32 patients who were referred to our center to investigate the genetic background of colorectal cancer between March 2016 and April 2018. Genomic DNA was isolated from peripheral blood-core cells according to the manufacturer's protocol. TruSight Rapid Capture Library Preparation (Illumina) kit and Onco-GeneSGKit IVD CE kits were used for the preparation of libraries containing the relevant genes. The obtained libraries were sequenced in the Illumina MiSeQ system and the data were analyzed using the Illumina MiSeq Software and Genomized Seq software, and the IGV (Broad Institute) program was used for the visual evaluation of the data. Pathogenic / probably pathogenic variations were observed in 12 out of 32 patients (37.5%). While 10 of these P / OP variants were identified in MSH, MLH, APC, MUTYH genes that directly related to colorectal cancer, in 2 out of 32 patients, pathogenic / probably pathogenic variations in other genes related to cancer susceptibility (BRCA1 and ATM) was detected. In one of the cases, pathogenic variation was detected in both the BRCA2 and APC genes. This study supports the determination of the genetic background of colorectal cancers by using the Next Generation Sequence Analysis method and the simultaneous screening of many cancer-related genes. In addition to hereditary colorectal cancer syndromes, the identification of pathogenic variations in other cancer-related genes and genetic counseling have contributed significantly to the clinical follow-up and early screening of cancer.

Key Words: Colorectal cancer, NGS, mutation, pathogenic

From Phenotype to Genotype

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The essential parts of a genetic evaluation consist of the medical history, family history, dysmorphic examination, literature review, and diagnostic testing. A genetics questioning should be include, consideration of which anatomical anomalies are, history of known maternal exposure to a teratogen, history of pregnancy loss and a familial disorders, increased carrier frequency or ethnic risks. During the evaluation period of the phenotype of the patient, the clinical geneticist catching for clues like a detective, feel accomplishment when all the pieces fit. Diagnosis in dysmorphology is depend on often knowledge which depends on experience, but no clinician can recognize all syndromes. It is all about unusual conditions that occur rarely and are usually difficult to diagnose. Differential diagnosis is also often difficult. In cases in which there is no clear diagnosis, treatment usually be symptomatic. The advancement of techniques utilized in genetic testing, such as chromosomal microarrays and next generation sequencing besides conventional techniques, has greatly improved the ability to make a genetic diagnosis. However, many aberrations or variations are novel or extremely rare, making clinical interpretation problematic and genotype-phenotype correlations uncertain. In some centers there is already an 'exome first' approach to diagnosis and this is likely to become more widespread, but assessment of the clinical phenotype remains essential to interpret the significance of variants. Going to the diagnosis through the phenotype of the patient is very important for choosing the appropriate diagnosis method. Such an approach would be both more scientific and more cost effective.

Key Words: Phenotype, Genotype, Dysmorphology

In Silico Analysis of Variants Using Prediction Tools

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A single nucleotide polymorphism (SNP) in a coding region of DNA that result in to change in the translated amino acid residue sequence is called a non-synonymous variant (nsSNV) or missense variant. Many of nsSNVs are known to cause human disease phenotypes. However, if using functional analyses are not possible to determine the pathogenicity of these variants, in silico tools are used. At least three of these tools are routinely used by diagnostic laboratories to advise clinicians of the possibility of disease. In the training course, a novel variant (for example: gh19-chr17, 18055426G> T) was analyzed using MutationTaster, SIFT and PolyPhen-2 tools. Using MutationTaster (http://www.mutationtaster.org/), ensembl transcripts and UniProt peptide information, the data of alteration type and region, frameshift effect, the informations in dbSNP/TGP/ClinVar/HGMD and ensemble regulation database, conservation information with phyloP/phastCons, the effect on splice sites, as well as the disease prediction is examined. Disease-causing nsSNVs generally occur at evolutionarily conserved sites that have an essential role in the structure and/or function of the encoded protein. The SIFT (http://sift.bii.a-star.edu.sg/) tool estimates whether an amino acid substitution affects protein function relative to sequence homology and physical properties of amino acids. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) is an estimation tool used to describe the possible effect of nsSNV on protein function and structure. This estimate also includes phylogenetic and structural information. This example SNV was shown to exchange the valine to leucine in the 2632th codon of MYO15A (p.V2632L). In MutationTaster, it was determined as the disease causing with 95% possibility ratio. This SNV was estimated to be damaging the protein function with a score of 0.01 using SIFT tool. This variant which conforms to the Mendelian inheritance model was estimated to be benign with 0.132 score when examined according to HumVar model using PolyPhen2. And this AA-substitution was found in an evolutionally protected region in the MYO15A. However, in the segregation analysis of the larger family, it was concluded that this variant was not an association with the disease. As a result, it should be noted that in silico tools only provide supporting information to researchers/clinicians and their accuracy may be low.

Key Words: SNV, missense variant, in silico tools, prediction

Reverse Genetics (Genotype to phenotype)

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Reverse genetics is a method that is used to help understand the function of a genes by analyzing the phenotypic effects of genome variants. Reverse genetics previously used with chromosome analysis nowadays it is mostly used with exome sequencing methods. The goal in reverse genetics is to investigate the impact of induced variation within a specific gene and to in gene function. But there are some limitations of the exome sequencing. Exome sequencing does not target 100% of the genes in the human genome; approximately 97% of exons are targeted. However, ~10% of exons may not be covered at sufficient levels to reliably call heterozygous variants. Each individual may have slightly different coverage yield distributions across the exome. But nowadays, clinical evaluation and clinical genetic importance remain more important and should not be forgotten than all these techniques.

Key Words: Reverse genetics, exome sequencing

The American Board of Medical Genetics and Genomics (ABMGG)-Accredited Training Programs

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The American Board of Medical Genetics and Genomics (ABMGG) certifies trainees in various specialty areas of medical genetics and genomics. Specialties in Medical Genetics and Genomics include Clinical Genetics and Genomics, Clinical Biochemical Genetics, and Laboratory Genetics and Genomics (http://abmgg.org). 1) Clinical Genetics and Genomics: A clinical geneticist is a physician who holds a U.S. or Canadian earned M.D. or D.O. degree, or equivalent, who has trained a minimum of one year in an ACGME-accredited residency (that includes 12 months of direct patient care), and then has completed an ACGME-accredited residency in medical genetics and genomics. In addition, combined residency training consists of a comprehensive educational experience in two related specialties or subspecialties. The combined training programs are approved by the corresponding Board of each specialty to assure that residents completing combined training are eligible for certification in each of the component specialties: (i) Internal Medicine & Medical Genetics and Genomics, (ii) Maternal Fetal Medicine & Medical Genetics and Genomics, (iii) Pediatrics & Medical Genetics and Genomics, (iv) Reproductive Endocrinology and Infertility & Medical Genetics and Genomics 2) Clinical Biochemical Genetics: A diplomate certified in clinical biochemical genetics is an individual with a U.S. or Canadian earned doctoral degree (M.D., D.O., Ph.D.), or equivalent, who can direct and interpret biochemical analyses relevant to the diagnosis and management of human genetic diseases, and who acts as a consultant regarding laboratory diagnosis of a broad range of biochemical genetic disorders. 3) Laboratory Genetics and Genomics (a combined three-year program of Clinical Cytogenetics and Genomics and Clinical Molecular Genetics and Genomics effective by July 2016): A diplomate certified in Laboratory Genetics and Genomics is an individual with a U.S. or Canadian earned doctoral degree (M.D., D.O., Ph.D.), or equivalent, who can direct and interpret both clinical cytogenetic and molecular genetic analyses relevant to the diagnosis and management of human genetic disease. These individuals act as consultants in laboratory diagnoses for a broad range of molecular and chromosomal-based disorders, including both inherited and acquired conditions.

Key Words: The American Board of Medical Genetics and Genomics (ABMGG), Clinical Biochemical Genetics, Laboratory Genetics and Genomics, Combined Residency Training Programs, Medical Genetics and Genomics

Transcriptomics-Basic Principles and Clinical Applications

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In the era of genomic medicine, the widespread use of next generation sequencing technology has been a breakthrough in terms of the rare diseases. This technology can reveal the whole sequence of the human genome as well as revealing different solutions such as gene panels for protein coding regions (exome) and for sequencing genes responsible for a particular disease. The widespread use of the whole exome sequencing has a critical impact on its contribution to both research and health care. However, only %40-50 of Mendelian phenotypes can be revealed by using whole exome sequencing. Moreover, this diagnostic yield can not be increased in complex Mendelian disorders by using an additional approach, whole genome sequencing. Importantly, some of the non-coding variants cause mis-splicing events such as introducing pseudo-exons. At that point, by using next generation sequencing based RNA sequencing, one could identify the biological impact of non-coding variants causing Mendelian phenotypes. In conclusion, transcriptomics may become a critical component of the diagnostic approaches for Mendelian diseases. In the near future RNA-based therapeutics, such as anti sense oligonucleotides, could be commonly used in rare diseases by exploring non-coding variants.

Key Words: Transcriptomics, pseudo-exon, RNA-seq, Rare disorders

Hemoglobinopathies

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Hemoglobinopathies are the most common single-gene diseases in the worldwide. Although their molecular and biochemical pathology is well understood, hemoglobinopathies are a group of complicated diseases that are difficult to understand since they are genetically heterogeneous. Hemoglobin is the oxygen carrier protein, which is containing four subunits- two α two β globins. HbA is the main hemoglobin form in healthy adults. There are two identical α genes and one β gene in each homolog, the genes for the α and α like globins are clustered on chromosome 16 in a tandem rearrangement. The genes of β and β like globins are clustered on chromosome 11. α globin and β globin genes are close family members and arose from a common ancestral gene, respectively. They all have highly conserved areas that lead to marked clinical findings when an alteration occurs. The regulation of the expression of globin genes at different stages of development is controlled by a mechanism called 'globin switching'. Understanding the expression patterns of α and β globin along with gene dosage is crucial for understanding the pathogenesis of hemoglobinopathies. Hemoglobinopathies can be classified into two main groups as structural variants and thalassemias. In structural variants frequently an amino acid sequence is changed, causing an alteration in oxygen transport or stability. In thalassemias, decreased abundance of one or more globin chains is the main cause. The clinical findings in thalassemias are due to deterioration in α:β chain ratio. It has long been known that there are some modifier factors for clinical severity in hemoglobinopathies such as the variations in the other globin genes, modifier genes etc. Hemoglobinopathies are also a serious public health problem due to their prevalence and morbidity/mortality rates. In regions where hemoglobinopathies are common, effective thalassemia control programs, containing premarital carrier screening, prenatal diagnosis, preimplantation genetic diagnosis are implemented by governments.

Key Words: Globin, hemoglobin, hemoglobinopathies, thalassemias

Sensitive Personal Data and Law

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Personal data means an identification of an individual through any information, directly or indirectly, relating to an identifiable individual. The personal data related to the race, political thoughts, philosophical belief, religion, sect or other beliefs, memberships for clubs, foundations and syndicates, health and private life and any type of conviction are called the special data or sensitive personal data. By the generally accepted approach the processing of these data is prohibited. Exceptionally, in cases of public interests, by the consent of a person these data can be processed. In fact, the term of “protection of data” is a misleading term. The main point expressed under this notion is that, the protected value is not the data itself, but the personal rights of an individual related with this data. But a personality can be protected as much as the data can be protected, and consequently, the strictness of the data protection implies the strictness of the protection of a personality. In this terms, the data protection is the protection of personal rights and therefore is the protection of fundamental rights of individuals under constitution. The common ground of the sensitive data is the risk factor that they have. This risk factor is the discrimination factor. The point is that in case of knowledge of the third persons these data can result in the unjust treatment of an individual. Personal data as a rule, is the subject of processing prohibition in the frame of a private life. The principle of a consent of a person and compliance with law are not valid for the processing of a sensitive data. Developments in the field of biotechnology makes a current issue of the important problems of the ethical and human rights in the health sphere and on the other hand accelerate the discussions on the topics like the disclosure, privacy and sharing of the genetic information. This circumstance puts in forward the issues like the importance of the respect of a person and his/her honor. Briefly, the genetic data of an individual and all illegalities must be protected. It is essential that all enforcements constituting an opposition.

Key Words: Personal Data, Sensitive Personal Data, Genetic information, Genetic data, Law.

Basic Principles and Distinct Platforms in Cell-Free DNA (cfDNA) Screening

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Large scale studies investigating Down syndrome prevalance in Europe revealed that the progress in maternal serum screening and fetal ultrasonography just kept the live birth ratio of Down syndrome constant. The findings of such studies exhibited the need for powerful prenatal screening methods. The need was more obvious in Turkey as the leading country of Europe by its birth rates which was about 1,4 million births per year. Investigating "circulating fetal cells", "digital PCR" and "cfDNA by shotgun or targeted massively parallel sequencing" were the main approaches. First commercial cfDNA screening products are presented in 2011 and in 2016 we had the test in our country for routine use. Following the declaration of American College of Medical Geneticists in 2016 the cfDNA screening was progressed which said "NIPS can replace conventional screening for Patau, Edwards, and Down syndromes across the maternal age spectrum, for a continuum of gestational age beginning at 9–10 weeks, and for patients who are not significantly obese". The presented workshop deals with basic principles of widely used cfDNA screening methods and new technologies such as: MeDIP, cSMART, COLD-PCR and NanoVelcro Microchips.

Key Words: Cell-Free DNA Screening, NIPT

Approach to Non-Syndromic Intellectual Disability

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According to the American Psychiatric Association's DSM-V definition, intellectual disability (ID) is defined by the fact that cognitive activity is below normal, at least two of the functions related to adaptation are below the expected standard according to the age and cultural level of the person, and the beginning of these two criteria before the age of 18 years. Cognitive activity is measured by the Intelligence Quotient and ID is classified as mild, moderate, heavy and very heavy. The Intelligence Quotient is normally distributed in the society with a mean of 100 and a standard deviation of 15 points. According to this, 2-3% of the population is mild, and 2-3% of the population is medium, heavy or very heavy ID. Sociocultural deficiencies leading to prematurity and its complications, nutritional deficiencies, systemic diseases and various deprivations are responsible for a higher rate than mild ID. On the other hand, it is more likely to detect chromosomal diseases, recognizable syndromes, various single gene disorders, and central nervous system malformations. To be able to perform a thorough examination including a clinical ID approach, detailed prenatal, natal and postnatal history, dysmorphological and neurological examinations, and to prepare a pedigree of at least three generations, and to prepare the laboratory investigations, accompanying phenotypic features and support the multifactorial basis. Also, in order to determine the other areas required, it should include the steps of conducting the psychometric and behavioral evaluation. Visual and hearing examinations, thyroid function tests and metabolic scans should be performed in every patient. In the presence of microcephaly and neurological findings, cranial imaging should be included. According to the American Academy of Pediatrics guidelines and clinical genetic guidelines, specific diagnoses and diagnostic tests directed by this basic assessment should be planned as prioritized. If no such tests are available or if the diagnosis cannot be reached, microarray analysis should be performed first for screening purposes, then Fragile X syndrome due to its frequency and Rett syndrome in girls should be considered first, then patients should be directed to Whole exome sequencing (WES). Hacettepe University Faculty of Medicine, Department of Pediatrics, Department of Pediatric Genetic Diseases has been formed by following the technological advances and laboratory tools developed in genetics over the years regarding non-syndromic ID. In our clinic, subtelomeric FISH were used for non-syndromic ID, and MLPA, microarray analysis (CGH and SNP) and WES were used for X-linked non-syndromic ID. The diagnostic yield of these tools was variable according to patient selection criteria, and was found to be 12-16% in microarray studies and 35% in all exom sequencing studies.

Key Words: Non-syndromic cognitive impairment, clinical approach, diagnostic tests, etiologic efficiency

The Diagnosis of Genetic Disorders of The Skeleton With New Techniques

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The skeletal dysplasias or osteochondrodysplasias are defined as disorders that are associated with a generalized abnormality in the skeleton. These genetic disorders of the skeleton are phenotypically and genetically heterogenous group with an estimated prevalence of 1 in 5,000 births. According to the Nosology and Classification of Genetic Skeletal Disorders 2015 Revision there are 436 disorders grouped under 42 groups involving mutations in one of 364 genes. These disorders are named and classified into groups based on genetic cause if known, or on similarities of clinical and radiographic manifestations. The number of these disorders has increased as application of high-throughput sequencing technology has expanded. The clinical manifestations may be restricted just to the skeleton or other nonskeletal tissues may all be involved as well. With some exceptions, there is a strong correlation between the age at onset and the clinical severity (from "precocious" arthropathy to perinatal lethality owing to pulmonary insufficiency). The individuals with these disorders can have significant orthopedic, neurologic, and psychological complaints. Affected individuals usually present with disproportionate short stature. As a general rule most individuals with disproportionate short stature have skeletal dysplasias, and individuals with proportionate short stature have endocrine, nutritional, or prenatal-onset growth deficiency or other disorders. A disproportionate body habitus may not be visible on physical examination. Anthropometric dimensions including upper-to-lower segment ratio and arm span must be measured when evaluating a patient with the possibility of a skeletal dysplasia and should be measured in centimeters. After obtaining a thorough family history, physical examination and necessary skeletal radiographs a clinical diagnosis may be established. However, this may not always be the case. Some molecular tests including chromosomal microarray, DNA sequencing, multiplex ligation probe amplification and whole exome sequencing may help in revealing the underlying genetic etiology. Clinical approach to a patient with a skeletal dysplasia and examples of some patients in whom the genetic etiology was revealed with the aid of molecular tests will be given in this talk.

Key Words: Skeletal dysplasia, molecular tests, disproportionate short stature.

The algorithm of mosaicism during prenatal diagnosis

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Chromosomal mosaicism, the presence of at least two cell lines with different karyotypes in one fetus derived from a single fertilized egg, is the dilemma of prenatal diagnosis. This phenomena occurs in approximately %1-3, and %0.1-0.5, in chorionic villi sampling (CVS), and amniocytes, respectively. There is two main mechanism underlying on the feto-placental mosaicism; one postzygotic, due to a non-disjunction error during a mitotic cell division of a diploic conceptus, or meiotic, due to the trisomic rescue of an aneuploidic conceptus. Mosaic condition confined to placenta (CPM) is classified in three category according to the distribution of the abnormal cell line; only on the cytotrophoblast and only on the mesenchyme, CPMI, and CPMII, respectively. If the abnormal cell line is located on both of the tissues, it is called CPMIII. The stage of the mosaicism is determined with levels, in which level I, the existance of a single abnormal cell in a culture from a single flask, is a cultural artifact and considered pseudomosaicism, while level II is the presence of two or more cells with the same chromosome abnormality in one flask. Level III, frequently addressing true mosaicism, is defined as the presence of two or more cells with the same chromosome abnormality that are distributed over two or more independent cultures. When the geneticists faced with the mosaic condition on CVS, almost always they want to repeat the karyotyping procedures on amniocytes to discriminate the mosaic confined to placenta, or one generalized to the fetus (true fetal mosaicism: TFM). After the confirmation on amniocytes, mosaicism can be classified according to the distribution of the abnormal cell line: if only distributed on cytotrophoblast it is addressing TFM type IV, if only the mesenchyme involves the abnormal cell line its name is TFMV, and if both placental tissues and amniocytes are affected by the abnormal cell line, it is named as TFMVI. Finally to evaluate this difficult condition, and to avoid the false negative and false positive results, carefull analyses should be performed via different fetal tissues, by the geneticists with deep experience.

Key Words: Chromosomal Mosaicism, Confined Placental Mosaicism, True Fetal Mosaicism, Prenatal Diagnosis

Genetic Counseling in Disorders of Sex Development

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Disorders of sex development (DSD) are described as atypical situations including chromosomal, gonadal, anatomical sex development and, the genetic causes of DSD are extremely heterogeneous. The frequency is 1 in 4500 newborns. The classification is made according to karyotype and, DSDs are divided into three groups as sex chromosomal DSD, 46,XY DSD and 46,XX DSD. Therefore, the first investigation to be done in the diagnostic process is cytogenetic examination and chromosomal sex should be revealed. Simultaneously, detailed clinical evaluation, laboratory and imaging techniques are performed to reveal the underlying cause. More specific tests can be planned for molecular diagnosis in the light of the information collected. The accuracy of diagnosis will enable more effective genetic counseling. Recently, advanced genetic tests have been performed in patients with DSD. With these tests, the rate of diagnosis in patients is observed to reach up to 50%. However, these opportunities may not always exist. For this reason, 46, XY DSD cases can be screened for pathological variants that may occur in *SRY*, *NR0B1*, *SRD5A2*, *AR* genes which are more frequently encountered with the guidance of clinical, laboratory and imaging findings. Congenital adrenal hyperplasia should be excluded in 46,XX DSD cases. In this presentation, genetic counseling in DSD has been discussed via cases.

Key Words: Disorders of sex development, Sex chromosomal DSD, 46,XY DSD, 46,XX DSD, Genetic counseling

Genetic Diagnosis of Hematological Malignancies: Cytogenetics and FISH

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The importance of genetic information in hematological cancers has started with the identification of the Philadelphia chromosome, which is considered to be a biomarker specific to individuals with chronic myeloid leukemia (CML). This genetic abnormality, which provides a definitive diagnosis in a patient with clinical and hematological findings incidental to CML, revealed the necessity of genetic evaluation in other hematological malignancies. Today, genetic analyzes have been used in the diagnosis of many hematological malignancies, in the formation of subgroups, in determining the prognosis, in the selection of the specific treatment and in the follow-up of the response to the treatment and even in many guidelines, genetic abnormalities have become available as benchmarks.

At the stage of diagnosis in hematologic cancers, the determination of genetic changes at the chromosomal level in the bone marrow sample is still considered to be the gold standard. In order to reach the most accurate results about the number and structure of the chromosomes of the malignant cell, both the number of metaphases in the material obtained from the bone marrow sample should be sufficient and the resolution of chromosomes on metaphases should be high. In recent years, commercially developed new cell culture mediums have been able to provide these conditions. On the other hand, malignant cells may not behave in vitro as in vivo, or because the cell population studied is heterogeneous, healthy cells can reproduce by giving superiority to malignant cells, or they can escape apoptosis without proliferation, as in Chronic Lymphoblastic Leukemia. Sometimes the chromosomal abnormalities such as microdeletions, microduplications, cryptic translocations, masked translocations, and variant translocations may occur at the subchromosomal level, in these cases abnormalities can not be observed during conventional cytogenetics analysis.

Fluorescent In Situ Hybridization (FISH) technique has been used as a complement to conventional cytogenetics. This technique can be very informative even in cases where metaphase cannot be obtained, or in cases where metaphase is not required, FISH test results are usually available after a short period of time of 24 hours, it is possible to evaluate a large number of interphase cells. FISH method is used to confirm a suspected finding in chromosome analysis, to determine the fracture points of chromosomal rearrangements, and to determine the origin of double-minute or homogenously stained region frequently observed in cancer and sometimes to update the cytogenetic report. One of the two most important points when applying the FISH method is the selection of the correct probe, and the other is the determination of the cut-off value for each probe used. However, the biggest limitation of this technique is that it allows only targeted analysis. On the other part, chromosomal analysis is essential to demonstrate additional findings that may arise with karyotypic evolution, while following a certain chromosomal finding in the disease process by FISH method. In addition, cytogenetic analysis is still needed to determine candidate chromosomal abnormalities that affect prognosis.

When the advantages and disadvantages of both tests are evaluated together, it is evident that concomitant use of conventional cytogenetics and FISH is indispensable to the correct outcome in routine practice.

Key Words: Cytogenetics, FISH, hematological cancers

Oral Presentations Abstracts

- A Case With Type 2 Kenny-Caffey's and Occult Macular Dystrophy and the Importance of Dual Diagnosis, One of the Important Factors Affecting the Diagnosis Success in Syndromic Cases

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Dual Diagnosis is an important factor that affects the diagnosis in clinical genetics. With this presentation, we aimed to emphasize the importance of dual diagnosis with a case having Type 2 Kenny-Caffey and Occult Macular Dystrophy phenotype.
A 12-year-old girl was referred to our department because of short stature, atypical facial appearance and progressive vision loss. She had microphthalmia, irregular teeth, nasal septum deviation, bilateral 5th fingers shortening, hydrocephaly and hypocalcemia history in her physical examination and anamnesis. Bone age was normal and his cranial CT revealed tetraventricular hydrocephalus. The patient's parent had a first kuzen and heterozygote mutation was observed in FAM111A and RPL1 genes with whole exome-sequencing analysis.
The clinical findings of the patient are consistent with Type 2 Kenny-Caffey and Occult-Macular Dystrophy phenotype due to mutations of FAM111A and RPL1 gene, respectively. Dual diagnosis is one of the important factors affecting the diagnostic rate in clinical genetic. With this case, the importance of dual diagnosis which began to be understood with the spread of all exom / genome analyzes was emphasized. In addition, it is reminded that de novo variants should be taken into account in cases where autosomal recessive gene mutations that we intensely concentrate in consanguineous marriages are not able to solve the etiology.

Key Words: Dual Diagnosıs, Type II Kenny-Caffey Syndrome, Occult Macular Dystrophy, Whole Exome Sequencing

- Two Ultra-Rare Recessıve Dısorders And Pseudodomınant Inherıtance In The Same Famıly

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Incidence of rare recessive single gene disorders increases among parents with consanguinity and multiple disorders can be detected in the same family. The aim of this presentation is to emphasize the importance of phenotypic findings and possibility of multiple recessive disorders while analyzing exome/genome data and assessing family trees involving multiple consanguinity.
11-month-old male infant (index) with consanguineous parents presented with congenital nystagmus. Developmental milestones were compatible with age. Pedigree revealed; his mother from a consanguineous parent had congenital nystagmus; mother's sister had congenital nystagmus, mild intellectual disability; mother's brother had nystagmus, moderate intellectual disability, speech delay, stereotypic behavior, tics, arched thick eyebrows. Father was healthy. Since mother was a teacher despite 80% visual loss, it was thought that nystagmus and intellectual disability had different causative factors and variant analysis was performed considering pseudodominant inheritance pattern due to consanguinity.
Whole exome sequencing (WES) was performed. Homozygous missense variant of PDE6C gene was detected in mother and index (Class 3). Mother's brother was heterozygous for this variant and homozygous for missense variant of TAF6 gene (Class 1) and he was diagnosed as Alazami-Yuan Syndrome (ALYUS, MIM#617126). Father of index was carrier for both genes. Additionally, WES analysis of index revealed heterozygous missense variant of MYBPC3 gene (Class 1), which was involved in variants that could be reported with family's consent based on the ACMG criteria.
Homozygous or compound heterozygous variants of PDE6C gene are related with autosomal recessive cone dystrophy type 4 (MIM#613093) with a wide spectrum of early onset cone dystrophy and complete achromatopsia. Ophthalmic findings haven't been reported in carriers. ALYUS related with TAF6 gene have previously been reported in Turkish and Arabic families and described as CorneliadeLange Syndrome (CdLS)-like phenotype. Homozygous variant in the Arabic family is the same in mother's brother. The nystagmus in mother's brother is possibly caused by TAF6 gene, since index is carrier for PDE6C gene, father of index is healthy and CdLS can present with nystagmus. Genetic counselling was given to the family and analysis of mother's sister and other family relatives is ongoing. Cardiology consultation was requested for the index patient for the MYBPC3 gene.

Key Words: Pseudodomınant Inheritance, Exome, Cornelia De Lange, Alyus

S-001 - Determination of the Relationship Between Early Preeclampsıa and MIR518B in Maternal Blood

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Preeclampsia (PE) is one of the causes of maternal and fetal morbidity and mortality and is a pregnancy-specific disease associated with hypertension and proteinuria and various symptoms. The C19MC microRNAs in miR-518 were found to be related to preeclampsia and intrauterine growth retardation (IUGR) in placental trophoblasts and maternal plasma in the first trimester. The aim of this study was to investigate the relationship between miR518b expression levels and preeclampsia in maternal leukocytes of pregnants between the 20th and 34th weeks of gestation.
In this study, pregnant women with early preeclampsia who were admitted between May 2017 and March 2018 to Istanbul Medeniyet University Göztepe Training and Research Hospital Gynecology and Obstetrics Department.The diagnosis of preeclampsia was determined by the criteria of the The American College of Obstetricians and Gynecologists (ACOG) 2013 guidelines. According to these criteria,mild PE pregnant (GW: 30.4 ± 3.9, average age: 30.5 ± 6.1,n=24), severe PE pregnant (GW: 30.2 ± 2.8, Average age: 30.8 ± 4.8, n=16) and healthy control group pregnants (GW: 28.6 ± 0.8 mean age: 28.2 ± 5.5 n=26). After total RNA isolation from the maternal blood, the expression level of miR-518b was determined by the ΔΔCt method using cDNA synthesis, SYBR-Green quantitative PCR and RNU-6 control miRNA values. The results were evaluated statistically.
Statistically significant differences were found in terms of birth weight, gestational age, IUGR and delivery type between the control group with early and mild preeclamptic pregnancies ($p<0.0001$). According to the results of the analysis between severe and mild preeclampsia and control group, the expression level of miR-518b was found to be 4.6-fold in pregnant women with severe preeclampsia and 2-fold in pregnant women with preeclampsia ($p=0.023$). Also, according to the severity of preeclampsia, the relationship between IUGR and miR-518b expression levels was not found to be significant in the mild case, while in the severe clinical situation, miR-518b expression level was 1.5 times higher in patients with IUGR compared to those not observed (6.22 ± 7.91 and 4.21 ± respectively, respectively). 4.6, $p>0.05$). The relationship between miR-518b expression levels and preeclampsia severity in maternal blood leukocytes was first demonstrated in this study.

Key Words: Preeclampsia, Maternal Blood, miR518b, Expression Level, Relative Quantitation

S-002 - A Comprehesive Studying on Thrombophilic Gene Poymorphisms and Mutations Role on Recurrent Pregnancy Loss

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Thrombophilic gene polymorphisms and mutations accepted as a risk factor for recurrent pregnancy loss. There are only a few studies which include comprehensive parameters and sufficient number of patients. This study includes following 2 mutations and 7 polymorphisms which are Factor V Leiden (G1691A) and Protrombin G20210A mutations , along with MTHFR C667 , MTHFR A1298C , PAI-1 4G/5G, PAI 4G/5G, Beta- fibrinojen G455A , FXIII V34L AND gp IIIa L33P polymorphisms. In this study we aimed to investigate the effects of these genetic changes on recurrent pregnancy loss.
This study includes 370 patients who referred to Pamukkale University Medical Genetic Department for thrombophilia testing , between the years 2017-2018 and evaluated the alterations in Factor V Leiden (G1691A) , Protrombin G20210A , MTHFR C667 ,MTHFR A1298C, PAI-1 4G/5G, PAI 5G/5G , Beta- fibrinojen G455A , FXIII V34L ve gp IIIa L33P. We analyzed 292 cases with recurrent pregnancy loss . Patients with thrombophilia without recurrent pregnancy loss were taken a control group. Oneway ANOVA test were used for statistical analysis.
When we analyzed the results, we obtained that Protrombin G1691A, MTHFR C667 , MTHFR A1298C ($p>0.05$) mutations were significantly increased in recurrent pregnancy lost patients, on the other hand Faktör V Leiden (G1691A), PAI-1 4G/5G , Beta- fibrinojen G455A , FXIII V34L ve gp IIIa L33P ($p<0.05$) were not different in between patients with recurrent pregnancy lost and control group .
Our results could have more significant data because of including large number of patients compared to previous studies .Till now, Factor V mutations role on trombophilia agreed as an important role. Similar to our results, last studies in the literature showed that FV mutations may not be an important role on recurrent pregnancy loss. Results of the study indicated that screening MTHFR polymorphism and F2 mutations are beneficial on understanding the reason of recurrent pregnancy lost.

Key Words: Recurrent Pregnancy Loss , Mutatıon, Poymorphism , Thrombophilia

S-003 - Chromosomal Heteromorphisms and Reproductive Health

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Heterochromatin located in pericentromeric regions of chromosome 1, 9 and 16, distal part of long arm of Y chromosome and short arms of acrocentric chromosomes differs among individuals. These variations, termed heteromorphisms, have been found to be associated with many clinical entities. The aim of our study is to determine the frequencies of heteromorphisms and to study their relationships with fertility problems.
A total of 1866 cases were included in the study. These cases were divided into 4 groups as infertility (n:602), IVF failure (n:224), recurrent pregnancy loss (RPL) (n:768) and control (n:272). Karyotypes of all cases were examined retrospectively. For the evaluation of heterochromatin regions in chromosomes 1, 9, 16 and Y, a scoring system based on 16p was conducted and the most frequent level was set as threshold to be considered as qh+. The criteria to be accepted as heteromorphism for the acrocentric chromosomes was "two-fold of its homologue". Frequencies of heteromorphisms, their associations within each other and with indications, were determined.
Frequencies of heteromorphisms in total for 1qh+, inv(9), 9qh+, 16qh+, Yqh+, Yqh-, chromosomes 13, 14, 15, 21 and 22 were 15.3%, 2.1%, 10.4%, 14.1%, 9.5%, 9.2%, 7.8%, 8.3%, 9.3%, 11.7% and 10.2%, respectively. The most frequent heteromophism among all groups was 1qh+ (except the Y chromosome). In males, Yqh+ was the most common heteromorphism. Inv(9) frequency was 2.1% in total group in concordance with the literature. Among D and G group chromosomes, the most frequent heteromorphism in all groups was of chromosome 21. There were no significant differences between the groups. Significant co-occurrences of 1qh+ and Y qh+, 16qh+ and Yqh+, 16qh+ and 22 in IVF failure; 1qh+ and Yqh+, 13 and 21, 15 and 22 in RPL; 1qh+ and 16qh+, 13 and 22, 15 and 22, 14 and 15 in infertility; 16qh+ and 14 in controls were observed. The co-existence of chromosome 15 and 21 heteromorphisms was apparent in all groups.
Association of particular heteromorphisms may indicate a relationship of these regions with the heterochromatin dynamics. The significant co-occurrences of these variants in certain indications necessitate further studies to elicit their impact on fertility problems.

Key Words: Heteromorphism, Infertility, Recurrent Pregnancy Loss

S-004 - Prenatal Diagnosis of a Case with Non-Mosaıc Tetrasomy 9p: A Case Report

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Tetrasomy 9p is a rare chromosomal disorder. This condition causes chromosomal imbalance because of an extrachromosomal material originated from the short arm of chromosome 9. Clinical severity varies widely according to the level of mosaicism and the content of the extra chromosomal material. Here, we present a tetrasomy 9p fetus in which the pregnancy was terminated at the request of parents.
Chorionic villus sampling (CVS) was performed on a 29-year-old pregnant woman at 13-week of gestation because of increased nuchal translucency (5.1 mm) detected in the ultrasonography (USG). This is followed by amniocentesis at 17-week of gestation to exclude placental mosaicism and to confirm the result. The material detected by karyotyping was analyzed further via fluorescence in situ hybridization (FISH) and microarray. USG at 17 and 23rd weeks of gestation revealed fetal anomalies. The elective termination was decided after genetic counseling was given to the family.
Karyotype analysis was performed from CVS and amniotic fluid and resulted with 47,XY,+mar. Fluorescent signals which belong to the short arm of chromosome 9p were detected on both arms of marker chromosome by using telomeric 9p-9q probes. The diagnosis of the marker chromosome was isochromosome of 9p. Microarray analysis revealed arr[GRCh37]9p24.p11.2x4. Moreover, a very short region of 9q13 was detected to be trisomic. USG at 23rd weeks of gestation showed unilateral cleft lip and palate, micrognathia, bilateral ventriculomegaly, left axis deviation of the fetal heart and partial atrioventricular septal defect. Examination of the fetus after termination of pregnancy confirmed USG findings besides hypertelorism, low-set and posteriorly rotated ears and hypospadias.
The severity of the clinical picture in the case was attributed to the non-mosaic pattern and 9q content of this marker chromosome. Our case will contribute to the literature due to the very rare presentation of this chromosomal anomaly.

Key Words: Tetrasomy, 9p, CVS, Mosaicism, Isochromosome

S-005 - Recurrent Pregnancy Loss (Rpl) Caused by Recurrent Aneuploidies: How Can The Predısposıtıon To Nondisjunction Be Explained?

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Approximately 50% of first trimester and 20% of second trimester spontaneous abortions are caused by chromosomal abnormalities. Most common aneuploidies involve chromosome 16,22,21,15,13 and 14 respectively. Chromosomes 13,18 and 21 are more important because of their viability potential. The value of cytogenetic examination to any spontaneous abortion is related to whether or not the possible abnormal result would cause a change in the medical management of the couple. In this presentation, we aimed to discuss possible mechanisms of recurrent aneuploidies based on a couple who has RPLs with different aneuploidies, and options that should be considered in case management.
Thirty five year-old female and 37 year-old male couple were referred to us with 8th gestational week G2A2 pregnancy without fetal heart rate(FHR). Chromosome analysis and rapid aneuploidy screen with quantitative fluorescent PCR(QF-PCR) were planned from the fetal tissue.
The QF-PCR result was consistent with trisomy 21. Cytogenetic result was 48,XY,+7,+21. Low mosaic 45,X[5]/46,XX[95] karyotype was observed in the female patient. She had no symptoms regarding mosaic Turner syndrome. Male patient's karyotype was normal. During follow-up, another natural pregnancy (G3A3) was terminated at the 8th gestational week due to negative FHR. Karyotype was found as 47,XX,+16. Assisted reproductive techniques (ART) and preimplantation genetic screening (PGS) were recommended. PGS analysis of 4 embryos obtained by ART revealed complex chromosomal abnormality.
It is controversial whether a history of abortion with chromosomal abnormality increases the risk in subsequent pregnancies. However, one could speculate several reasons for recurrent trisomy. Chance, trisomic gonadal mosaicism or the presence of factors that may cause meiotic error can be evaluated. In our case, 45,X mosaicism may be the triggering factor by decreasing the oocyte reserve. But age related loss of X chromosome might also be the reason behind low mosaicism. Highly invasive ovarian biopsy would be required to prove that hypothesis. Genetic counseling which involved a suggestion for prenatal diagnosis in future pregnancies along with the advantages and limitations of PGS were given to the couple. Further studies are needed for the evaluation of other factors (recombination-related genes, genes that regulate oocyte-sperm development, toxic agents…) that might cause a meiotic error.

Key Words: Aneuploidy, Double Trisomy, Recurrent Pregnancy Loss, Recurrent Trisomy

S-006 - Extra Chromosome, Extra Love

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Down Syndrome (DS) is a genetic disorder seen in every 700 live births and occurs due to chromosomal abnormalities. Clinical findings are variable. Individuals with Down Syndrome can participate social life through special training. In our study, we aimed to detect the level of DS awareness on our society.
A survey study was conducted with randomly selected individuals over 18 years of age, applied to Eskişehir Osmangazi University Medical Faculty Hospital.
The study group consisted of 120 (42.3%) males and 163 (57.6%) females with an age range of 18 to 81 (40.37 ± 15.05). Of the cases, 117 (41.3%) were undergraduate or above and 75 (26.5%) were 51 years old or over. 89,8% of cases stated that they have heard about DS. It was observed that 70% of the cases knew individuals with DS could adapt to society through education and 14.1% were prejudiced against individuals with DS. Significant differences were detected in awareness of prenatal diagnostic tests (PDT) for DS between groups (gender, age, and educational status). The frequency of PDT awareness was higher in women and cases with higher education (undergraduate or above). There were significant differences in the awareness of high risk factors like advanced maternal age and history of DS on previous pregnancies between different education levels ($p = 0.001$).
As a result of our study, it's observed that awareness of PDT and risk factors for DS (advanced maternal age,familial history of DS) increased with education level. Also younger population was more conscious about PDT. We believe that the awareness increases with easy access to information through internet and social media in the young population. The awareness for DS in all segments of the society may facilitate the solution of medical and social problems. Thus, increasing the life quality of individuals with DS and their families and adapting them to society would be possible. There is a need for special education and social projects to raise DS awareness.

Key Words: Down Syndrome, Survey, Eskisehir

S-007 - Alagille Syndrome and Gonadal Mosaicism

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In this case, the importance of presence of gonadal mosaic in families with a history of children and the prenatal diagnosis is recommended in later pregnancies, even if there is no mutation in the family.
Alagille syndrome (ALGS) is an autosomal dominant multisystemic disease with a frequency of 1/30000. ALGS is caused by mutations in the JAG1 and NOTCH2 genes. The main findings of the syndrome are cholestasis, cardiac disease, skeletal anomalies, school anomalies and characteristic facial appearance. In the JAG1 gene analysis performed in the girl with butterfly vertebral and cholestasis findings, c.3164-3167delTAAG heterozygote mutation was detected. Prenatal diagnosis was made for the next pregnancy of the family and the same mutation was determined. No mutation was detected in the JAG1 gene in the mother and father. The results of the analysis suggest that gonadal mozaisim in the family.
In the JAG1 gene analysis, c.3164-3167delTAAG heterozygote mutation was detected in the first child of the family. Prenatal diagnosis was made for the next pregnancy of the family and the same mutation was determined. No mutation was detected in the JAG1 gene in the mother and father.
The results of the analysis suggest that gonadal mozaisim in the family. In ALG syndrome, approximately 30-50% of individuals have an inherited pathogen variant and about 50-70% of them have de novo pathogenic variants. For the parents of a child with de novo pathogenic variant, the risk of child recurrence with Alagille syndrome is higher than the general population due to the possibility of germline mosaicism. If a pathogenic variant of an affected family member is known, a prenatal test is recommended due to an increased risk of pregnancy.

Key Words: Prenatal Diagnosıs, Alagille Syndrome, JAG1

S-008 - Management of 2 Cases with Microdeletion and Microduplication Detected By Non-Invasıve Prenatal Test (NIPT)

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Noninvasive prenatal testing (NIPT) is started to be used widely as a strong screening tool to detect common aneuploidies. However, its application for detection of rare chromosomal abnormalities and copy numder variations remains controversial. Here, we will discuss the availability of NIPT for copy number changes with two cases presenting to our clinic.
Case1: A 17-week pregnant woman admitted to our clinic with the NIPT risk for dup(16p13.11-p12.3,4.04M) –M at the external center. It was evaluated with detailed obsteric USG. Amniocentesis was performed for invasive prenatal diagnosis after genetic counseling. Case 2: A 19 week pregnant woman admitted to our clinic with the high NIPT risk for del (10q25.2-q26.3, 22.30). It was evaluated with detailed obsteric USG. Amniocentesis was performed for invasive prenatal diagnosis after genetic counseling.
Case 1: Fetal microarray analysis was normal. In the microarray analysis of maternal peripheral blood, arr [hg19] 16p13.11p12.3 (15,450,289-18,770,811) x3 was detected. Case2: Fetal microarray analysis was normal. Maternal microarray analysis revealed arr [hg19] 3q26.1 (162,521,296-162,831,325) x1 arr [hg19] 8q24.23 (137,677,895-137,849,821) x0 and was evaluated as normal.
It is likely that NIPT will be effective in the use of copy number changes in screening testing, as in common aneuploidies. However, the use of NIPT for chromosomal copy number changes seems to continue to be discussed for a while. In conclusion to determine the results cohort studies are needed.

Key Words: Non-Invasive Prenatal Test, Mıcrodeletion, Microduplication, Microarray

S-009 - The Results of NIPT in Pregnancıes

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In recent years, extracellular free fetal DNA has been shown in the mother's blood. The extracellular free fetal DNA is outside the cell in the form of small particles and circulates freely in the mother's blood. The rate of extracellular free fetal DNA in maternal blood increases with gestational week and generally varies between 13-20% after 10th week.This fetal genetic material originates from the shredded placental cells and is continuously released into the mother's blood. This method is considered to be a screening test and is commonly referred to as atal Non-Interventional Prenatal Diagnostic Test or Non-invasive Prenatal Test ve (NIPT). The aim of this study is to present the results of NIPT screening test for pregnant women who underwent a double, triple or quad biochemical screening test.

Key Words: Pregnancy, NIPT

S-010 - Possible Reflection of the Parental Karyotype Abnormality To Fetus

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Chromosomal abnormalities found in the fetuses are generally comparable with parental karyotype alternatively they can also arise de-novo. With this case, we aimed to discuss the different reflection of parental karyotype abnormality to a fetus in light of our classical cytogenetic information.
Twenty nine year old mother with prior primary infertility diagnosis was followed with 16 week, G1P0A0, in vitro fertilization (IVF) assisted pregnancy. In one of the twins nuchal translucency was found as 3.7 millimeters. The amniocentesis samples were taken for diagnosis and analyzed with quantitative fluorescence PCR (QF-PCR) and cytogenetic analysis. Chimerism analysis was done to confirm paternity because assisted reproductive techniques had been used. Parental karyotype analysis is also performed to future explain the abnormal karyotype found in fetus.
In both twins according to QF-PCR no abnormal findings were observed in the markers (belonging to 13,18,21, X and Y chromosomes) of the five different chromosomes. In the karyotype analysis performed on the twin with increased NT thickness, 46,XX,t(7;14)(q11.2;q11.2) was found. The cytogenetic analysis of the other twin was normal. In the parental karyotype analysis, paternal karyotype was 46,XY,t(14;21)(q11.2;q11.2), maternal karyotype was normal. Postnatally physical examination revealed no major clinical findings in neither of the twins.
It has been shown that cytogenetic anomalies may have alternative inheritances. The case may result form a chance of probability alone. But it is also possible that the chromosomes may be prone to fracture from specific regions and once fractured; same region may also had a vulnerability for further breakage.

Key Words: Chromosomal Abnormality, Amniosynthesis, Alternative Heritability, Translocation, Prenatal Diagnosis

S-011 - On the Contribution of Computational Biology to the Functional Exploration of Missense Mutants: A Case-Based Overview

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Non-synonymous single nucleotide polymorphisms in human genes can result in phenotypes where the pathobiologic basis may not be clear due to the lack of mutant protein structures. One of the unifying themes in protein science is that function correlates more highly with structure than with sequence. Protein structures can therefore be considered as “molecular phenotypes” potentially linking genetic variation to human disease. Experimental investigation of the structure and function of missense mutants is a time-consuming and cost-intensive task. Such an investigation may well be facilitated by the employment of a diverse array of in silico tools which allow for the modeling of amino acid substitutions in wild-type proteins, and also help analyze the interactions of the mutant proteins with their binding partners including metal ions, small-molecule ligands, and other proteins.
We present here, from our own experience, three clinical cases with autosomal-dominant disorders, namely achondroplasia, Marfan syndrome, and Treacher–Collins syndrome. The single genetic alteration in each case is a non-synonymous single nucleotide polymorphism in the gene responsible for the disease phenotype (c.1138G>A [p.G380R] in FGFR3 for achondroplasia; c.7828G>C [p.E2610Q] in FBN1 for Marfan syndrome; and c.299T>C [p.L100P] in POLR1D for Treacher–Collins syndrome).
First, the previously established roles of the wild-type proteins of interest in human health are briefly introduced. Next, the steps, tools, and techniques required to build three-dimensional models corresponding to their mutant counterparts (whole proteins or domains thereof) are described. Last, the use of the predicted models to better understand the molecular mechanisms underlying the above connective tissue diseases are discussed.
Our studies provide new insights into the structural consequences of pathogenic missense mutations and allow for the rational design of further research of in vitro and/or in vivo kind.

Key Words: Computational Biology, Missense Mutation, Achondroplasia, Marfan Syndrome, Treacher–Collins Syndrome

S-012 - Using Machine Learning Techniques for Clinical Interpretation Of Copy Number Variations; Proof Of Concept

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Copy number variations (CNV) are one of the most common forms of genomic structural variations. CNVs are more commonly determined by use of new techniques . CNVs are associated with many clinical manifestations, especially growth retardation but also it is common in healthy individuals. In addition, the clinical interpretation of the variations found in the individual contains difficulties. It is important that the CNV is inherited or de-novo in the evaluation of the changes that are not found in the databases. However, an important CNV group is defined as variant of unknown significance. Although machine learning or artificial intelligence theories have become old, it has gained importance in the last years with the increase of data processing feasibilities. In this study, it is aimed to show the clinical interpretation of CNVs by using machine learning methods.
In this study, we have used ISCA (International Standards for Cytogenomic Arrays consortium) data set in the dbVar database. In this data set, labeled 11989 variant information data was used. Data were analyzed using cloud computing technology with Microsoft Azure Machine Learning Studio. Seventy percent of the data set was used as a training set, and thirty percent was used as test data. Different algorithms have been tried as the training model and the multi-class decision forest has reached the highest data accuracy.
As a result of machine learning analysis, it has been reached 89.241% overall and 96.4137% in average accuracy. The pathologically described samples were marked as 93.2% pathological 5.6% variant of unknown significance, 1.2% benign, while the benign samples were marked as 90.3% benign, 5.3% pathogenic and 4.4 variant of unknown significance.
This study is the first step of the study on the analysis and clinical interpretation of copy number variations which planned to be made on a larger scale by using machine learning methods. Basically, this study is aimed to evaluate the success of the analysis in a well-organized and curated data group. The current data group is not adequate for clinical use and analysis for the entire genome. It is planned to increase data sharpness by adding larger healthy population data.

Key Words: Copy Number Variatıons, Machine Learning, Data Mining

S-013 - Gaps of the Whole Exome Sequencing

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Whole exome sequencing (WES) has been increasingly applied to discover the disease causing genes and variants in Human Genetics laboratories. Mutation detection rate is varying from 10% to 60% by WES, depending on sample selection criteria. In cases where no mutation was detected, could be explained by biological (tissue specific somatic mutations), technical limitations (deep intronic, regulatory or intergenic mutations, large translocations, deletions, duplications, UPD etc.) and methodological reasons.In this study, we evaluated technical and methodological weak points of WES from library preparation to the conclusion section in order to find out the favourable algorithm in cases with no identified mutations.
Most important problems are uncovered exonic regions, insufficient repeats, failure to meet variant calling parameters by filtering.
It is particularly important to re-evaluate the test data from this angle.

Key Words: Whole Exome Sequencing, Next Generation Sequencing, Bioinformatic Analysis

S-014 - In Silico Analysis of 5'UTR Variants Creating uORF and Their Possible Pathogenicity-Related Features

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Five-prime untranslated region (5'UTR) defines the upstream region of the translation initiation codon in an mRNA. It is known that 5’UTRs can code separate small peptids through upstream open reading frame (uORF). Because the translation of uORFs reduces translation rates of main protein coding sequences, 5’UTR located variants migth become pathogenic if they cause the formation of a novel uORF, or the loss of preexisting uORF. In this study, we aimed to identify the uORFs formed through known and hypothetical 5’UTR variants, and to assess their features in term of pathogenicity. For this purpose, we evaluated certain features like minör allele frequency (MAF) of known variants and length, initiation codon position and stop codon position of the resultant uORFs.
5’UTR sequences of known transcripts and known 5’UTR variants were extracted through Biomart. With Python 3.2, hypothetical variants were created through replacement of each base at each position with other three bases, and consequently the potential uORFs were identified. All 5’UTR variants creating potential uORF were joined with known variants in Galaxy platform. Statistical analyses were performed with RStudio.
The base replacement gave 840.318 hypothetical variants in 14.979 genes that create a new uORF. Of these, 41.639 hypothetical variants (approximately 5%) in 3.610 genes were found in SNP database as known variant. Considering the disease-related genes, we found that 800 of 3.610 genes (approximately 22%) were included in MIM genes. Statistical analyses performed in whole data has shown that the distance between stop codon position of uORF and the initiation codon of main ORF has wider range for variants with <0,01 than that with >0,01 MAF value (p=0,0001).
Preliminay results of our ongoing study suggest that rather than the position of the uORF-causing variant and the length of resultant uORF, the distance between stop codon of the uORF and initiation codon of main ORF may have importance in its pathogenicity. Together with the results of similar studies, final results of our study are expected to contribute to more accurate prediction of the pathogenicity of the novel variants which are frequently identified in 5'UTRs during next generation sequencing, but not easily interpreted.

Key Words: Non-Coding Varıants, UTR, Translation

S-015 - Whole Exome Sequencing Applications in Cases of Microcephaly with Imental Learning Disability

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Intellectual learning disability is the situation begins up to the age of 18 and cognitive, social and practical adaptation skills significantly limited. Microcephaly is a significantly lower head circumference measurement calculated by age and gender scale. Microcephaly can isolated, but also observed with mental learning disability, developmental retardation, vision, hearing and movement disorders, and epilepsy. In this project, we investigated gene variants in the patient individuals, whose parents were relative, diagnosed with microcephaly and mental learning disability using whole exome sequencing (WES) method.
The raw genome data were obtained using WES applied only in the patients. In our laboratory, data analysis was performed with developed bioinformatics analysis processes. The exom data that we provided annotation were analyzed for the detection of rare disease variants in five steps using allele frequency filters with appropriate inheritance model. Firstly, known autosomal recessive primary microcephaly genes, which are thought to be compatible with the genotype of patients, was investigated in the data. Then, homozygous and / or compound heterozygous variants based on recessive inheritance pattern, recessive hemizygous variants especially in male cases based on X-chromosome dependent inheritance pattern, heterozygous variants based on dominant inheritance pattern were investigated. In heterozygous variant analysis, especially the variant is de novo or a parent being mosaic for this variant is firstly examined.
Homozygous nonsense variation was found in AP4M1 gene in a 2.5 years old female patient, heterozygous missense variation was detected in TRIO gene in an 11 year old female patient. Heterozygous missense variation was detected in the SOX11 gene in a male patient with typical dysmorphic findings, while a 10-year-old female patient had a WDR62 gene homozygous nonsense variation. Confirmation of possible variants associated of the disease obtained from WES and familial segregation were performed by Sanger sequencing.
The effectiveness of WES method has increased based on the presence of patients correctly associated with disease phenotype, knowledge of disease inheritance model, severity of the disease and frequency of the variant in population. Detection of possible pathogenic variants with multidimensional analyses by considering these components can be achieved to a great extent.

Key Words: WES, Microcephaly, mental learning disability

S-016 - A Meta-Analysis Approach to miRNA Expression Profiling Studies

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Meta-analysis; helps to combine qualitative and quantitative research results made in different places, time and centers about the same subject. It makes possible to determine the biomarkers that predict the diagnosis and prognosis of diseases and also may contribute to their treatment. The number of meta-analysis on miRNAs have increased recently. Our aim is to present some programs that will save time to researchers working on this subject.
Pre-filtering is mostly time consuming part of the meta-analysis that many studies can be obtained, so researchers use various electronic and manual methods. Rayyan is a free, easy-to-use program designed to expedite the initial scan of summaries and headings. Research type, language and duplications can easily be determined by using this program. With the machine learning function, program make suggestions for labels based on user's selection pattern, learn inclusion/exclusion criteria and provide an evaluation of articles that it thinks user should include. There are inconsistencies in miRNA profiling studies due to technological differences, small sample size, discovery of new miRNAs, and use of different methods for data analysis. The preferred method for gene expression meta-analysis is the aggregation of raw data, but it can't be performed as this data is not often available in resources. Therefore, the primary approach is to collect lists of differential expressed miRNAs from studies. Robust Rank Aggregation (RRA) method found in free R Studio program which uses probabilistic model via given p values to aggregate ranked gene lists and facilitates the calculation of significance probabilities for all the elements. In databases miRNAs can be added, deleted or renamed; therefore there may be inconsistencies in miRNA names found in different MiRBase versions that leads to overlaps in studies. In meta-analysis the miRNA names should be updated. miRNAmeConverter found in Bioconductor package in R Studio is the only free, publicly available tool that can translate large sets of miRNA names into the current versions.
In miRNA meta-analysis studies, Rayyan, RRA, miRNAmeConverter are the applications that may be used in filtering, analyzing and name updating respectively.
As these applications are time-saving and easy-to-use, they are recommended to researchers to facilitate their studies.

Key Words: miRNA, Meta-Analysis, R Studio

S-017 - Investigating The Molecular Basis Of Glioblastoma Using Transcriptome And Pathway Analysis

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Glioblastoma (GBM) is the most common and aggressive primary central nervous system malignancy, with an average survival of approximately 12 months. Although the etiology of GBM has not been fully elucidated, viruses, ionizing radiation, occupational exposure to rubber and petrochemical materials are associated with increased risk. To gain deeper insights into the molecular processes involved we studied transcriptome-wide expression profiles of normal/tumor tissue pairs from GBM patients using RNAseq and analyzed the differentially expressed genes (DEGs).
Fresh paired normal and tumor tissue samples were obtained from patients with GBM undergoing surgery in the Neurosurgery Department at Istanbul University Medical Faculty. Immunostaining was performed by pathologists to validate the nature of both tissue groups. After RNA extraction and reverse transcription, we prepared libraries for 12 pairs of tumors with the Ion Ampliseq Transcriptome Human Gene Expression Kit. Templated spheres were achieved by emulsion PCR using Ion One Touch system and were sequenced with an Ion S5 system. Subsequently we performed an extensive pathway analysis using Ingenuity Pathway Analysis. qRT-PCR was performed in 26 tissue pairs with QuantStudio Open-ArraySystem for verification and replication.
Three of 12 pairs were excluded as a result of the principal component analysis (PCA), as normal tissue from these patients showed tumor-like characteristics. Detection of the most significant pathways, upstream regulators and target genes in glioblastoma was done by IPA with 3,062 DEGs($p<0.001$). A total 54genes were selected as candidates for their possible role in tumor development or technical validation and analyzed in 26 pairs. The results of RT-PCR were in agreement with NGS when analyzed by Pearson Correlation(Pearson Correlation=0,88).
The pathways displaying most frequent changes were the Axonal Guidance Signaling, GABA and Glutamat receptor signaling pathways. Expression of well-known factors involved in glioblastoma formation, such as ERBB2 and TGFB1 were also different in the tumors. In addition to these, we found new regulators like MED1 and ACER3 previously not shown in GBM. Besides these candidates, DMBX1 and FAM180A were overexpressed and KCNV1 was downexpressed target genes in GBM. We suggest that the genes detected in this study may provide candidate biomarkers in glioblastoma which warrants further investigation by functional tests.

Key Words: Glioblastoma, RNAseq, Upstream Regulators

S-018 - Genetic Mapping of Candidate Gene Locus by SNP Microarray Method and Identification of C19ORF70 Gene Mutatıon in a Family with Inherited Metabolic Disease

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In this study, we aimed to localize the gene locus responsible for the disease by genome-wide genotyping and homozygosity mapping in a family with metabolic disease and to identify the disease causing mutation among candidate genes. Detailed clinical and laboratory evaluations were performed for all patients. The prominent clinical findings of the patients are microcephaly, pontocerebellar hypoplasia, hepatopathy, 3-methyl glutaronic aciduria, lactic acidosis and dysmorphic findings.
In this study, genome-wide genotyping were performed by Affymetrix 250K SNP array technology in a consanguineous Turkish family having two affected children. Genotype files were generated in Affymetrix GTYPE software and transferred to VIGENOS Program. This software was used to analyse the genotypes and identify homozygous regions. Automatic DNA sequencing was performed for mutation screening.
Haplotypes were constructed based on autosomal recessive mode of inheritance , as a result 4 different homozygous chromosomal regions larger than 5Mb were detected in the affected children. When the candidate genes in these homozygous chromosomal regions were evaluated together with the clinical findings of the patients, C19orf70 gene located on chromosome 19 was selected as a first candidate gene related with the disease in the patients. C19orf70 gene were examined by DNA sequence analysis for all family members and it revealed a homozygous IVS3-2A> G splicing mutation in the patients The parents were heterozygous carriers of the mutation with full segregation in the family.
Recent studies have reported that IVS3-2A>G mutation in the C19orf70 gene encoding QIL1 cause severe mitochondrial encephalopathy consistent with psychomotor retardation, hepatopathy lactic acidosis, 3-methylglutaconic aciduria and muscle weakness. One of the complex proteins of MICOS (Mitochondrial Contact Site and Cristae Organizing System), QIL1 protein is very important for MICOS complex stability. In regard to difficulties for diagnosis, follow-up, treatment and pathogenesis, mitochondrial diseases are considered one of the most unrecognized rare diseases. In this study, the gene locus responsible for the disease was determined by homozygosity mapping using SNP arrays and the disease causing pathogenic mutation responsible for the disease in the C19orf70 gene which is members of MICOS complex was identified successfully.

Key Words: Inherited Metabolic Disease, SNP Microarray, Genetic Mapping, C19ORF70, MICOS

S-019 - Usage Of DTP-PCR as an Easy and Effective Method in the Dıagnosis of Myotonıc Dystrophy Type 1

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Myotonic Dystrophy Type I (DM1) is a trilucleotide repeat disease resulting from mutations in the dystrophia myotonica-protein kinase (DMPK) gene. The expansion of CTG nucleotides in the 3' UTR region of the exon 15 of the gene, causes changes in the mRNA level in the DMPK gene, resulting in abnormal splicing. Abnormal splicing causes myotonia and endocrine problems, which are the main findings in DM1 patients. Expansion of CTG triple nucleotides have also been shown to cause epigenetic changes in the chromatin structure and in adjacent genes. Since the disease is clinically similar to other neuromuscular diseases and detection of premutation carriers is important for genetic counseling, the molecular genetic diagnosis of the disease is important. Since the GC-rich DNA regions are refractory to amplification in PCR, the diagnosis of DM1 is traditionally made by Southern blot analysis. Southern blot analysis is a method that requires a high level of work and a large amount of DNA, thus it is not suitable for routine analysis and screening approaches. In this study, the results of the analysis of "Direct Triplet-Primed PCR" (dTP-PCR) method of 94 patients referred to our department with the diagnosis of Myotonic Dystrophy Type I are presented.
In our department, dTP-PCR analysis is routinely performed in patients with DM1 clinical diagnosis. dTP-PCR is an simple and effective method that bases on the fragment analysis technique and requires mainly a capillary electrophoresis system.
Of the 94 patients routinely analyzed, 50 (53%) had a CTG expansion of more than 180 repeats on one of the two alleles in the DMPK gene.
Molecular genetic diagnosis of DM1 disease is important both for the determination of the etiology of neuromuscular disease and for the identification of premutation carriers who has the risk of transmiting larger repeats to future generations. For diagnostic and screening purposes, we recommend to use a simple, low cost dTP-PCR method, instead of Souther Blot analysis.

Key Words: Myotonic Dystrophy, dTP-PCR

S-020 - Investigation of Mental Retardation and/or Multiple Congenital Anomaly Cases with Next Generation Sequencing Technique

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Mental retardation (MR) is defined that significantly lower average general intellectual function caused by the loss of all ability to affect intelligence and progress. Currently, the term "intellectual disability (ID)" is being used instead of MR. Approximately 1-3 percent of the global population has an intellectual disability.
In this study, eight of undiagnosed ID and/or MCA cases supposed to depend on genetic factors were investigated by a new generation sequencing technique.
The results revealed that three of four cases had the X-linked inheritance pattern and one of them showed the autosomal recessive pattern of inheritance. The diagnosis was established for these four cases (50 percent diagnosis). The mutations found in cases placed on IQSEC2 (p.Val900Ile), PLAG2G6 (p.Leu542Phe), AGTR2 (p.Tyr189X), FRMPD4 (p.Asp1033Asn) genes. All of the mutations identified in our patients had diagnosed the first time. Furthermore, PMS2 and MSH2 mutations were coincidentally identified in two patients and their parents, and these genes are proposed to be reported by American College of Medical Genetics.
This study purpose to figure out the etiology of undiagnosed ID and/or MCA cases via new generation sequencing. The identification of genetic etiology for these kind of cases will contribute to prevent complications and growing of a healthy generations.

Key Words: Next-Generation Sequencing, Multiple Congenital Anomaly, Mental Retardation, Mutation

S-021 - The Importance of Next Generation Sequencing for Clinical Diagnosis

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Next generation sequencing systems have become a major method of diagnosing complex genetic diseases by analyzing many genes simultaneously. Also it is a cheap, fast and reliable method.
Here we have A 17-year-old male with multiple anomalies was referred to our polyclinic for genetic evaluation and clarification of the diagnosis. There were chronic cough, torticollis, short stature, glaucoma and microphthalmia on the anamnesis and physical examination. Computerized spiral tomography of chest and magnetic resonance imaging of brain performed respectively, there were widespread bronchiectasis, multiple arachnoid cysts, ventriculomegaly and microphthalmia. 6 cousins and 2 siblings of the patient died due to similar findings.
PRESS56(c.571G>T)(p.D191Y), MCIDAS(c.904C>T)(p.R302W) and CD40(c.779C>T)(p.P260L) were both detected homozygous. Mother and father were found to be carriers in terms of these mutations.
Next Generation Sequencing systems show a significant affect at the diagnosis of complex genetic disorders in terms of time and cost.

Key Words: Clınıcal Dıagnosıs, NGS

S-022 - OCLN Gene Variants Identified by Exome Sequencing Among Cases with Neurodevelopmental Disorders

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Whole exome sequencing (WES) is powerful method to identify genetic causes of neurodevelopmental disorders (NDD). OCLN gene which is located on the long arm of chromosome 5,contains 9 exons plus an alternative first exon. OCLN encodes an integral membrane protein named occludin, that is required for cytokine-induced regulation of the tight junction paracellular permeability barrier.There is evidence that the occludin plays a role in the pathogenesis of malformations of cortical development.It was reported that homozygous mutations in OCLN cause syndromes resembling congenital infection, and therefore is named pseudo-TORCH syndromes.This syndrome is also called BCL-PMG (band-like calcification with simplified gyration and polymicrogyria) which is an autosomal recessive neurological disorder.
We performed WES in 25 unrelated families with NDD and identified homozygous recessive variants in OCLN gene in two unrelated patients. Both patients had severe mental retardation, microcephaly, epilepsy, hypotonia. Additionally,thin corpus callosum, cerebral and cerebellar atrophy, diabetes insipitus, bilateral optic atrophy were observed in first patient. Also nonketotic hyperglycinemia, agenesia of corpus callosum and dilatation of lateral ventricles were observed in second patient.The validation of the detected mutations was carried out using Sanger sequencing.
We identified two different recessive variants in OCLN gene in two probands.The proband in family 1 has a rare homozygous frameshift deletion variant (c.173_194del22; p.Trp58Phefs)(maxAAF: 0.0019; no CADD score). The proband in family 2 has a homozygous rare missense mutation (c.199A>T; p.Ile67Phe)(maxAAF:0.0005; CADD score:27.2), which is defined as rs766112658. Both of variations are located in the third exon. rs766112658 was observed in 3 alleles in European population (non-Finnish) among the available data of 121412 alleles in ExAC.The in silico prediction of the rs766112658 is harmful. [
Both variants we identified in two families are rare and predicted to be pathogenic.The rare missense variant was observed homozygote in one case in gnomAD. Overlaping phenoype in two patients could be related to OCLN gene. Different phenoypes in two patients could be related to pathogenic or likely pathogenic variants in other genes.The identification of the genetic basis of NDD could be allow suptyping, accurate diagnosis and genetic counseling and facilitates primary preventive measures.

Key Words: Whole Exome Sequencing, OCLN Gene, Neurodevelopmental Disease

S-023 - The Usage of Whole Exome Sequencing for the Diagnosis of Autosomal Recessive Diseases Among Families without Consanguinity

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Whole exome sequencing(WES) is an increasingly common method for the identification of the diseases that have phenotypic/genotypic heterogeneity. The crucial points of analysing WES data are having the knowledge of the clinical/laboratory/ radiologic findings of the undiagnosed patient. Family history such as consanguinity of parents or knowledge of an extra affected patient in the family could be an important clue for determining the inheritance mode of the searched disease. However, after investigating causative genes for autosomal dominant or X-linked inherited diseases in families without consanguinity; compound heterozygosity should be investigated for autosomal recessive diseases even if there is only one affected patient in the family. Here we present three nonconsanguinous families that were diagnosed for recessively inherited disorder with WES, in order to emphasize that any possibility should be kept in mind during analyses.
7.5-year-old male patient with congenital myopathy, mild learning disability and hypotonia; 22-year-old male patient with pre-diagnosis of ichthyosis and 4-year-old female patient with neuromotor developmental delay, hypotonia, microcephaly and corpus callosum hypoplasia were evaluated. All of the three families were nonconsanguineous. After performing WES to the patients,variants were filtered against public databases to retain variants that were found at an allele frequency of less than 5%. Data interpretation rules are set according to the American College of Medical Genetics and Genomics recommendations and guidelines.
In the first family, a compound heterozygous mutation was detected in PYROXD1 gene that leads to “Myopathy8” in the affected patient; in the second family the diagnosis was “Ichthyosis2” with two mutations in different alleles of the causative gene ALOX12B and in the third family there were also compound heterozygous mutations in RARS2 gene that causes “Pontocerebellar hypoplasia6” respectively. All of the identified mutations were confirmed by Sanger sequencing and allele distributions were determined with family studies.
During WES analysis; clinical and laboratory findings and family history of the patients are very important. After interpretation of variants for inheritance type that was directed by family history or pedigree, the analyzes should be deepened according to other possible inheritance patterns. Allele distributions of variants should be determined with family study before reporting.

Key Words: Bioinformatic Analyses, WES, Compound Heterogeneous, Autosomal Recessive Inheritence

S-024 - PCR Free Mutation Detection By Polythiophen (Pt): Initial Results

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In contrast to other laboratory methods, these techniques are relatively expensive and need more hands on time. We aim the development of fast and sensitive "Color Change Dependent DNA Analysis Based Microfluidic Screening Platform" which is easy to use in basic genetic laboratories. By this report, the initial results of “probe free, DNA analysis method by implementation of conjugated copolymers on microfluidic platforms” are planned to be shared.
To achieve fast and accurate medical therapy, there is need for easily accessible, cheap, highly sensitive, new approaches. Commonly used molecular genetic techniques include RT-PCR (Quantitative Real Time- Polymerase Chain Reaction) and Next Generation Sequencing and they have about 1% sensitivity. Application of newly synthesized “poly(3-alchoxy-4-methylthiophen)” to single strand (ssDNA) and double strand (dsDNA) DNA molecules reveals colorimetric changes which may be seen by naked eyes and the method used in presented study.
Alterations in absorbance values by spectrophotometry are observed in 7 distinct samples with gradient ssDNA concentrations. Five samples without prototype MEFV M694V mutation are studied by new method and the results are concordant with gold standard diagnostic tests.
The presented method may distinguish ssDNA and dsDNA, after a successful validation by real patient samples; we hope to have a new tool for medical genetic studies.

Key Words: Polythiophen, SsDNA, dsDNA

S-025 - The Results of Whole Exome Sequencing and Mitochondrial Genom Analysis in Our Center

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The human genome contains approximately 180,000 exons. All exons are close to only 2% of the genome. However, about 85% of the changes that are known to be related to the disease take place in these regions. With all Exon Sequencing (WES) testing, exsomination can be studied effectively using advanced sequencing techniques. The coding regions of thousands of genes can be tested at the same time without having to select a particular gene or gene group to study the WES. Nowadays, this method can be used in the investigation of genetic variants of both common and rare diseases, in the identification of single nucleotide polymorphisms (SNP) related conditions and in pharmacogenetics.Mitochondrial disorders are a common cause of hereditary metabolic diseases and may be due to mutations affecting mitochondrial DNA or nuclear DNA. The current diagnostic approach involves targeted resizing of mitochondrial DNA and candidate nuclear genes, usually progressing step by step and is time-consuming and costly. Recently, it has been shown that the variations in the mitochondrial DNA sequence can be obtained from all exom sequence data, and the possibility of a comprehensive single diagnostic test to detect pathogenic point mutations.In this study, our aim is to present the results of Whole Extraction Analysis (WES) and / or Mitochondrial Genome Analysis (MITO) in patients who were not diagnosed at our center.

Key Words: Whole Exome Sequencing, Mitochondrial Genome

S-026 - Liquid and Volatile Biopsies in Personalized Molecular Diagnosıs and Biomonitoring of Lung Cancer

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In order to determine the most appropriate option in lung cancer treatment, real-time molecular structure of the disease must be revealed and relative changes should be noted. The analyses performed during the diagnosis are mostly not repeatable since they require invasive tumor biopsies. Therefore, novel and repeatable non-invasive analysis methods should be necessary for the molecular diagnosis in follow-up of the patients. In this ongoing project, determination of driver mutations are under investigation not only by routine bronchoscopic tissue samples, but also from blood as “Liquid Biopsy“ and from Exhaled Breath Condensate (EBC) as “Volatile Biopsy“ specimens by next generation sequencing (NGS) in the diagnosis and follow-up for lung cancer patients.
Genomic DNA was extracted from the EBC (4 case), plasma (8 case) and FFPE tissue (3 case) specimens of patients (8 case) with lung cancer by using Invitrogen PureLink™ Genomic DNA Kit (Thermo Fisher). For amplifying DNA targets (KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2), Ion Ampliseq Colon and Lung Cancer panel v2 (Thermo Fisher Scientific) was used. One thousand eight hundred and forty-one cosmic mutations in 22 gene are sequenced on the Ion Torrent PGM instrument using the Ion PGM™ Hi Q™ Sequencing Kit and 318™ Chip according to the NGS protocol.
According to sequence analysis results; 3 patients (C001, C008, C010) had a PIK3CA mutation (c.3141T>A) and 1 patient (C002) had a EGFR mutation (c.2361G>A) in their plasma specimens. For Patient C001, PIK3CA mutation (c.3141T>A) and for Patient C007, a novel mutation in FGFR2 and another mutation in TP53 (c.729C>A) were detected in their EBC specimens. In the tumour DNA of Patient C003, a mutation in PIK3CA (c.3141T>A) was determined.
In this study, hotspot mutations were able to be determined in EBC samples and plasma from patients with lung cancer. These non-invasive methods could provide promising detection of hotspot mutations in lung cancer.

Key Words: Lung Cancer, Next Generatıon Sequencing, Volatile Biopsy, Liquid Biopsy,Hotspot Mutation

S-027 - The Importance of Blood miRNAs and Exhaled Volatile Organic Compounds as Biomarkers in the Asthma

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Asthma is a chronic inflammatory disease of airways which shows heterogeneity in terms of clinical phenotypes and underlying mechanisms and contributes with environmental exposures and genetic factors. Asthma can be divided into many subgroups but cellular and molecular approaches are the most used ones in forming subgroups. The aim of this study is defining molecular asthma endotypes in different clinical asthma phenotypes via novel biomonitoring approaches Volatil Organic Compounds (VOCs) in exhaled breath and peripheral blood microRNAs (miRNAs).
In the study, the VOC analyses of 31 asthma patients and 22 healthy controls were realized using needle trap system. Principal Component Analysis and Hierarchical Cluster Analysis were used for chemometric evaluation of the results. Total RNAs of 21 asthma patients and 24 healthy controls were isolated from blood samples and cDNA synthesis were performed. The expression level changes of asthma-related miRNAs (Let-7e, miR106a, miR10a, miR126, miR133a, miR145a, miR155, miR17, miR19a, miR21, miR221, miR708) were determined using qRT-PCR instrument by normalising housekeeping miRNAs(SNORD61, and RNU6-6p). Fold changes of miRNAs were calculated using 2-ΔΔCT method.
n-pentane, 2-methylpentane, 2-methylhexane and terpinolene were below LOD value in all samples. Isopropanol, 2,4-dimethylheptane and 4-methyl2-pentanal compounds were detected in only healthy individuals; 2,6,10-trimethyldodecane, 2-undecanal, 1,7-dimeylnaphthalene were detected in only asthma groups. Since the incidence rates were very low in the cases, these compounds were excluded from the chemometric analysis. Chemometric evaluation showed that 2,3-dimethylheptane, 2-octenal, 4-methyl-2-pentenal, benzylalcohol, isopropanol and octane compounds were higher in healthy cases and aceticacid, allylmethylsulphide, ethylbenzene and tridecane compounds were higher in asthma group. It was determined that octane and aceticacid compounds were volatile biomarkers to seperate healthy and asthma cases, respectively. In asthma group the expression levels of miR106a, miR10a, miR126, miR17, miR19a, and miR221 upregulated 4.16, 2.71, 2.68, 2.26, 10.97 and 2 folds, respectively. Contrary, miR708 was downregulated 2.74 folds in asthma group.
As a result, the data showed that target miRNAs and VOCs can be used to differentiate between asthmatic and healthy subjects. With the increase in the number of data, it is predicted that a better separation success percentage will be achieved.

Key Words: Asthma, miRNA, Volatile Organic Compounds

S-029 - Screening of Mitochondrial DNA (MtDNA) Genes in Neurology, Psychiatry, Metabolism Patients Rarely Encountered, Considered To Have No Diagnosis But Mitochondrial Inheritance

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Although mitochondrial diseases are mostly caused by nDNA mutations, mtDNA can also be effective and this patients remain undiagnosed for a long time. In this study, we screened mtDNA genes using Next-Generation-Sequencing in the patients who are considered to have mitochondrial disease but remain undiagnosed from Neurology,Psychiatry and Metabolism clinics. The aim of the study was to determine the mtDNA effect in these patients and to investigate common mtDNA mutations or genes in Turkey.
DNA samples were isolated from mitochondrial diseases suspectible twenty-five cases and their family members. mtDNA was screened by Next-Generation-Sequencing(Illumina-Miseq) method and determined variants were validated both in patients and family members by Sanger Sequencing. The variants were classified according to Human-Gene-Mutation-Database and CentoGene Database. Polyphen, Varsome, Provean, MitoMAP and MitoTIP databases were also used to investigate variants for pathogenesis and phenotype/genotype correlation.
Fifteen different variants in 11 patients were identified in 25 patients examined.Fourteen of the patients were found to be normal in terms of mtDNA changes.Two of the patients were diagnosed as Leigh (Class1; mt-ATP6 m.9185 T>C p.L220P 88% homoplasmic and mt-ND5 m.13513 G>A p.D393N 34% heteroplasmic mutation). Six new (mt-TK m.8296 A>G 54% heteroplasmic pathogenic; mt-ND1 m.3316 G>A p.A4T 93% homoplasmic benign; mt-ATP6 m.8633 A>G p.Y36C 82% heteroplasmic pathogenic; mt-TV m.1646 T>C 37% heteroplasmic benign; mt-CYB m.15446 C>T p.L234F 90% homoplasmic pathogenic; mt-CO3 m.9840 T>A p.S212T 76% heteroplasmic pathogenic) variants which are thought to be associated with mitochondrial disease were first described in the literature. 2 detected variants in these 11 patients were found to be irrelevant in terms of mitochondrial disease and 2 new variants detected (mt-RNR1 m.1547 dupT %90 homoplasmic and mt-CO1 m.7440 p.S212T 90% homoplasmic benign) in the patient with MNGIE pre-diagnosis but TYMP gene mutation was negative.
In our study,we observed nine disease associated changes in mtDNA in 25 patients.The results showed that, 6 out of 7 (about 85%) patients with Leigh suspicion were detected as mtDNA causative. We think that, especially in patients with Leigh pre-diagnosis, mtDNA screening should be among the primary clinical tests and especially Complex I, IV and V genes should be taken into consideration in terms of mitochondrial diseases.

Key Words: Mitochondrial Diseases, Mitochondrial DNA(MtDNA), Heteroplasmy, Homoplasmy, Next Generation Sequencing

S-030 - A Retrospective Evaluation in Fabry Cases

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Fabry disease (FD, OMIM#301500) is a progressive, life-threatening, multisystemic, rare lysosomal storage disease that occurs by mutation in the GLA gene on the X-chromosome(Xq22.1), which encodes the α-galactosidase-A enzyme. The estimated incidence is 1:117,000 in the general-population. It's estimated the incidence is higher in high-risk populations. As a result of the enzyme defect globotriaosylceramide(GL-3) accumulates in the body, end of this accumulation the clinical manifestation occurs. Main clinical manifestations are severe pain attacks in the extremities, dark vascular skin lesions, sweating abnormalities, characteristic eye findings, abdominal pain, diarrhea, vomiting and urine protein. Heart, kidney, and brain involvement are complications that can be affected by the disease and can be life-threatening or significantly affect quality of life. in our study we aim that, evaluation of the age, gender, city, clinics, mutation, follow-up and treatment of the patients who were referred to our medical genetics clinic with an initial diagnosis of FD and the increase the awareness.
Medical documents, of the FD patients, who had presented to the department of Medical Genetics, between 21.10.2016-2018, were analyzed retrospectively
In our study,352 cases were evaluated (mean38.6y;1-76y) 147 Male(mean39.2y;1-75y)205 Female(mean38,1y;3-76y). 289 cases were evaluated in the first evaluation. We found 10 cases with mutation(3,5/100) and then we did 63 cases of family screening. Cases have been consulted in 14 different cities and 15 different clinics. A total of 42 cases had mutations. We found 4 different mutation types D170N(1),D313Y(12),P205S(11),S126G(18). 15 cases were treated, 22 cases were followed-up and 5 cases were not followed-up
FD is a metabolic disorder with a congenital X-linked that is more common than predicted. It should be noted that the degree of the effect depends on the early diagnosis and treatment of the disease. In addition, the correct diagnosis is important in the diagnosis and follow-up of risky-family-members. FH is phenotopically heterogeneous disorders and its diagnosis may take many years. FD investigation and identification is important in high-risk disease groups; renal insufficiency, left-ventricular-hypertrophy, neuropathic pain, premature cerebrovascular disease, hypohyrosis-anhydrosis, angiokeratom. Pediatrics, nephrology, cardiology, neurology, hematology, ophthalmology and other related clinics roles and awareness in this disease screening is important. Therefore, awareness about FD needs to be increased.

Key Words: Fabry Disease; Awareness

S-031 - Turkish Fabry Patients; Alpha Galactosidase Gene Mutation Profile

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Fabry disease is a pan-ethnic and progressive X-linked lysosomal storage disorder. Mutations in GLA gene cause a complete or partial deficiency of the enzyme alfa galactosidase A(α-GalA) that is a lysosomal enzyme. The diagnosis of Fabry disease can be made by the enzyme analysis in men, while the genetic diagnosis is accepted as the first step test in women who are carriers. Recently, increasing attention has been focused on assessing the association between genotype and phenotype in FD patients. In this study, our goal is to provide the mutation spectrum in patients with the molecular diagnosis of Fabry disease from one of the centers of reference in our country in terms, our department and to provide an overview of the molecular etiology of Fabry disease in Turkey by identifying the mutations.
Between December 2012 and September 2018, GLA gene sequence analysis was performed in the subjects who applied to the Department of Medical Genetics of the Department of Medicine with a preliminary diagnosis of Fabry Disease. For the evaluation of mutations, HGMD, ClinVar and ExAC databases and Alamut, MutationTaster, PolyPhen, SIFT and Varsome analysis programs were used.
The mutation analysis was performed in 453 cases from 347 families within the specified period. In this study, we analyzed 55 individuals (23 male and 32 female) susceptible for FD from 39 unrelated families. We detected 25 different mutations as 5 novel and 20 previously reported GLAmutations. These mutations included 13 missense mutation (c.167G>A, c.335G>T, c.206T>C, c.352C>T,c.427G>A, c.613C>A, c.647A>G c.680G>A, c.823C>T, c.937G>T, c.983G>T, c.989A>G, c.1010T>C), 4 nonsense mutation (c.679C>T , c.708 G>A, c.1024C>T, c.1196G>A), 1 frameshift mutation (c.844delT), 1 small deletion (c.1072_1074delGAG), 1 small deletion/insertion (c.963_964delinsCA). Additionally, 3 missense (c.512G>T, c.613C>G, c.1226C>T), 2 small insertion (c.722_723insA, c.848_849insA) mutations were described first time in the literature.
In conclusion, in our study, a 6-year GLA gene mutation spectrum of one of the important reference centers in our country was presented. The results show that repetitive mutations are absent and that mutations are mostly family-specific. In addition, 11.23% of the mutation detection rate in cases showed difficulty in compliance with the diagnostic criteria of Fabry disease.

Key Words: Turkey, Fabry, Gla, Mutation, Alfa Galactosidase A

S-032 - A Rare Missense Mutation in DMD Gene in a Turkish Family.

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Duchenne muscular dystrophy (DMD) is an X-linked recessive genetic disorder in which skeletal and cardiac muscle are dysfunctional. DMD is caused by an absence of dystrophin, an intracellular muscle protein. This absence corresponds with a genetic mutation that disrupts normal dystrophin translation. The gene for DMD is located on the Xp21 band of the X chromosome and is expressed primarily in males since this genetic defect is a recessive trait. Approximately 2/3 of the DMD are caused by deletions/duplications in DMD gene. The remaining variants are small deletions/ insertions, splice site changes and single nucleotide variants. Among these changes; pathogenic missense variants are very rare. We aimed to demonstrate the mutation patterns of the DMD gene in a Turkish family.
Genomic DNA was extracted from 8 individuals of the Turkish family with a familial history of DMD. For an obligatory carrier, after excluding gross deletion/ duplication of the DMD gene with multiplex ligation-dependent probe amplification (MLPA) method, all coding and splice site sequences of the DMD gene were analyzed with Next Generation Sequencing (NGS).
We analysed 8 individual of the family, two were patient and the others were suspected obligatory carrier. MLPA analysis of the proband didn't show any deletion/ duplication where NGS results of the family have shown that the they were carrying pathogenic c.10018 T>C (p. Cys3340Arg) mutation except older sister and grandmother. Additionally, we found 4 missense mutations except c.10018T>C(p.Cys3340Arg); including c.2645 A>G (p.Asp882Gly), c.5234G>A (p.Arg1745His), c.8810G>A (p.Arg2937Gln) and c.7096A>C (p.Lys2366Gln). These variants are predicted to be benign according to in-silico algorithms, online databases and also reported as polymorphisms in the literature.
We found a rare pathogenic missense mutation, c.10018T>C(p.Cys3340Arg) in exon 69. A cysteine 3340 substitution has been reported to be associated with DMD with mental retardation and an absence of the electroretinography b-wave. Determination of carrier status is very important in DMD for genetic counseling especially prenatal/preimplantation genetic diagnosis. We demonstrate that NGS can be used for an initial genetic diagnosis test of DMD and NGS step ahead to have the advantage of identifying mutations in MLPA- negative patients.

Key Words: DMD, NGS, MLPA

S-033 - Novel Thyroid Stimulating Hormone Receptor (Tshr) Gene Mutation in a Patient With Congenital Hypothyroidism

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Thyroid stimulating hormone receptor (TSHR) gene encodes a functional receptor that activates adenylate cyclase in response to thyroid stimulating hormone (TSH), and this receptor is the major regulator of thyroid cell metabolism. Many different clinical phenotypes can be seen in mutations of TSHR gene. Somatic activating mutations are associated with toxic thyroid nodules, while germline activating mutations are associated with non-autoimmune hyperthyroidism. Inactivating mutations of this gene have been reported in patients with hereditary TSH resistant hypothyroidism. There are also mutations identified in patients with hyperfunctioning thyroid carcinoma.
An 8-year-old girl with congenital hypothyroidism due to dyshormonogenesis was referred to us for molecular analysis to elucidate the pathogenesis of the disease. Before the treatment, TSH was 11.9 nglU/ml (0.38-5.33 TlU/ml) and fT4: 1.2 ng/dL (0.5-1.51 ng/dL). In thyroid scintigraphy, activity distribution in both thyroid lobes was homogenous and iodine involvement was slightly decreased. When the pedigree was examined, there was a history of late-onset hypothyroidism in the upper generations of both parents, and the patient's father. TSHR gene analysis was requested from the parents to investigate the parental origin of the detected mutation. The next generation sequencing analysis revealed a heterozygous, pathogenic, frameshift c.404_405delAC (T136Wfs*3) mutation in the exon 6 of the TSHR gene (ENST00000541158.2).
Novel c.404_405delAC mutation is found in the extracellular leucine rich repeats (LRRs) domain of TSHR protein as in most inactivating mutations. This mutation causes truncated protein due to stop codon. TSH binding site mutations disrupt the receptor-ligand interaction. Although inactivating TSHR mutations show autosomal recessive inheritance, compensatory hypothyroid cases with heterozygous mutation have also been reported. This mutation may elucidate molecular pathogenesis of the disease and contributes to the phenotype-genotype correlation.

Key Words: TSHR, Congenital Hypothyroidism, Truncated Protein, Inactivating Mutations

S-034 - The Evaluation of Clinical and Development Findings of DiGeorge Syndrome Cases

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Individuals with 22q11.2 deletion syndrome (22q11.2DS) have a range of findings including the following: 1)Congenital heart disease (74% of individuals), particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus) 2)Palatal abnormalities (69%), particularly velopharyngeal incompetence, submucosal cleft palate, bifid uvula, and cleft palate 3) Characteristic facial features (present in the majority of individuals of northern European heritage) 4) Learning difficulties (70%-90%) 5) An immune deficiency (regardless of the clinical presentation) (77%) The aim of this study is to investigate the clinical findings in individuals with definite Digeorge syndrome.
A total of 7 patients were included in the study. Prenatal, natal and postnatal period findings, birth weights, forms of labor, motor, language and social development were evaluated. The birth APGAR scores of the patients were determined. Patients' surgery operations, seizure stories and chronic diseases were evaluated. The pedigrees were analyzed by drawing. Dysmorphological findings, radiological and laboratory findings were determined.
One patient had oligohydramniosis in the prenatal period and one patient's mother had preeclampsia. The average birth weight of the patients is 2331 gr. SGA was detected in 3 patients. APGAR score was below 7 in 3/7 patients. Pedigree analysis revealed a 3rd degree cousin marriage among the parents of a patient. 2/7 patients found epilepsy. In addition, a total of 30 parameters were compared in OMIM's "clinical synopsis" section.
As seen in our study, among individuals who have the same deletion even phenotypic differences are possible. That's why; A detailed approach is necessary when evaluating syndromic individuals. One important consideration is the family inheritance of microdeletion syndromes. Each individual should be treated as a separate case. In addition, a multidisciplinary and holistic approach is important for diagnosis.

Key Words: DiGeorge Syndrome, 22q11,2 Deletion Syndrome, Velocardiofacial Syndrome

S-035 - Targeted Exome Sequencing Analysis: Two Novel Mutatıons In TCF12 and AXIN2 Genes Related To Non Syndromıc Cranıosynostosis

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Sutures of the skull are the junctions between cranial bones and provide not only differentiation of the bones but also interaction between them. Early closure of sutures results in craniosynostosis which occurs as syndromic or non-syndromic. Seventy-five percent of the diagnosed cases have non-syndromic craniosynostosis, and the estimated prevalence is between 0.4 - 1/1000. Non-syndromic craniosynostosis (nsCRN) is a heterogeneous disorder and has both clinically and genetically multifactorial characteristics. Although many variants/mutations were identified nearly in 60 genes, the genetic cause is still mostly unknown. In this project, we aimed to perform a comprehensive genetic screening by using targeted exome sequencing.
Unrelated 21 nsCRN cases with normal karyotype and wild-type FGFR2 exon IIIa/IIIc, have been sequenced by using Dysmorphia and Dysplasia Research Panel that included 519 genes. The results have been compared with the clinical findings and aimed to clarify the possible genotype-phenotype relationship.
After filtering the analysis, possible pathogenic variants compatible with the phenotype were detected in four of the cases (~%20). In two of the cases who had bilateral coronal synostosis, two different heterozygous pathogenic variants (p.M260fs*5 and p.P369fs*26), one of which is novel, were detected in TCF12 gene. A reported mutation (p.G299fs*9) in ERF gene was identified in a case with unilateral (right) coronal synostosis, closed fontanelles and left frontal bone dysplasia. We also identified a novel truncating p.L349fs*24 variation in AXIN2 gene of a case with sagittal synostosis. Interestingly, the effect of AXIN2 on craniosynostosis had only been shown in mouse models.
The diagnostic rate of the TCF12 and ERF genes in craniosynostosis was determined as 10% and 5%, respectively. Besides, it has been shown for the first time that AXIN2 gene may be the cause of craniosynostosis in human. In conclusion, comprehensive genetic studies are of great importance for better understanding of nsCRN. In the light of our data, we believe that choosing spesific genes that depend on the type of closed sutures will speed up the diagnosis (postnatal, prenatal), especially in the non-syndromic craniosynostosis cases. Acknowledgement: This project was supported by Akdeniz University Scientific Research Projects Council [Project # TDK-2015-933].

Key Words: Non-Syndromic Craniosynostosis, Molecular Genetics, Next Generation Sequencing, Exome Sequencing

S-036 - Investigatıon of Genetic Causes in Oculoauriculovertebral Spectrum Etiology

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Oculo-Auriculo-Vertebral Spectrum(OAVS) is a genetically and phenotypically heterogeneous disorder which occurs due to a developmental defect in the first and second pharyngeal arches. Main clinical findings consist of microtia, preauricular skin tag, hemifacial microsomia, epibulbar dermoid and vertebral anomalies. Cardiac, genitourinary anomalies and radial defects are also included in the spectrum. There is not a consensus regarding the clinical criteria for diagnosis, but generally the presence of microtia or preauricular tags with hemifacial microsomia is accepted as the minimum criteria. The etiology is heterogeneous since genetic, epigenetic and environmental factors are involved. Copy number variations (CNV) have been described as potentially pathogenic for the disorder and mutations of MYT1 have been recently identified in some patients.
Patients were screened for copy number variations using the Affymetrix CytoScan Optima array Kit and also were screened for MYT1 mutations using BigDye terminator on an ABI Prism 3500 genetic analyzer. Furthermore, two patients underwent WES analysis.
We report on 23 OAVS patients with diverse clinical and molecular findings. All patients fulfilled the minimal diagnostic criteria suggested by Tasse et al. The mean age of the patients was 7 years and 8 months and 65.2% of the study group was male (Male / Female ratio 15: 8). Middle and inner ear anomalies were also observed among patients. Developmental delay, epilepsy and behavior abnormalities were seen in some patients. Using methodical approaches, three CNVs (one deletion, two duplications) in chromosomes 8, 15, 16 and one unbalanced translocation between chromosomes X and 4 were found and were considered potentially pathogenic. No causative mutation was found in MYT1. WES analysis revealed novel heterozygous mutations in RNF213 and EFTUD2 that were previously suspected as candidate genes for OAVS in both patients.
Duplication of 16p11.3 region, aneuploidies of X chromosome and single point mutations were previously implicated in OAVS molecular etiology. This study provides further genetic heterogeneity to this disorder, confirming the importance of microarray-based studies and whole exome sequencing analysis in patients with a complex phenotypic disorder such as OAVS.

Key Words: OAVS, Microarray Analysis, 16P13.11, EFTUD2, RNF213

S-037 - Craniofrontonasal Syndrome: Two Siblings With Atrial Septal Defect As A Rare Phenotype

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Craniofrontonasal syndrome (CFNS; OMIM 304110) is a rare X-linked developmental disorder caused by mutations in the EFNB1 gene(OMIM 300035). Typical manifestations include craniofacial abnormalities, wiry-curly hair, grooved nails and skeletal defects. According to the literature, there are few cases with heart defects in CFNS. We hereby report two siblings with molecularly diagnosed CFNS and atrial septal defect (ASD) and discussed with the literature.
A 4-years-old girl was referred to our department for craniosynostosis. She had brachycephaly, hypertelorism, bifid nose, malocclusion, wiry-curly hair, narrow shoulders, pectus excavatum and umblical hernia. Craniosynostosis, ASD and mild pulmoner stenosis were confirmed by imaging. The 13-year-old second case was our proband's sister. She had brachycephaly, hypertelorism, bifid nose, malocclusion, wiry-curly hair, narrow shoulders, pectus excavatum and Sprengel deformity. When we evaluated, she was already diagnosed with ASD and mental retardation.
The cytogenetic studies revealed 46,XX karyotype in two cases. Molecular analysis disclosed a heterozygous deletion c.635_636delTG in exon 5 of EFNB1.
CFNS is a very rare genetic syndrome with an incidence varying from 1:100,000 to 1:120,000. Mutations of EFNB1 gene lead to disrupt the normal development of the frontonasal neural crest. It's one of the few X-linked conditions in which heterozygous females are more severely affected than hemizygous males. Furthermore phenotype is highly variable among individuals. When we reviewed the literature, we determinated only four cases with heart defects in CFNS. ASD, Patent ductus arteriosus (PDA) and dextrocardia are among the heart defects reported so far in CFNS. In the literature, the same mutation with our patients was detected in one patient with coronal craniosynostosis and congenital diaphragmatic hernia. There is no genotype-phenotype correlation in any of the studies. In conclusion, cardiovascular deformities should be evaluated in these cases.

Key Words: Craniofrontonasal Syndrome, Craniosynostosis, EFNB1 Gene, Atrial Septal Defect

S-038 - KAT6B Mutations in Ohdo Syndrome

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KAT6B gene mutations have been associated with Genitopatellar syndrome and Ohdo syndrome in the literature. Both syndromes are characterized by global development delay /intellectual disability, hypotonia, patellar agenesis / hypoplasia, and cryptorchidism in males. Congenital heart defects, dental anomalies, hearing loss and hypothyroidism are common in both syndromes. Especially in Ohdo syndrome, stiffness in the lower extremity joints, long thumbs and toes, mask face, blepharophimosis, ptosis, lacrimal duct abnormalities are observed. Inheritance is autosomal dominant and most cases result from de novo mutations.
Patient 1: A three-year-old female patient was evaluated for global developmental delay in our clinic. She had no speech, she did not recognize her mother. Physical examination revealed microcephaly, bilateral flexion contracture of the knees and elbows, and long thumbs. The cranial imaging of the patient revealed corpus callosum agenezis. Optic atrophy was detected in the ophthalmological examination. The patient was under L-thyroxine treatment due to congenital hypothyroidism. Echocardiography showed aortopulmonary collaterals and patent ductus arteriosus. There was no deletion or duplication in microarray analysis. Patient 2: The male patient, who was follow up due to global development delay and multiple congenital anomalies , underwent a shunt operation due to Fallot tetralogy and was operated for cleft palate. The patient had no speech or walking. The patient received special training due to intellectual disability. He also used thyroid hormone due to hypothyroidism. Other findings in our patient were narrow and upslanted palpebral fissures, ear helix anomaly, clubbing, camptodactyly, joints contracture, pes equinovarus, umbilical hernia, hypospadias, bifid scrotum and cryptorchidism.
Mutations were detected in KAT6B in both patients.
Major and minor clinical features guide planning for planning KAT6B analysis. Major features are long thumbs and toes, mask face, blepharofimosis/ptosis, lacrimal duct anomalies and patellar hypoplasia/agenesis. Minor features are congenital heart defect, dental anomalies, hearing loss, thyroid abnormalities, cleft palate, genital anomalies (cryptorchidism in males), hypotonia, global developmental delay / intellectual disability. Clinical findings in Ohdo syndrome may show variation within a wide range and this syndrome should be kept in mind in the presence of intellectual disability, dysmorphic facial features and multiple congenital anomalies.

Key Words: KAT6B, Ohdo Syndrome, Genitopatellar Syndrome

S-039 - Novel Variants Underlying the Pathogenesis of Relatively "Common" Rare Disorders in Cyprus

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Cyprus, the third largest island in the Mediterranean Sea, has been at the crossroads of multiple civilizations throughout human history. Today, the Turkish-Cypriots and the Greek-Cypriots constitute two major ethnic groups in Cyprus, along with minor groups including the Maronites, the Armenians, and the Latins. Even though Turkish-Cypriot paternal lineages have an autochthonous quality, some Y-DNA haplotypes are shared between the Turkish-Cypriots and the Greek-Cypriots, the neighboring Near-Eastern populations such as Southeastern Anatolians, Lebanese, etc. Considering the former inhabitants of this island, it should be no surprise that the genetic characteristics of the current Turkish-Cypriot population have been determined by the interactive forces of migrations, admixture, genetic drift, etc. Exploring genetic variation in a population is important, allowing researchers to trace the pattern of disease-causing DNA sequence variants in this population. It is only in the last two decades that nearly half of the genes causing 7,000 rare monogenic disorders, which are often difficult to diagnose based solely on symptoms, were identified. More than 50% of individuals with rare genetic disorders are yet to be diagnosed and treated in order to improve their life quality. Generally, suggestive clinical features can be used to distinguish one condition from another; however, in some cases these clinical features overlap with several other genetic conditions. Here, we aimed at elucidating the path from the interesting or unusual clinical phenotypes of some more common rare diseases to potentially novel gene variants.
In the present study, the most recent high-throughput genomic technologies, which involve whole-exome sequencing (WES), were employed to study the genetic etiology of such diseases. Accordingly, WES was used to sequence trios as well as larger pedigrees, and an in-house bioinformatics pipeline was used to select pathogenic variants.
As a result, we identified a number of novel population-specific gene variants, each of which causes Treacher–Collins syndrome, tricho-rhino-phalangeal syndrome type 1, Joubert syndrome, late-onset glutaric aciduria type 1, amyotrophic lateral sclerosis, etc.
This study emphasizes the importance of revealing rare-disease-causing variants in a particular population for immediate use in accurate diagnosis, for improved understanding of the underlying molecular mechanisms and for developing effective preventive medicine strategies.

Key Words: Rare Disorders, Variation, Cyprus, Treacher–Collins Syndrome, Tricho-Rhino-Phalangeal Syndrome Type 1, Joubert Syndrome, Late-Onset Glutaric Aciduria Type 1, Amyotrophic Lateral Sclerosis

S-040 - Identification of a De Novo Mutation in HBB Gene

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Beta thalassemia is a single gene disorder, characterized by decreased synthesis of beta globin chains and generally inherited autosomally recessive. Beta-globin gene (HBB) mutations on chromosome 11p15.5 causes the disease. More than 250 mutations have already been reported to be the cause beta thalassemia including approximately 40 of them in a dominant manner. Dominant mutations generally located at third exon of HBB gene. We here present a case with a de novo mutation on the second exon of HBB gene resulting in phenotypic expression in heterozygous form.
A Two-year-old female patient who had non-immune hemolytic anemia since 4 months of age was referred to our clinic for differential diagnosis of hemoglobinopathies and genetic evaluation. There was no enzyme deficiency, neither any pathological finding in the membrane defect tests. Initial testing revealed anemia with hemoglobin 8,8 g/dL, Hct: %27, MCV 90 fL, MCH: 29 pg, MCHC: 32 g/dL and reticulocyte count was %10. The peripheral blood smear showed significant anisocytosis, poikilocytosis, policromasia and %5 rate of normoblasts.
High-performance liquid chromatography (HLPC) was performed; HbF: %40 and HbA2: %0,8 were detected. There was no mutation detected on alpha thalassemia or beta thalassemia reverse hybridisation tests. The results of patient's mother were Hgb: 13,5 g/dL, MCV: 86,2 fL, RBC: 4,8x106 /µL, ferritine: 53,81 ng/ µL and HLPC results were HbA: %90,6, HbA2:%2,7, HbF:% 0.3. The results of patient's father were Hgb: 15,1 g/dL, MCV: 81,9 fL, RBC: 5,2x106 /µL and HLPC results were HbA: %88,6 HbA2: %2 HbF: % 0.2. HBB sequence analyses were performed firstly on the patient and then on her parents. On second exon of HBB gene, previously unreported de novo heterozygote c.295_300delinsTGTGACAAGCTGCAC mutation was detected. Sequence analyses of the parents were normal.
Generally biallelic mutations are detected in patients with the clinical findins of beta thalasemia and the inheritance of the mutations is from either parent. Although very rare, de novo, expressed in heterozygous form mutations resulting in thalasemia clinic might be detected. The genetic screening of hemoglobinopathies in patients with unexplained chronic non-immune hemolitic anemias may be beneficial for the correct diagnosis.

Key Words: Hemoglobinopathies,Thalassemia

S-041 –Urofacial Syndrome: Two Cases Presented with the Same Novel Mutation Defined in the LRIG2 Gene

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Urofacial syndrome (UFS) (OMIM # 615112, 236730) is an autosomal recessive inherited, prenatal or infantile characterized by urinary problems, unusual facial expressions(caused by abnormal co-contraction in the corners of the mouth and eyes) and intestinal dysfunction (constipation or encopresis). Urofacial Syndrome was considered in the prediagnosis of patients who were not consanguineous. As a result of LRIG2 gene sequence analysis, the same homozygous variant was detected in both patients (c.133C> T / L446P). This change was evaluated as likely pathogenic in the 6 different variant prioritization programs (DANN, GERP, LRT, MutationAssessor, MutationTaster and PROVEAN). As a result of clinical and molecular studies, the diagnosis of Urofacial Syndrome was confirmed. The fact that a rare disease in two different patients had the same mutation was thought to be explained by genetic shift or founder effect. Patients were presented as Urofacial Syndrome is a rare disease.

Key Words: Urofacial, LRIG2, c.133C>T, Mutation

S-042 - Detailed Ophthalmologic Examination Findings in Patients with Noonan Syndrome: Preliminary Study

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Noonan syndrome (NS) is a rare genetic disease with autosomal dominant inheritance. It is a craniofacial syndrome characterized by dysmorphic facial features, congenital heart defects and mild intellectual disability. The aim of this study was to evaluate the ophthalmologic findings in patients with Noonan syndrome.
Five patients who were considered to have NS with clinical findings and were found to have a heterozygous mutation in PTPN11 gene were included in the study. External ocular findings, eye movements and strabismus were evaluated. In addition to refraction examinations, anterior and posterior segment findings were noted using biomicroscopic examination. Anterior segment parameters were evaluated with anterior segment imaging device and retinal nerve fiber thicknesses were noted by optical coherence tomography.
Three male and two female NS patients were included in the study. The mean age was 11.8 years (10-15). All of the patients had signs of hypertelorism and ptosis which are known dysmorphic features in NS. Three patients had refractive errors and 4 had visual impairment. Corneal nerves were prominent in 3 cases, keratoconus in 2 and strabismus in 3 cases. Although 4 of the cases had increased cup / disc ratio in the optic nerve, all of them had normal eye pressure. Central corneal thickness was found to be thin in 2 cases. Retinal nerve fiber thickness was determined to be thin in 2 cases.
A detailed ophthalmologic examination of patients with NS, a relatively common craniofacial syndrome, has different features than the normal population. In this respect, further studies are needed to determine ophthalmologic findings and their effects on the cases.

Key Words: Noonan, Hypertelorism, Ptosis

S-043 - A Novel Mutation in ATP8A2 Gene with the Coexistence of SGCG Mutation

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Cerebellar ataxia, mental retardation, and dysequilibrium syndrome (CAMRQ) is a genetically heterogeneous disorder characterized by congenital cerebellar ataxia and mental retardation. It is inherited as an autosomal recessive manner. Four variants have been described. CAMRQ4 is caused by mutations which disrupt the ATP8A2 gene, which is present on chromosome 13q12. Limb-girdle muscular dystrophy is a group of disorders characterized by muscle weakness and wasting, particularly in the shoulders, hips, and limbs. Forms of limb-girdle muscular dystrophy caused by gene mutations that affect the sarcoglycan complex are called sarcoglycanopathies. Approximately 40 mutations in the SGCG gene have been identified in people with limb-girdle muscular dystrophy type 2C. In this study, we present a family with a new mutation in the ATP8A gene. The cases had carried two rare diseases simultaneously.We also aimed to share the experiences in the genetic counseling process.
The patient was referred to our clinic with MMR and hypotonia etiology and a full exom sequence was performed. WES was applied to the patient who had different genetic tests before. Blood samples were taken from the affected patient, her parents and her brother.
ATP8A2 gene, c.578C> A p.Ser193Tyr homozygote mutation and SGCG gene, c.784T> C p.Tyr262His homozygote mutation (rs776357413) were detected as a result of whole exome sequencing. The mutations were confirmed in other family members by sanger sequencing. The ATP8A2 gene, c.578C> A p.Ser193Tyr homozygote mutation has not been previously reported in the literature. However, it is thought to be responsible for the disease because it is detected in two brothers with CAMRQ4 clinic. Additionally, SGCG gene, c.784T> C p.Tyr262His homozygote mutation (rs776357413) was detected.
As in our case, the use of exom analysis in patients who cannot be diagnosed is important in terms of clarification of the clinic and giving hope to families planning pregnancy. In addition to the availability of the test, access to the family members, and the financial means of the family are important for the health of the next pregnancies and for effective genetic counseling.

Key Words: CAMRQ4, Whole Exome Sequencing, ATP8A2, SGCG

S-044 - Expanding the Mutational Spectrum of CSC-KT

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Circumferential Skin Creases-Kunze type (CSC-KT, OMIM #156610, #616734) is a rare disorder characterized with skin creases mostly of the limbs, intellectual impairment, cleft palate and dysmorphic features. The syndrome was first described by Ross in 1969, as "Michelin Tire Baby Syndrome" (MTBS). Although this syndrome is usually inherited in an autosomal dominant pattern, autosomal recessive inheritance has also been reported. CSC-KT is characterized with genetic heterogeneity, it is caused by mutations in either MAPRE2 or TUBB gene.
The patient is a 7-year-old male, fourth child born to the fourth pregnancy of his 40-year-old mother. His parents are healthy second degree cousins. Phenotypic examination revealed dysmorphic features such as elongated and flat face, hypertrichosis of the forehead, hypertelorism, microphthalmia, short palpebral fissures, epicanthus, a broad and depressed nasal bridge, microstomia, downturned corners of the mouth, low-set posteriorly rotated small dysplastic ears, helix anomaly, low posterior hair line, bilateral circumferential skin creases on upper extremities, overriding of the third toe and scoliosis. The patient has been operated for cleft palate and undescended testes. Developmental stage evaluation revealed that the patient can sit up without support but can not walk and can vocalize only a few single words indicating severe mental and motor delay. Cranial CT showed brainstem and vermian hypodysgenesis and bilateral ventriculomegaly and cranial MRI revealed Dandy Walker malformation.
Chromosome analysis from peripheral blood was normal. Sanger sequencing of the MAPRE2 gene showed a homozygous missense mutation in MAPRE2, which is a novel mutation. His parents were found to be heterozygous MAPRE2 mutation carriers.
CSC-KT is characterized by genetic heterogeneity but with a highly consistent and recognizable clinical phenotype. Our case further supports the possible recessive inheritance pattern and also strenghtens the idea that the same clinical phenotype can be caused by either a recessive or a de novo mutation. Nevertheless further studies are required to elucidate the exact pathophysiology of MAPRE2 mutations.

Key Words: CSC-KT, CSCSC, Michelin Tire Baby Syndrome, MAPRE2, Genetıc Heterogeneity

S-045 - Evaluation of Clinical and Genetic Findings of a Turkish Family Who is Thought to Have ELP2 Gene-Related Neurological Dysfunction

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Elongator complex is a protein complex consisting of highly conserved protein subunits (ELP 1-6), which is required for transcription elongation, histone acetylation and tRNA modification.Mutations affecting this complex are associated with neurodevelopmental disorders.There is limited clinical information in the literature about patients with ELP2 mutation associated with OR inherited mental retardation. In this study, we aimed to present the clinical and genetic findings of the 3 siblings with homozygous loss of function mutation in the ELP2 gene with the phenotypic spectra of previously reported cases.
Neurodiagnostic tests such as cranial MRI, electromyogram, electroencephalogram, routine biochemical and metabolic tests were performed.DNA was obtained from peripheral blood samples and karyotype analysis was performed. Array-CGH analysis was performed with Cytoscan Optima Assay (Affymetrix). Whole exom sequencing was performed on İlumina-Miseq platform.
As a result of whole exsome sequencing, it was detected that all three patients had homozygous (c.1385G>A) variant in exon 13 of the ELP2 gene.Variants were confirmed by Sanger sequencing and parents were shown to be carriers for this variant. Together with the available data, c.1385G>A variant was classified as ”likely pathogenic and was thought to be associated with patients' clinics.
ELP2 is one of the subunits of the Elongator complex. The mechanism of neurological dysfunction in our patients may be related to the deterioration of Elongator protein function.We think that our cases will contribute to more accurately evaluate the phenotype of ELP2-related neurological disorders.In this context, we need to say that functional studies are needed to explain how ELP2 gene-related neuronal dysfunction develops.

Key Words: ELP2 GENE, Elongator Complex, Mental Retardation, Neurological Dysfunction

S-046 - Lattice Corneal Dystrophy Caused By Same Novel TGFBI Mutation in Two Unrelated Turkish Families

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To report a novel pathogenic variant (mutation) of TGFBI gene in two Turkish families diagnosed as clinacally unilateral and late onset Lattice corneal dystrophy.
Detailed ocular examination was taken from two unrelated patients and proband 1’s close relatives (3 affected 5 unaffected). Peripheral blood leukocytes from each participant were extracted to obtain DNA. PCR of all seventeen exons and exon-intron boundaries of TGFBI gene was performed. The products were sequenced by Sanger method and analysed.
We observed a novel exon 14 mutation within TGFBI gene in two unrelated Turkish families. Genetic analyses showed a novel heterozygous c.1864 A>T mutation at codon 622 which changes asparagine to tyrosine (p.N622Y). p.N622Y mutation was found positive in all affected relatives of proband 1 and negative for all unaffected ones. To predict possible consequences of the novel p.N622Y mutation MutationTaster, Poly-Phen2 and SIFT/Provean in silico analyses were performed. Both analyses predicted this variant as pathogenic.
We reported a novel exon 14 mutation and phenotypic features in harmony with late onset variant forms of Lattice corneal dystrophy. Our results confirm the fact that the position and nature of the primary mutation is the major determining factor about phenotypic outcome along with other genetic and environmental factors. We can perform this analysis from healthy control cases and protein functional arrays could perform to determine the precision of pathogenity of this variant.

Key Words: Lattice Corneal Dystrophy, TGFBI Gene

S-047 - T704M Mutation and a New Clinical Entity in HOKPP

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Periodic paralyses (PPs) are a group of rare disorders, characterized by episodic, sudden onset, flaccid paralysis of skeletal muscles with usually complete recovery after the attacks. PPs are caused by abnormal, mostly potassium-sensitive excitability of the muscle tissue. Hypokalemic and hyperkalemic periodic paralysis (HypoKPP and HyperKPP) have been described according to their characteristic phenotypes and the serum potassium level during the attack of weakness. In HypoKPP, during an attack, serum potassium is <2.5 mmol/L, wherease, in HyperKPP serum potassium is elevated or normal. A third disorder, paramyotonia congenita (PC) is also included in this group because myotonia and episodic weakness occur both in paramyotonia congenita. The T704M mutation on the SCN4A gene is the most common mutation in HperPP, and some other mutations on this gene cause PK. On the other hand, different mutations of the SCN4A gene have been reported in a small proportion of HoKPP cases. In this study, a large Turkish family carrying the T704M mutation on the SCN4A gene with HoKPP disease was examined.
The proband had a history of recurrent paralytic attacks induced by carbohydrate intake, cold exposure and exercise. The attackes started at the age of 3. Serum potassium level during the attack was low. During the attacks she has hallucinations of smell and a few days following the episode, she has diplopia when she turns her eyes to another direction. Attack frequency was reduced by using Calinor tablet and avoiding the triggering factors
T704M mutation on the SCN4A gene was determined by sequence analysis of the patient. A similar history was recorded in a total of 17 subjects in the pedigree. T7014M mutation was detected in all subjects.
T704M mutation was indicated that it was the most common mutation in HyperPP cases. But, in the current study, this mutation was presented with the clinic of HoKKP in the family. In addition, the symptoms of hallucination and diplopia seen in patients weren’t indicated in literature . This report expands the phenotypic variability of the T704M, further confirming the lack of genotype-phenotype correlation in SCN4A mutations.

Key Words: HOKPP SCN4A

S-048 - Environmental Risk Factors in Young Breast Cancer Patients

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A “risk factor” is anything that increases risk of developing breast cancer. Mainly there are two main risk categories, certain risk factors that are out of one's control and the ones which are under control. Uncontrollable risk factors for breast cancer are age, family history, and medical history. However, there are some risk factors that can be controlled, such as weight, physical activity, and alcohol consumption.
Breast cancer patients that were categorized as "young" and selected for this study were those who were under 50. These were referred for genetic counseling according to NCCN age criteria. All the patients were categorized according to their individual habits like smoking and alcohol consumption, family and medical history, as well as hormonal status such as menarche, contraceptive usage history. The results were also categorized individually with their genetic backgrounds of BRCA status and other genes.
All the patients were 50 years of age and younger. Personal history of all were categorized. First all were asked where they were in 1986 and then, after the chernobyl disaster. Most of the patients were in Istanbul and northern parts of Turkey. The menarch age, pregnancy, breast-feeding status were not significantly aggregated to any category. Same results were obtained for smoking and alcohol consumption habits, hormon usage and hormonal risk factors such as PCOS. These were evaluated with genetic risks of carrying any mutation keading to hereditary cancer susceptibility.
Many women faces breast cancer, the estimated ratio is one in eight. Although age is the main risk factor, this survey was done from younger patients. The question is "why me?" ... Although we know that some of these are due to hereditary predisposition, it is only the 10 to 15 percent of all tested. So there should be more. It seems that consequences of Chernobyl disaster is one of the main suspects in neighborhoods and the countries nearby like Turkey. Then comes the hormonal issues like contraceptive usage and history of assisted reproductive techniques. In conclusion, all these risk factors should be taken into account as well as genetic test results in a comprehensive genetic counseling session.

Key Words: Young Breast Cancer, Environmental Risk Factors

S-049 - The Importance of Genetic Counseling and Patient’s Management in Families with Hereditary Cancer Syndromes

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Hereditary cancer syndromes account for 5-10% of all malignancies. They are frequently seen in patients at younger ages and in patients with a positive family history. Lynch Syndrome (LS) and Adenomatous Polyposis Syndromes [e.g. Familial Adenomatous Polyposis (FAP), MUTYH-associated Polyposis (MAP)] are responsible for a substantial part of hereditary cancer syndromes. Long-term follow-up and/or prophylactic surgery is recommended for patients in this group. The aim of this study was to emphasize the importance of genetic counseling, diagnosis and management of patients suspected with hereditary cancer syndrome.
Three different families were evaluated for three different hereditary cancer syndromes in this study. One patient, who was diagnosed with sebaceous carcinoma (SC) in the first family, was referred to genetic diagnostic center by medical oncologist. One patient in the second family and one patient in the third family, who were diagnosed with colorectal carcinoma (CRC), were referred from the department of general surgery. All of them had positive family histories. After they were underwent genetic counseling, it was decided to perform germline testing for LS in patient with SC and for FAP and MAP in patients with CRC. For this purpose, next generation sequencing (NGS)/Sanger sequencing and deletion/duplication analysis were performed in mismatch repair genes (MMR), and APC, MUTYH genes.
Exon3-16 heterozygous deletion was detected in MSH2 gene in patient with SC. p.Asn1546Lysfs*19 heterozygous novel pathogenic variant in APC gene, and p.Pro295Leu homozygous pathogenic variant in MUTYH gene were found in the second and third family respectively.
After the identification of pathogenic variants in this study, patients were underwent detailed genetic counseling and were referred to the relevant units for follow-up. However, the investigation of the same variant was proposed to the other family members at high risk. Because they can benefit from surveillance programs that will be expected to increase the chances of earlier diagnosis and to reduce cancer risks. In conclusion, patients suspected of hereditary cancer syndrome should always be referred for genetic counseling. The diagnosis and management of patients suspected with hereditary cancer syndromes requires interdisciplinary cooperation between the respective specialty and medical geneticists.

Key Words: Lynch Syndrome, Adenomatous Polyposis Syndromes, Genetic Counseling, Next Generation Sequencing, Novel Mutation

S-050 – HMGB1 in Differential Diagnosis of High PSA

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In this study; the diagnostic role of HMGB1 levels measured in serum were analyzed both prostatitis and prostate carcinoma diagnosis in the diagnosis of these two diseases.
In total, 78 samples were involved in the study, comprise of 30 (38.5%) prostatitis patients, 25 (32%) prostate carcinoma patients and 23 (29.5%) healthy subjects. HMGB1 was determined as 11.9±2.6 (Range 6.7-18.4) ng/ml in the prostatitis group, 15.1±4.5 (Range 8.4-24.8) ng/ml in the prostate carcinoma patients and as 9.2±3.1 (Range 4.7-18.7) ng/ml in the control group. The difference between the groups were investigated using the Friedman test as HMGB1 did not demonstrated normal range. Significant difference was determined between the three groups ($p<0.001$). When the groups were compared in pair, significant difference was detected between the prostatitis group and the control group ($p=0.001$). Significant difference was again determined between the prostate carcinoma group and the control group ($p<0.001$). Significant difference was determined between the prostatitis group and the prostate carcinoma group ($p=0.006$). Measurement of serum total prostate specific antigen (tPSA) levels were conducted automatically with the electro chemiluminescent method. Although the difference between PSA and HMGB1 ($p = 0.276$) was moderate, it was found highly significant positive correlation ($p = 0.009$).
In study, we demonstrated that high PSA and high HMGB1 were notably correlated. HMGB1 measured in serum could be a beneficial marker in the differentiation of prostatitis and prostate carcinoma, in the early diagnosis of suspected prostate carcinoma and that HMGB1 value was significantly higher in prostate carcinoma patients.

Key Words: Prostate Carcinoma, Prostatitis, HMGB1, PSA, Diagnosis

S-051 - Association Between EGFR Mutations and Metastases Foci in Turkish NSCLC Patients: The First Results

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The frequency of EGFR mutation in patients with NSCLC ranges between 36.4-66% in East Asia, 6-24% in USA and 6-16% and 30-45% in Turkey. The most common EGFR mutations are in exon 19 and 21. EGFR mutations have important roles in many pathways in the tumor cell, especially at invasion and metastasis processes. In this study, we evaluated the subtypes of EGFR mutations and metastases foci in Turkish non-small lung cancer patient at the time of the diagnosis.
Between 2015 and 2017, in paraffin embedded tissues of 97 NSCLC patients who had EGFR mutations at the time of the diagnosis were included in this study. DNA isolation and pyrosequencing were carried out from paraffin embedded tissues. Statistical analyses were done using SPSS 17.0 statistical package program.
The frequencies of EGFR mutations were as follows: 17 (17.5%) had exon 18, 45 (46.4%) had exon 19, 4(4.1%) had exon 20 and 31 (32%) had exon 21. We found statistically significant correlation between the subtypes of EGFR mutations and metastases foci (p: 0,037). Brain metastasis has only subtypes of exon 19 and 21 in EGFR mutations (respectively 4,4). Liver metastasis has only subtypes of exon 19 and 20 in EGFR mutations (respectively 3,1). Lymph node metastasis has only subtypes of exon 19 and 21 in EGFR mutations (respectively 2,1). Patients with mutations in exon 19 and 21 had the highest incidence of two and more focus of metastasis (respectively 16,12).
This study we suggested that exon 19 mutation within EGFR gene has been both cause of autophosphorylation and many adaptor proteins phosphorylated. Also, other point mutations within EGFR gene has phosphorylated specific adaptor protein. Er (2017) reported that exon 19 mutations within EGFR gene is related with brain metastasis. We offer that subtypes of EGFR mutations have activated from different pathway which is leading different metastasis foci.

Key Words: Lung Cancer, EGFR, Metastasis

S-052 - Three Genotypes Causing Three Distinct Phenotypes in a Hereditary Cancer Family

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Hereditary cancer syndromes (HCSs) are rare, count for only about 5% of all malignancies. Most hereditary cancer syndromes are inherited in an autosomal-dominant manner. Also biallelic mutations are responsible for some of hereditary cancer syndromes like MUTYH-associated polyposis (MAP) which causes a rare form of colorectal cancer. In recent studies monoallelic mutations in MUTYH gene were found to be associated with increased risk of colorectal cancer without polyposis. Here we report three mutations in two cancer susceptibility genes in a cancer prone fanily including both MAP and breast cancer patients.
A 48-year old male, colon cancer patient who underwent right hemicolectomy and 23 polyps were removed a year ago is referred to us. MUTYH and APC genes screened via next generation sequencing, heterozygous c.884C>T and c.1437_1439delGGA mutations were detected in MUTYH gene. Segregation analyses showed that mutations were at compound heterozygous state. Siblings of index case screened for the same mutations via sanger sequencing. The same mutations were detected in a brother having more than 20 polyps in colon. A brother having 4 polyps in ascending colon had heterozygous c.1437_1439delGGA mutation whereas one of the brothers carrying c.1437_1439delGGA mutation had no polyps in colon at the date of examination. During this study, a cousin of index case carrying none of the mutations was diagnosed as unilateral breast cancer. Screening for hereditary breast cancer panel including 25 genes revealed c.1409A>G mutation in BARD1 gene which is a known pathogenic mutation associated with hereditary breast cancer.
Although hereditary cancer syndromes are rare, it is important to identify these patients not only for themselves but also for healthy family members for early diagnosis and long term-care. In hereditary cancer syndromes, similar cancer types in different tissues may accumulate in the family according to penetrance of cancer susceptibility gene. So it is recommended to screen other family members for known, family-specific molecular genetic defects. In this study three distinct cancer prone genotypes were detected unexpectedly, associated with three distinct phenotypes: hereditary breast cancer, MAP and increased colorectal cancer risk.

Key Words: Hereditary Cancer Syndromes, MUTYH, BARD1

S-053 - Identification and Analysis Of Novel Variants Associated with Breast and Ovarıan Cancer in BRCA1 and BRCA2 Genes

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BRCA1 and BRCA2 genes are tumor supressor genes involve in cell cycle, DNA repair mechanism and chromosome stability. Studies in different populations have reported that functional variants in these genes increase the risk of developing breast and ovarian cancer. BRCA1&BRCA2 gene mutation analysis is performed for patients with history of early-onset breast and ovarian cancer or positive family history. In this study, exon sequencing of BRCA1&BRCA2 genes were performed by aiming to determine and analyze novel variants that could be related to the phenotype.
In six months period (March 2018 - September 2018), BRCA1 (35 amplicon) and BRCA2 (56 amplicon) genes from DNA isolated blood of 125 patients (117 females, 8 males) with a history of breast and ovarian cancer or positive family history. Exon and the exon-intron boundries were amplified using BRCA MASTR Plus Dx Assay kit and sequence analysis was performed on the Miseq device. Sophia DDM platform and Sophia Genetics' MOKA were used in variant analysis and annotation. Variant Classification was performed according to mutltiple databases, in-silico tools and ACMG variant pathogenicity classification. Allele frequencies were calculated by Haploview program.
We determined 98 variants (60 exonic, 38 intronic) of which 4 were intronic novel in the BRCA1 gene while 3 intronic and 3 exonic variants were novel in the BRCA2 gene. Eighteen variants in the BRCA1 genes are rare (MAF<0.01) and 18 were common (MAF≥0.05) whereas 37 variants were rare and 19 were common in the BRCA2 gene. Two of three exonic variants were pathogenic and one was VUS. Patients with novel pathogenic and VUS variants had a history of ovarian and breast cancer and had no other variants were detected in their BRCA1 and BRCA2 genes. Novel variants were validated by Sanger sequencing method.
Our analysis revealed novel variants that may be associated with disease and leaded to detect several rare variants. Novel pathogenic variants detected in the BRCA2 gene are thought to have higher functional effects on protein and thought to be associated with ovarian cancer. Genetic counseling was already performed and functional as well as in slico analyses were planned to reveal the functional importance of the variants.

Key Words:BRCA1, BRCA1, Next-Generation Sequencing, Rare Variants, Breast Cancer, Ovarian Cancer

S-055 - Investigation of NF1 Gene Variations in Patients with Preliminary Diagnosis of Neurofibromatosis by Next Generation Sequence Analysis

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Neurofibromatosis 1 (NF1) is characterized by cafe au lait spots, axillary and inguinal freckling, cutaneous neurofibromas, iris Lisch nodule and choroidal hamartomas and has autosomal dominant hereditary. The NF1 gene is located on the 17th chromosome and consists of 57 exons. We aimed to present the results of patients who were referred to our center with the preliminary diagnosis of neurofibromatosis between January 2017 and June 2018 and who underwent molecular analyzes with new generation sequencing.
DNA was obtained from peripheral venous blood of 27 patients (20 females, 7 males, mean age: 12) who were referred to Trakya University Medical Faculty Medical Genetics Department Genetic Diseases Diagnostic Center Polyclinic with the preliminary diagnosis of neurofibromatosis (cafe au lait spots, widespread neurofibromas, hamartoma findings). NF1 gene was sequenced with the Illumina MiSeQ system from DNA samples.
Pathogenic variation (8 missense, 5 termination- one novel, 1 deletion) was found in 14 cases (52%) and variant of unknown clinical significance was found in 5 cases. Pathogenicity evaluations were performed using ACMG 2015, Human Genome Mutation Database, ClinVar and Leiden Open Variation Database.
Neurofibromatosis is a multisystemic disease which causes various clinical findings in many systems. Considering that the NF1 gene is a large gene and the novel variants can be detected in different regions of the gene, we think that the whole analysis of the gene will be more accurate. The findings of the disease should be well known, should be diagnosed by careful physical examination and should be closely monitored for complications. With early diagnosis, monitoring and treatment of problems of patients and genetic counseling will be provided.

Key Words: Neurofibromatosıs, Next Generation Sequencing, Pathogenic Variation

S-056 - Elevated TUBB2A Expression in T-All and its siRNA Mediated Modulation

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Microtubules function in cell structure, movement and intracellular transport. There are several known tubulin isotypes encoded by different genes. Since microtubules take role in spindle formation within, they are targeted by antimitotic cancer drugs. In this study we aimed to study TUBB2A's expression levels, its prognostic significance in pediatric T-ALL. and its effects on the survival of leukemic cell line.
We used R program for differential gene expression analysis of pediatric T-ALL microarray dataset generated in our previous study (GSE46170). Expression levels of TUBB2A, β tubulin isotype, was validated in a different pediatric T-ALL cohort (n=48). TUBB2A's siRNA mediated downregulation was performed in a T-ALL cell line (MOLT4) and its effects on cell survival were assessed by flow cytometer.
TUBB2A's expression levels were significantly increased (p value<0.05) in T-ALL samples compared to thymocyte subsets. This finding was validated with qPCR (p<0.05). Patients, with high WBC counts at the time of diagnosis (>50 000/mcL) and patients who were classifed in a high risk group were found to have elevated TUBB2A expression compared to their respective counterparts (p=0.035 and p=0.026 respectively). Overall survival and relapse free survival of patients with higher TUBB2A expression levels were found to be significantly shorter. Cox regression analysis revealed that high TUBB2A expression levels are associated with relapse risk (p=0.182) and induction failure (p=0.011). siRNA transfection had achieved approximately 50% TUBB2a downregulation and siRNA treated cells showed increased apoptosis at 48th hour, whereas no difference was detected at 72nd hour.
Here we showed for the first time, that TUBB2A's elevated expression is associated with poor prognosis and worse survival. Tubulins are among antimitotic drug targets used in cancer treatment, since they take part in cytoskeleton formation. Several studies have reported that some tubulin isotypes have correlation with induction response. siRNA treated samples had higher apoptotic cells at 48th hour, but no difference was seen at 72nd hour, which may be due to tubulin isotypes' redundancy in cytoskeleton, which might have compensated TUBB2A's downregulation. Our futher studies will aim to identify functional significance of this gene's expression and its response to chemotherapeutic drugs. Study was supported by BAP-TYL-2016-21490 fund.

Key Words:T-ALL, Microarray, siRNA

S-057 - Investigation of FHIT Gene Region in Peripheral Blood by FISH in Small Cell and Adenocarcinoma Lung Cancer Cases

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To examine FHIT gene status in peripheral blood of the SCLC and adenocarcinoma patients by FISH method and investigate its prognostic significance.
Interphase FISH applied to peripheral lymphocyte preparations of untreated 30 adenocarcinoma, 24 SCLC and 20 healthy control subjects using custom designed and quality controlled FHIT (3p14.2) gene probe and at least 200 cells were evaluated for each case.
No significant difference was found between adenocarcinoma and SCLC groups in terms of anomalies such as monoallelic and biallelic deletions, monosomy and rearrengements (p>0,05). Monoallelic deletions were significantly higher in both adenocarcinoma and SCLC patients compared to the control group (p<0.001 for both groups). Biallelic deletions were significantly higher only in adenocarcinoma cases than the control group (p<0,05). Monozomic cells were significantly higher in both adenocarcinoma and SCLC patients than the control group (p<0.01, p<0.001,respectively). Rearrengements were significantly higher in both adenocarcinomas and SCLC patients compared to the control group (p<0.05, p<0.01,respectively). We compared our results according to disease stages and metastasis status as well. Monosomic cells were observed significantly higher(p<0,05) in adenocarcinoma cases with metastasis than the cases without, but in SCLC cases such a correlation was not found. Since there was no difference according to FHIT gene abnormalities between adenocarcinoma and SCLC groups, the data of the two groups were combined while comparing the results and disease stages of cases. Monosomic cells in stage II cases were found significantly higher than in stage IV.
In our study, FHIT gene anomalies were found to be significantly higher in both adenocarcinoma and SCLC patient groups than in control group by FISH method. In literature search, we did not find any report on studies of FHIT gene by FISH in neither peripheral blood nor tumor tissue samples of lung cancer cases. This study is a preliminary study to demonstrate the potential prognostic significance of the FHIT gene in lung cancer, and our plan for further studies is to examine both peripheral blood and tumor tissue samples in parallel to investigate the role of FHIT gene in lung cancer pathogenesis in more detail. This work was financially supported by Istanbul University Scientific Research Projects. Project No:23831

Key Words: Small Cell Lung Cancer, Adenocarcinoma, Fluorescence In Sıtu Hybridization, FHIT

S-058 - Investigation of Genetic Basis of Colorectal Cancers by Usıng Next Generation Sequencing

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Colorectal cancers, one of the common types of cancer in our country and all over the world, are cancers that can be seen as sporadic or hereditary, affecting the colon and the rectum. Hereditary colorectal cancers are rare and are classified as familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP) and hereditary non-polyposis colorectal cancer (HNPCC). Pathogenic variations in the APC gene cause autosomal dominant inherited FAP, whereas pathogenic variants in the MUTYH gene cause an autosomal recessive MAP phenotype. The HNPCC's are caused by defects in DNA mismatch repair genes (MMRG). In this study, we aimed to present the determined variations in cancer-related genes screened by Next Generation Sequencing Analysis in 32 patients who were referred to our center to investigate the genetic background of colorectal cancer between March 2016 and April 2018.
Genomic DNA was isolated from peripheral blood cells according to the manufacturer's protocol. TruSight Rapid Capture Library Preparation (Illumina) kit and Onco-GeneSGKit IVD -CE kits were used for the preparation of libraries containing the relevant genes. The obtained libraries were sequenced in the Illumina MiSeQ system and the data were analyzed using the Illumina MiSeq Software and Genomized Seq software, and the IGV (Broad Institute) program was used for the visual evaluation of the data.
Pathogenic (P)/ probably pathogenic (PP) variations were observed in 12 out of 32 patients (37.5%). While 10 of these P/PP variants were identified in MSH, MLH, APC, MUTYH genes that directly related to colorectal cancer, in 2 out of 32 patients, pathogenic / probably pathogenic variations in other genes related to cancer susceptibility (BRCA1 and ATM) was detected. In one of the cases, pathogenic Preparation was detected in both the BRCA2 and APC genes.
This study supports the determination of the genetic background of colorectal cancers by using the Next Generation Sequence Analysis method and the simultaneous screening of many cancer-related genes. In addition to hereditary colorectal cancer syndromes, the identification of pathogenic variations in other cancer-related genes and genetic counseling have contributed significantly to the clinical follow-up and early screening of cancer.

Key Words: Colorectal Cancer, Genetics, Next Generation Sequencing

S-059 - Diagnostic Validity of Tests For Analyzing Pediatric Acute Lymphoblastic Leukemia

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Acute Lymphoblastic Leukemia (ALL) is a heterogeneous disease with different subtypes as typical clinical, biological and prognostic features. More than half of the ALL cases were from pediatric patient group. In the adult age group, the incidence of disease varies between 1-2/100000. Genetic and environmental factors are effective at its pathogenesis and the prevalence of Down syndrome, Bloom syndrome and neurofibromatosis type 1 has been increased. Chromosomal translocations that activate specific genes are a characteristics identifier for human leukemias, especially for ALL. Approximately 25% of precursor B cell ALL cases, the most common form of pediatric ALL, carry the TEL-AML1 fusion gene generated by chromosomal translocation of t(12; 21) (p13; q22). Our aim is to investigate the cytological, molecular and clinical status of ALL patients which were treated at Pediatric Hematology Department between 2005 and 2018.
The reports of 51 pediatric ALL patients, who admitted between 2005 and 2018 were included. TEL-AML1 fusion gene with t(12; 21) (p13; q22) was tested with both cytogenetic and molecular techniques. The patient variables were analyzed via IBM SPSS 11.0.
Sixtytwo percent (n = 32) of the patients were males and 36.5% (n = 19) were females. The patients were between 0 to 16 years of age and 17.6% (n = 9) were diagnosed at the age of four years. PreB ALL was diagnosed in 84.31% and T ALL was diagnosed in 13.72% of the patients. The mean number of CD10, CD79A, and TdT positivity were 86.3%, 84.8% and 62.7%, respectively. In addition 21.6% of patients had t (12; 21) translocation. Herein, the most common symptoms and clinical findings were weakness (35.3%), fever (33.3%), hepatomegaly (39.2%) and lympadenopathy (31.4%). There was no statistically significant relationship between the blast count of bone marrow and risk classification (p> 0.05).
Down Syndrome for PreB ALL is a major risk factor and 2% of our patients were diagnosed as Down syndrome with milder clinical findings. Although the detection of t(12,21) considered an important diagnostic value for ALL, it is observed at only 21,6% of our patients. Also, CD79A and TdT detection were found crucial for diagnostic work-up.

Key Words: ALL, Diagnostic Validity, Translocation Analysis

S-060 - Genetic Variants Detected By Multigene Panel Are Associated With Hereditary Cancer

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The identification of pathogenic variants in highly penetrating genes is useful for the diagnosis, treatment and survival of hereditary cancers. Genetic testing for hereditary cancers is rapidly evolving with the emergence of multigen panels that are able to identify more mutations than previous screening methods. In particular, hereditary breast and ovarian cancer syndrome (HBOC) represents 5% to 10% of all patients and is associated with high-risk pathogenic alleles in BRCA1 / 2 genes, but only 25% of cases. The purpose of this study is to use the Next Generation Sequencing panel to find genes that play a role in cancer susceptibility.
In 25 patients diagnosed with hereditary cancer, we aimed to find new pathogenic alleles with the help of a multigen panel containing 25 genes in cancer susceptibility. MLPA analysis for BRCA1 and BRCA2 genes [Multiplex ligation-dependent probe amplification (SALSA MLPA P002-D1 BRCA1 / P045-C1 BRCA2-CHEK2 kit). For this, all patients were studied using BRCA Hereditary Cancer MASTR Plus, (Multiplicom) and Miseq Sequencing System (Illumina). Sequence results were analyzed by Seqgenomize, (https://seq.genomize.com/) CNV Calculator v1.2.1 (Multiplicom).
In the cancer patient group, 13.2% (7/53) of the variants were pathogenic variant, while 60% (32/53) were variants of clinical significance (VUS). The genes with the most intensive variant were BRCA2 in 20.8% (11/53), in 9.4% (5/53) CHECK2, in 7.5% (4/53) MSH6. 10 new variants were detected. The most repetitive variant, the 8th exon 1928G> A p.Arg643His change of the BLM gene was found in 3 of the 25 patients. In this panel, no variant was observed in 10 of the 25 genes.
As a result, detection of new pathogenic variants may alter individual clinical management by contributing to the disclosure of the inheritance of hereditary cancer. Multigen panel testing is a more effective method for identifying germline variants in cancer patients than single-gene approaches, and should therefore be included in clinical laboratories. However, Turkey also large-scale studies are needed to determine the suitability of future tests and variant classification process.

Key Words: Multigene Panel, Hereditary Cancer, Next Gene Sequencing

S-061 - Association of 1p/19q Co-Polysomy and Prognosis in Glial Tumors

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Genetic markers of glial tumors derived from glial cells in the brain have an important role in the diagnosis and prognosis. Co-deletion of 1p / 19q is one of the diagnostic criteria for gilal tumors and is associated with increased survival and sensitivity to chemotherapy and / or radiotherapy. Although there have been several studies in the recent years that the numerical increases in the 1p / 19q regions examined by the FISH method in terms of deletion were also of clinical significance, the relationship with the prognosis could not be clarified. In this study, 1p / 19q polysomy and retrospective analysis of clinical processes will be presented in 221 glial tumors.
221 FFPE samples from patients who diagnosed as glial tumor were analyzed for 1p36.13-p3631 ile 19q13.2-q13.33 regions by using FISH procedures. Clinicopathological features associated with 1p/19q status were analyzed by Chi-square test including patient Age, Gender, P53, Ki67, EGFR, WHO Grade, Recurrence, Pathological Type.
The patient cohort consisted of 221 patients with glial tumor including 50 Grade II Oligodendroglioma,13 Grade III Oligodendroglioma, 38 Grade II Astrocytoma,11 Grade III Astrocytoma, 75 Grade II Oligoastrocytoma,18 Grade III Oligoastrcytoma and 16 Grade IV GBM. Of 221 patients, 76 had 1p/19 co-deletion, 48 had 1p/19q co-polysomy and 97 had normal genotype for 1p/19q. All grade II and III olgodendroglioma cases revealed co-deletion. Polysomies were observed on cases grade III oligoastrocytomas and grade IV glial tumors. Univariate analysis revealed that 1p/19q deletion was negatively correlated with P53 expression whereas 1p/19q polysomy was positively correlated with P53 over-expression in our patient cohort (p=0.0009).
Our results demonstrated that 1p/19q co-polysomy was associated with decreased overall survival time, high P53 expression and frequently located in temporal lobe whereas 1p/19q co-deletion was vice versa. Furthermore, classification of patients based on both 1p/19q status and P53 expression revealed that patients with 1p/19q co-polysomy and P53 positivity had the worst prognosis. Lastly, our bioinformatic survival analysis showed that high expression of SRM, ICMT, and FTL located in 1p36.13-p36.31 and 19q13.2-q13.33 region was related with decreased OS time in patients with glial tumor.

Key Words: Glial Tumor, 1p/19q Co-Polysomy, Prognosis

S-062 - Molecular Genetic Approach to Craniosynostosis Patients and Whole Genome Array CGH Analysis of Nonsyndromic Cases

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Craniosynostosis is a craniofacial malformation in which one or more sutures of the cranial vault are fused prematurely. It is estimated that craniosynostosis affects 1 in 2,000 to 2,500 live births worldwide. Early and accurate diagnosis of craniosynostosis is very important since premature suture closure causes to not only a deformity of skull but also can directly affect the development of brain. Craniosynostosis occurs in all racial groups and more than 85% of all cases are non-syndromic. Until now, mutations in TWIST, EFNB1, FGFR1, FGFR2 and FGFR3 are shown to play role in craniosynostosis, whereas genetics factors of 85% non-syndromic cases haven't been fully identified yet. The aim of this study is to identify novel genes and gene regions for non-syndromic craniosynostosis cases through utilizing a genetic approach to craniosynostosis cases and high resolution aCGH teqnique.
Out of 10 patients included in the study, 2 patients were diagnosed with Craniosynostosis syndrome and Apert syndrome. For these patients, molecular analysis of EFNB1 and FGFR2 gene were carried out using Sanger sequencing. Patient diagnosed with Craniosynostosis syndrome has been shown to carry a novel mutation (c.402T>C). Our other patient has been demonstrated to have one of the most common mutations of FGFR2; c.755 C>G. For remaining 8 non-syndromic cases, `SurePrint G3 Human CGH Microarray Kit, 2x400K (Agilent Technologies)` microarray chips, which are made up of 60 mer-long 411.056 probes with 5.3KB resolution, were used to perform aCGH analysis and various deletions and duplications were detected.
Patient diagnosed with Craniofrontonasal syndrome has been shown to carry a novel mutation (c.401T>C). Our other patient with diagnosed Apert syndrome has been demonstrated to have one of the most common mutations of FGFR2; c.755 C>G. For remaining 8 non-syndromic cases, `SurePrint G3 Human CGH Microarray Kit, 2x400K (Agilent Technologies)` microarray chips, which are made up of 60 mer-long 411.056 probes with 5.3KB resolution, were used to perform aCGH analysis and various deletions and duplications were detected.
Results of this study are estimated to provide preliminary information about pathways playing role in the pathogenesis of craniosynostosis, whıch contribiute to the further studies in the field.

Key Words: Craniosynostosis, Nonsyndromic, Comparative Genomic Hybridization, Array CGH

S-063 - The Pathogenic Role of Xp22.31 Copy Number Variations and Literature Review

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Copy number variations (CNVs) play an important role in the etiology of intellectual disability (ID) and autism. Recurrent microdeletions / duplications can be detected in these diseases. The aim of this study was to discuss the clinical effect of recurrent Xp22.31 CNVs in patients with ID or autism.
Patients who had a copy number variation of Xp22.31 in the array CGH (Agilent 8x60K ISCA) analysis performed in 600 patients with ID / autism ± additional anomaly were evaluated.
Eight patients (1.3%) had CNVs in the Xp22.31 region with a size of 565-1820 kb. Six patients (3 females, 3 males) had duplications (1%) and 2 male patients had deletions (0.33%). The duplication regions included only VCX, PNPLA4, MIR651 genes in the three patients, while STS, VCX, VCX2, HDHD1, PNPLA4 and MIR651 genes were found in deletions or duplications regions in the five patients.
The two male patients with deletions had mild to moderate ichthyosis. Interstitial deletions of the Xp22.31 region should be considered among the preliminary diagnoses in patients with ID / autism and ichthyosis. There is no consensus on the clinical significance of duplications of the Xp22.31 region in the literature. There have also been some authors who have considered this duplication as a pathogen due to the fact that the findings of ID / autism, microcephaly and short stature were common as in some of our patients, as well as those who claim to be benign because they are inherited from a healthy parent. Recent studies in large patient and control groups have suggested that the probability of this duplication to be a rare population variant cannot be completely excluded, but it has been suggested that it may be a risk factor or modifier that contributes to the abnormal phenotype in patients. Further molecular analyzes for the exclusion of other genetic etiologies in these patients will contribute to the clarification of the clinical impact of recurrent Xp22.31 duplications.

Key Words: Xp22.31 Deletion, Xp22.31 Duplication, Intellectual Disability, Autism, Ichthyosis

S-064 - The Evaluation of Cytogenetics Results Obtained from Behçet Disease with Gastrointestınal Involment

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In a limited number of cytogenetic studies associated with Behçet's syndrome (BS), it has been reported that chromosomal abnormalities and frequency of breakage have increased. In the studies, 2% malignancy was observed in Behçet's patients and 20% of these patients were associated with MDS. Most of the patients with Behçet's disease associated with MDS had gastrointestinal (GIS) involvement and the frequency of trisomy 8 was reported to be high. In this study; The aim of this study was to determine the chromosomal abnormalities in patients with Behcet 's disease with gastrointestinal involvement in Cerrahpaşa Medical Faculty Gastroenterology Clinic.

Key Words: Cytogenetic,Behçet Syndrome, Cytokines, Pokeweed, PMA

S-065 - Case Diagnosed with Smith-Magenis Syndrome

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To describe a patient diagnosed with Smith-Magenis (SMS) syndrome and inform the scientific audience about this rare disease.
SMS is a rare neuro-developmental disorder with a prevalence of 1/15000 to 1/25000. SMS patients generally display developmental delay, cognitive impairment, and behavioral abnormalities. Research on SMS suggests that interstitial deletions in 17p11.2 (approximately 3.7 megabases) or specifically loss of RAI1 (retinoic acid induced 1). Brachycephaly, broad-square shaped face with deep-set eyes, enlarged forehead, synophrys (monobrow), midfacial hypoplasia (flatten short nose and midface area), full cheeks with a prominent lower jaw, abnormal dentition, hearing problems and global developmental delay are physical properties for SMS patients. Behavioral problems including temper tantrums or outbursts, aggression, excessive anxiety, attention deficit hyperactivity disorder,self-injurious behavior, sleep disturbances and stereotypy (repetitive movements like self-hugging) are characteristic of SMS). Sporadic, not inherited in most cases.
A 15-year-old male patient was born on the term and via NSVD with 3400 g birthweight to a nonconsanguineous couple. His main neuro-behavioral complaints were of childhood epilepsy, mental retardation, hyperactivity (treated with olanzapine), attention deficit, sleep disorders, self-hugging, nail-biting, needless aggressiveness. Main dysmorphic features were a broad face, broad forehead, synophrys (monobrow), deep-set eyes, down-slanting palpebral fissure, large nasal root, low-set ears, short filtrum, thick lips, prognathism, low-set hairline, and muffled voice. On his MRI results, atrophy of the frontotemporal region was observed. His audiometry results revealed that he has a conductive type hearing loss (65%). His right eye was -9 and left eye was -11.5 degrees myopia. His epileptic seizures were dating back to more than one year, and his EEG was normal. He had a regular 46, XY karyotype and Fragile X fragment analysis was within a normal range, 44 CGG repeats. A 1.430 kbp microdeletion in 17p11.2 was detected in array CGH. All these data were enough to describe the case as SMS.
Repetitive self-hugging is a characteristic differential diagnosis element for Smith-Magenis syndrome, and it was perfectly displayed by the patient in our case. Although a careful eye can diagnose the 17p11.2 with a routine G-banding, array CGH analysis is beneficial in revealing critical microdeletions covering RAI1.

Key Words: Smith Magenis Syndrome, Rare Diseases, RAI1

S-066 - A De Novo Interstitional Deletion of Chromosome 4p Presenting Epilepsy, Hypotonia and Dysmorphic Features

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To date, more than 40 cases of 4p15 deletion have been reported but, 4p15.33-15.1 interstitial deletion has not been previously reported. And the cases reported with array comparative genomic hybridization are relatively few. We aimed to contribute to the literature and to compare genotype–phenotype association with literature data with this study.
Our patient referred to us with frequent respiratory infections, epilepsy, hypotonia and some dysmorphic features. She was at the age of 16 months and the second child of nonconsanguineous parents. She has a healty brother 4,5 years old. She has been delivered at 36 weeks of gestation with cesarian sectio. Her birth weight was 3500 g and APGAR score was low. She has remained at an intensive care unite about 25 days because of the respiratory insufficiency. She was hypotonic infant until 5 months, her development was also delayed.
In the physical examination we observed a round face with long philtrum, thin upper lip, strabismus, nistagmus, long palpebral fissures, bitemporal narrowing, hypertelorism, sparse eyebrows, prominent big ears, tapering fingers, shortness of fifth metacarpals, widespread mongolian spots on the dorsal region and a 3x3 cm hemangioma on lumbar region. Transfontanelle ultrasound was normal, cranial magnetic resonance imaging revealed a neuroglial cyst nearby right hippocampus and hypoplasia of corpus callosum. Serum amino acids profile was normal. EEG was abnormal due to focal epileptic activity. Chromosomal analysis showed 46,XX,del(4)(p15.2p16.1) karyotype. The parental karyotypes were normal. In order to exclude cryptic translocation on parents, subtelomeric FISH analysis showed no chromosomal abnormality. Chromosomal microarray analysis revealed a 15,272 Mb interstitional deletion of 4p15.33-p15.1; arr[hg19]4p15.33-p15.1(13823997_29096762)x1
As a result of the increasing number of microarray studies we hope that a common phenotype will be created for this region deletions .

Key Words: 4p Deletion, Microarray, Epilepsy, Hypotonia, Dysmorphic Features

S-067 - Cytogenetic and Molecular Cytogenetic Analyses of a Case with 47, X, idic (Y) (q11.22)x2, Associated with Neuromotor Delay and Dysmorphology

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In this study, we present a male patient with neuropsychiatric disorders and dysmorphological findings with non-mosaic isodicentric chromosome structure accompanied by Y chromosome q region deletion and p region amplification, although there are four SRY gene copies and gender development normal.
Our case is four years old and the first child of the healthy mother and father, he was born at 2600 gr, and there were no problems during pregnancy and delivery. He was referred to a doctor with complaints of delay in his walk (first step, 22 months), delay in speech (first meaningful word 30 months). He was not responding to stimuli sufficiently, and neuromotor delay was diagnosed by his doctor. Physical examination revealed a height of 106 cm (50-75p), the weight of 19.6 kilograms (75-90p) and head circumference of 50.1 cm (25-50p). Dysmorphic examination results of the patient are; high palate, bitemporal shortness, dolichocephaly, kyphosis, elbow hyperextension were detected.
Other laboratory results except for mild anemia (10.7 g / dL) were found to be normal. Urinary system USG normal and external genital development show male morphology. Karyotype analysis of peripheral blood cells revealed 47, X, idic (Y) (q11.22) x2. Fluorescent in situ hybridization (FISH) method using metaphase and interphase cells for SRY and CEP X / Y probes were revealed following results. For CEP X/Y 47,X,idic(Y)(q11.22)x2.ish idic(Y)(q11.22)x2(DXZ1+,DYZ3++++). For SRY 47,X,idic(Y)(q11.22)x2.ish idic(Y)(q11.22)x2(SRY++++,DXZ1+,DYZ1-). Also the SNP-array CGH method was used and the following result were obtained arr[GRCh37]Yq11.22q11.23(15634354_28609922)x0, arr[GRCh37]Yp11.32q11.2(10701_8875193)x4, arr[GRCh37]Yq11.21q11.221(14543044_15571838)x4.
According to literature, the isodicentric (Y) cases are usually mosaic and accompanied by gender development disorders. Also, neuromotor delay and a wide range of dysmorphology are observed in rare chromosomal tetrasomies. In our case, we represent a rare condition in which there are no mosaic features, no unambiguous genitalia, but there are dysmorphic findings and neuromotor delay. We believe that this case will be useful for the clinical signs of the patients with structural abnormalities of the Y chromosome and for the follow-up of treatment.

Key Words: Isodisentric (Y), SRY, Neuropsychiatric Disorders

S-068 – Clinical Findings in a Patient with 1p36 Microtriplication

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Copy number variatons are found throghout the genome and while some of them have pathological phenotypical effects, the others do not .CNVs in 1p36 region always result in a pathological consequences.1p36 microdeletion syndrome is the one of the most common microdeletion syndrome. Nevertheless, two pure microduplication and only one pure microtriplication of the same region have been reported in the literature so far.We present the second pure microtriplication of 1p36 and discuss similarities and differences with previouly reported patients.
The patient was a 9 month old, full term male infant whose parents were consanguineous(second degree cousins).He was first referred to our center with the complaints of feeding problems and hypotonia.On physical examination, his head circumference was 43 cm(<3p),length was 70 cm(<3p), weight was 6300 gr(<3p) and he had dysmorphic features including hypertelorism,brachicephaly,low nasal bridge,upslanting palpebral fissures,broad philtrum.he was also hypotonic and had global developmental delay.Magnetic resonance imaging of central nervous system demonstrated widened subarrachnoidal space along with subdural hemorrhagia and echocardiography revealed both secundum Atrial septal defect and left pulmonary artery stenosis.
Microarray analysis revealed 2.447 kb triplication in 1p36.33p36.32 region.This region involves 27 OMIM genes including PEX10,PANK4 that are considered to play an important role on the pathogenesis of tetrasomy 1p36 syndrome.
It is known that there is a large clinical heterogeneity between patients with 1p36 rearrangments. Developmental delay,hypotonia and seizures are common clinical findings found in most of the patients reported in the literature. Although the patient had global developmental delay,hypotonia and dysmorphic futures similar to the previously reported case with 1p36 microtriplication,he did not have any seizure history and also, he had cardiovascular defects which were not detected in the previously reported 1p36 tetrasomy case.In addition, another difference between these two cases is the size of triplicated segment and number of the genes involved.Taken all together, the involvement of different genes in these two patients might have contributed to the clinical differences between them.

Key Words: Microtriplication,Tetrasomy 1p36, Copy Number Variants

S-069 - The Importance of Increased Spontaneous Chromosomal Breakages in the Differential Diagnosis of Chromosomal Breakage Syndromes

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Chromosomal breakage syndromes are a group of rare genetic syndromes inherited in an autosomal recessive fashion. The most common ones are Fanconi anaemia, Nijmegen breakage syndrome, Bloom syndrome and Ataxia telangiectasia. Their common characteristic of this group of diseases is the chromosomal instability and their susceptibility to cancer. Cytogenetic investigations are important in the diagnosis of these syndromes. In this study, we present a case who was referred to the cytogenetics laboratory for DEB test on suspicion of Fanconi anemia and was considered to have Bloom syndrome as a result of the re-evaluation of the case after the cytogenetics analysis.
A 17-year-old male who was referred for DEB test was subjected to cytogenetic examination and DEB test. Chromosomal anomaly was not found in the cytogenetic analysis performed in 72 hours of culture. Control culture revealed 34 chromosomal breakages in 50 metaphases and examination of the blood sample induced by the DEB before the 72-hour culture revealed 49 chromosomal breakages in 50 metaphases. The rate determined in the DEB test was found to be 0.3 which was in the normal ranges. Re-evaluation of the patient in the light of cytogenetic analysis in which high chromosomal breakage rate was found both in DEB and control cultures, Bloom syndrome was considered.
Spontaneous chromosomal breakages and rearrangements are seen particularly in Bloom syndrome, Fanconi anemia and Ataxia Telangiectasia syndrome. Normal rate of DEB testing and increased number of breakages detected both in the control and DEB tests required re-evaluation in terms of other chromosomal breakage syndromes. Cytogenetic examination and the results of DEB test should not only be considered as just a laboratory result but also they should be evaluated together with the clinical findings of the patients.

Key Words: DEB Test, Fanconi Anemia, Bloom Syndrome

S-070 - A New Family with 3q27.3q29 Interstitial Deletion

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Microdeletions affecting the 3q27.3q29 region are very rare and have previously been reported to cause characteristic facial appearance, marfanoid habitus, and intellectual disability, psychosis and mood disorders. Here we present a family with two different deletions in the distal part of chromosome 3 with the length of 7.4 Mb and 442 kb, on the q27.3q29 and q29 region, respectively.
One of two brothers, whom ages are 8 and 12, displayed behavioral disorders, EEG disorder, hypospadias and slender build while skin dryness and short stature were observed in the other one, and both were accompanied by intellectual disability. Also, the father had behavioral problems, slender build and strabismus.
Cytogenetic, FISH and array CGH (Agilent Array SNP + CGH 4x180K) analysis from the affected patients and the father revealed two deletions with the length of 7.4 Mb and 442 kb, in the q27.3q29 and q29 region of the chromosome 3, respectively.
Different clinical findings among three patients presented here could be associated with variable expressivity, reduced penetrance and change or disappearance of symptoms as age progressed, although all had the same deletion. Since the SST(somatostatin), which has been suggested as a candidate gene in the literature for the psychiatric findings observed in the patients with deletions in this region, is intact in our patients, different single gene or genes could be responsible for these findings in the deletion site or that the phenotype could be exposed due to the position effect.

Key Words: 3q27.3q29, Microdeletion

S-071 - Importance of Indication Criterıa in Determining Diagnostic CNVs in Patients with Multiple Congenital Anomaly/Mental Retardation

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Developmental delay/intellectual disability is an important group of disorder.Etiology is heterogeneous including genetic factors. In recent years, array-comparative genomic hybridization (Array-CGH), by which genomic copy number variations may be identified, has been used as a first-tier genetic test in this patient group with a diagnostic yield of 10-20% (Bartnik et al.,2014). In our study, it was aimed to determine the CNVs that could be associated with the clinic of the patients.Besides, major aim of the study was to investigate ways to increase diagnostic yield of array-CGH in a well-selected patient population.
Samples from 30 patients with multiple congenital anomaly and/or mental retardation whose cytogenetic analysis with at least 550 band-level, subtelomeric FISH and additionally fragment analysis for fragile X in males, were routinely carried out and reported to be normal; were analysed with array CGH in the context of this study.
With array-CGH, pathogenic copy number variants were detected in eight cases (27%). Three cases had well-defined microdeletion syndromes (17q12, 1q43-44 and 14q11-q22 Deletion Syndromes). Another three had well documented microdeletions that are known to have variable penetrance and expression (CNTN4 deletion in 3pter-p25 Deletion Syndrome region, 15q11.2 and 16p11.2 Deletion Syndromes). One case presented with 8p23.1 deletion which spans GATA4 gene and last had Lowe Oculocerebrorenal Syndrome due to deletion of the OCRL gene.
Genomic changes which could be associated with the patients' clinic were identified at a rate of about 27% in this study. Although this ratio was higher than the literature data, it could be due to patient selection criteria which is clinical symptoms of more than one system accompanying intellectual disability, including non-consanguineous parents. As a result of these, cost-effectiveness of array-CGHs rises. Well-defined microdeletion syndromes make up approximately half of the patients who have CNVs. Thus, for increasing cost-effectiveness, an array-CGHs analysis that encompasses targeted regions covering all well-defined microdeletion syndromes' locus may be suggested as a first-tier genetic test.As a consequence of decrease in the cost of the test by developing methods like loop hybridization or increase in the platform diversity creating a competitive atmosphere, we can assume that test utilization may increase in the near future.

Key Words: Array-CGH, Multiple Congenital Anomaly, Mental Retardation, Loop Hybridization

S-072 - A Case with 414 Kb Duplications at 15q13.3

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Examining the case with hearing loss and 414 kb duplication detected in 15Q13.3 by microarray analysis
Copy number variants are associated with mental disability, multiple congenital anomalies and craniofacial anomalies. Changes in the region of 15q13 are particularly associated with highly variable phenotypes in the literature. Boundary intelligence and learning difficulties are associated with cleft palate and cleft palate as well as in healthy societies. The cholinergic receptor, neuronal nicotinic, alpha polypeptide 7 (CHRNA7) gene found in this region has also been associated with epilepsy. The wide variability of the problems associated with duplication of 15q13.3, even among members of the same family is related variable expressivity; The lack of any medical, developmental, or behavioral problems of persons with some 15q13.3 duplication is explained by reduced penetration. in our case with 15q13.3 duplication, hearing loss is different from the literature. Our case, which was born from the first pregnancy of a 17-year-old mother, had loss of vision for up to 8 months in addition to congenital hearing loss. Other system examination findings of the patient were normal. In the second pregnancy in the family with a consanguineous marriage (cousin marriage), the fetus IU was ex-37 weeks.applied to the family genetics department a few months later
Primarily from the case,whole gene sequence analysis GJB2 gene for the hearing loss and karyotype analysis was planned. No pathological mutation was detected in the GJB2 gene, but c.79G> A p.Val27i rs2274084 was detected. Karyotype analysis revealed that shortening of 13 chromosome satellites and the clinic could not be explained. Karyotype analysis of the parents was normal. At the end of the microarray analysis, a duplication of 414 kb was detected in 15q13.3. The study was started to investigate whether the same duplication was in the parents.
Changes in region 15q13 are associated with a highly variable phenotype. We are still working on whether the clinical picture in our case is caused by the duplication of 15q13. Considering that the duplication of 15q13.3 is of low penetrance, it is thought that the father may have a 15q13.3 duplication and the possibility of being normal or a denova variation.

Key Words: Hearing Loss, 15q13.3 Duplication, Microarray

S-073 - A Rare Form of Interstitial Deletion of Chromosome 9q21.33q22.31: A Case Report

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9q22 interstitial deletions, where PTCH1 gene (9q22.32) associating with Gorlin syndrome is conserved, are very rare and have been reported to cause microcephaly, developmental delay, delayed speech and language development, specific speech disabilities, and behavioural problems. Here we present a patient diagnosed with a 6.6 Mb interstitial deletion at the 9q21.33q22.31.
A 7-year-old male patient was referred to our clinic due to intellectual disability, speech disabilities, behavioural problems, and dysmorphic features. In physical examinations, he had a short stature, dysmorphic features including microcephaly, triangular face, thick and small ears, fifth finger clinodactyly, and toe brachydactyly. He was suffering from feeding difficulties and chronic constipation.
As a result of chromosomal microarray (Agilent 8x60K ISCA) analysis, a 6.6 Mb microdeletion toenails at 9q21.33q22.31 region. The deletion did not involve the PTCH1 gene, but instead 82 other genes.
Although the microdeletions encompassing 9q22 are not very exceptional, there are only 9 case reports, 3 of which are familial cases, which were reported by clinical information and results of microarray analyses revealing that deletions do not include PTCH1 gene. According to data obtained from our case and other reports in the literature, genotype-phenotype correlations figured out that behavioural problems would be associated to an approximately 3.1 Mb deletion between 90th Mb and 93rd Mb (hg19) while delayed speech and language development and specific speech disabilities could be linked to a 2.1 Mb deletion between 93rd Mb and 95th Mb region of chromosome 9. Other phenotypic properties and genotypes could not be correlated.

Key Words:9q22 Interstitial Deletion, 9q21.33q22.31, Speech Disabilities, Intellectual Disability, Array CGH

S-074 - A View from Cytogenetıcs to Clinic: Evaluation of 40019 Peripheral Blood Chromosome Analysis

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In this study, we aimed to evaluate 40019 peripheral blood chromosome analysis studied at Haseki Training And Research Hospital, Diagnostic Center Of Genetic Diseases, Postnatal Cytogenetics Department between August 2016-September 2018.
Lots of clinical entities such as; growth and developmental delay, multiple congenital anomalies, aneuploidies, fertility problems, habitual abortus, puberty problems, ambigious genitale cases, familial chromosomal abnormalities can be investigated by cytogenetics evaluation. For accurate identification of those clinical entities that arised from numerical and structural anomalies of chromosomes, a series of work should be performed. After obtaining peripheral blood sample, culture, spreading, staining, banding processes ought to be done according to quality standarts and also karyotyping should be reported with a suitable genetic counseling note according to ISCN criteria.
40019 peripheral blood chromosome analysis evaluated according to frequencies by means of indications, age, gender, and results. The most common referral reason was habitual abortus couples with14797(37%) cases. Infertility was the second most one with5148(12,9%) cases. Other common indications were, Down's syndrome1312(3,3%), syndromic/dysmorphic babies1124(2,8%), short stature1100(2,7%), child history with anomalies/neonatal deaths1058(2,6%). Most frequent age group was 18-44 with27552(%68,9) cases. 20680(51,7%) of cases were female gender. The most common anomalies were aneuploidies. Beside 1008 classical trisomy21, Down's syndrome cases reported with 28 robertsonian translocation which 15 of have 21q21q translocation. Klinifelter's syndrome(47,XXY)was the second most common aneuploidy with219 cases. There were 75 Turner's syndrome with 45,X karyotype, and also there were 14 of 46,X,i(Xq), 21 of 45,X/46,X,i(Xq) mosaic cases. The most common structural anomaly was reciprocal translocations which seen at409(1%) of cases. 69 of 96 robertsonian translocation carriers had rob(13:14) chromosomal structure. The incidence of pericentric inversion of 9th chromosome that alreday known as polymorhism was725(1,8%).
Cytogenetic studies are still have an important role at clinical genetics despite recently developed platforms in genetics. Peripheral blood chromosome analysis is considered as gold standart at plenty of diseas by means of diagnostic and cost calculations beside being a sensitive work requires experiment. We have reviewed 40019 chromosome analysis that studied in our laboratory and aimed to present by means of indications and results, according to numerical and structural anomalies,and also polymorphisms and mosaicisms

Key Words: Cytogenetics, Chromosome Analysis, Aneuplodies, Translocations, Polymorphisms

S-075 - Geneotype Phenotype Correlation in a Very Rare Case with De Novo Interstitial 12q15q22 Deletion

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12q interstitial deletion syndrome is a very rare entity that presents variable clinical findings depending on the gene contain and the size of the deletion. Growth retardation, developmental delay, hypotonia, facial dysmofism and 2-3. syndactyly of toes have been described in these patients. In the literature only a few case have been reported with intersitisial deletions of the 12q15 region
We are presenting a 2-month-old male patient with growth retardation, developmental delay, hypotonicity, and dysmorphism. He was born to a nonconsanginous parents. Bilateral ventriculomegaly and megasisterna magna were detected in the prenatal period. At 2 months age, his weight was at 3p, his height and HC measurements were at 3-10p. He had midfacial hypoplasia, large anterior fontanel, broad forehead, micrognathia, long philtrum, high palate, hypertelorism, microphthalmia and ptosis, broad depressed nasal root, bulbous nose, and low-set ears. Pectus excavatum, rocker bottom feet and 2-3. partial syndactyly, corneal dystrophia, and PFO were also detecte. At 19 months of age, patient's weight, height and HC was under 3p and could only sit with asist.
In the karyotype analysis, derivative chromosome 12 indicating an interstitial deletion of 12q15-q22 was detected. The array-CGH analysis also verified the interstitial deletion of 23.3 Mb in this region. Karyotypes of the parents were normal.
In the literature, deletions of the 12q15 region have been defined in only 14 cases. In these patients, developmental delay, growth retardation, hypotonia, facial dysmorphism and 2-3. syndactyly of toes were described. In our patient, these findings were also present. Also additionally ventriculomegaly, nystagmus and corneal dystrophia were present in our patient. The CNOT2 involved in mRNA processing, KCNMB4 involved in the control of smooth muscle tone and neuronal excitability, PTPRB involved in cell division and differentiation were critical for typical fascial features. Corneal dystrophia in our patient aslo could be associated with PACD, CNA1 and DCN gene deletions. We report a case that refines the genotype-phenotype correlation of a very rare syndrome.

Key Words: Dysmorphism, Developmental Delay, Interstitial 12q15q22 Deletion

S-076 - Maternal Deletion of 14q32.2 Causing Kagami-Ogata Syndrome (KOS14)

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Kagami-Ogata Syndorme (KOS14, MIM#608149) is reported in about 60 individuals around the world. KOS14 can occur as a result of paternal uniparental disomy of chromosome 14 (UPD14), maternal deletion of the imprinting region of 14q32.2, hypermethylation of IG-DMR and/or MEG3-DMR. Affected individuals are characterized by prenatal polyhydramnios, growth retardation, distinctive facial gestalt, small bell-shaped thorax, pathognomonic “coat-hanger” appearance of ribs during infancy, kyphoscoliosis. There are only several reports of individuals that reach adulthood and the aim of this presentation is to discuss a female child with maternal deletion of 14q32.2, resulting in KOS14.
Patient presented at the age of 2.5 as the term child of a healthy non-consanguineous couple. Prenatally, polyhydramnios was detected at the 24th week and she was followed at newborn-intensive-care-unit with mechanical ventilation support after birth. It was noted that she hospitalized frequently due to respiratory distress in early months requiring tracheostomy and PEG. Initial examination revealed; global developmental delay secondary to hypoxia, prominent forehead, bitemporal narrowing, deep-set eyes, wide prominent nose root, pinched nose tip, cupid’s-bow upper lip, dome-shaped narrow palate and severe kyphoscoliosis. Since severe hypotonia was detected, further evaluation planned for muscle disorders but the patient quit follow-up.
She re-evaluated when she admitted for kyphoscoliosis surgery at the age of 5 and initial diagnosis of paternal UPD14 was considered. Chromosomal microarray (CMA) and UPD analysis was planned. CMA detected 1.08 MB deletion in arr[hg19]14q32.2q32.1 region. 6 STR markers from the deleted region was analyzed both in mother and the child, and revealed 3 markers of the child were only from the father and maternal copies were missing.
KOS14 should be considered in infants with respiratory distress during newborn period, especially if narrow thorax and “coat-hanger” appearance of ribs is detected. Even a deletion is not detected by CMA, further evaluation should be planned for paternal UPD and other mechanisms. When KOS14 is considered, performing CMA and methylation analysis together should shorten the time of diagnosis. Despite from developmental delay that occurred due to hypoxic episodes during early infancy, further follow-up of our patient after a successful surgery for kyphoscoliosis should contribute to the literature about KOS14.

Key Words: Uniparental Disomy, Kagami-Ogata Syndrome, KOS14, Imprinting

S-077 - A Novel Homozygous Frameshıft Mutation in PVRL4 Causes Ectodermal Dysplasia-Syndactyly Syndrome 1

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Ectodermal dysplasias (EDs) are a group of genetic diseases that are characterized by changes in ectoderm-derived tissues such as hair, nails, teeth and sweat glands. Ectodermal dysplasia-syndactyly syndrome (EDSS1) is a rare form of ED that occurs as a result of homozygous or compound heterozygous missense and nonsense mutations in Nectin-4, a cell adhesion molecule, encoded by the Poliovirus Receptor Releated-4 (PVRL4) gene. We aimed to report a case with homozygous mutation in the PVRL4 (NECTIN4).
A 29-year-old woman was referred to Medical Genetics outpatient clinic because of skin tension and mask like facial appearance. In physical examination; complete alopecia, conical teeth and enamel hypoplasia, thickened and dysplastic nail structure, cutaneous syndactyly in hands and feet were detected. There was a second degree cousin marriage between his parents and no other family member had similar findings. PVRL4 gene study was planned for the diagnosis of EDSS.
DNA obtained from the peripheral blood sample of the case was amplified by PCR and NGS targeted sequencing was performed. Although the change has not been previously reported in the literature, it is predicted to be pathogenic because it couses a frameshift mutation and creates an early stop codon.
EDSS1 results from homozygous / compound heterozygous mutations in the PVRL4 gene. This gene contains 9 exons, which encodes the 510 amino acid-sized nectin-4 protein, which cooperates with cadherins to form cell-cell adhesion, especially at adherence junctions. In the literature, a few families from different ethnic origins have been identified mutations known to be pathogenic in the PVRL4 gene. Affected cases have, sparse or absence hair, eyebrows and eyelashes, wide range of conical and peg-shaped teeth, bilateral cutaneous syndactyly, hyperhidrosis, palmoplantar keratoderma, and flat, thickened hypoplastic hand and toenails. Although the present case has the clinical features of EDSS1, the change is important because it has not been previously reported in the literature.

Key Words: PVRL4, NECTIN4, Ectodermal, Dysplasia, Syndactyly

S-078 - Investigation of FBN1 Gene Mutations in Clinically Diagnosed 10 Pediatric Marfan's Syndrome Patients

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Marfan's syndrome(MFS) is an autosomal dominant multisystem disorder of connective tissue caused by mutations in FBN1 gene. FBN1 gene located on 15q21.1, encodes fibrillin-1 protein. Although the incidence of Marfan syndrome is reported to be approximately 1/5000-10000, the exact incidence is unknown due to the high clinical variation and the difficulties in the molecular diagnosis. Cardinal manifestations of Marfan's syndrome depend on typically involvement of the cardiovascular, skeletal, and ocular systems. Due to high clinical variability, diagnosis usually establish according to revised Ghent (Ghent-2) criteria. The aim of this study, investigation of FBN1 gene mutation spectrum and genotype-phenotype correlation in 10 pediatric Marfan's syndrome patients referred to molecular genetics laboratory of Medical Genetics Department, Ege University for molecular analysis between the period of 2016-2018.
Ten pediatric patiens were diagnosed as MFS according to Ghent2 criteria, by experienced clinic genetician. FBN1 gene exons and exon-intron boundaries were molecularly analysed using a NGS platform and genotype-phenotype correlation was investigated.
FBN1 gene mutation was detected in 7 (70%) of 10 patients with a average age 12,8. In three patients, three previously described mutations, c.2585G>A (p.C862Y), c.529T>C (p.C177R) and c.6037+2 T>C were detected in FBN1 gene. Family history of MFS was found in 2 of 3 patients. All those patients' Ghent scores were >7 and they have ocular involvements. In four patients whose Ghent scores were also >7, four novel muatations were identified. Those novel mutations were c.6821 G>T (p.C2274F), c.1528_1531dup, c.7027delG (p.V2343Cfs*55) and c.5077_5078insT (p.S1693Mfs*10) and they found to be pathogenic using in slico tools. Aortic dilatation was observed in all the patients having novel mutations but they do not have significant ocular findings.
Marfan syndrome is a multisystemic disorder, causes life-threatening complications especially due to cardiovascular manifestations. The definitive) diagnosis of Marfan syndrome in pediatric cases is important to prevent complications, genetic counseling and to offer prenatal or preimplantation genetic diagnosis options to the families.

Key Words: Marfan's Syndrome, FBN1, Mutation

S-079 - Birt-Hogg-Dube Syndrome: Three Case Reports

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Birt-Hogg-Dube Syndrome (BHD) is an autosomal dominant genodermatosis characterized by benign tumors of the hair follicle, pulmonary cysts, spontaneous pneumothorax and renal tumors. Several germline mutations in the folliculin (FLCN) gene located at the 14th exon of the p11.2 region of the 17th chromosome encoding the protein called folliculin were found to cause disease. According to the literature, more than 100 cases have been reported in the world. We presented three cases diagnosed as BHD including two mothers and one daughter referred to our outpatient clinic from the dermatology department. Case 1; A 55-year-old woman with colon carcinoma who had been suffering for 10 years, had gradually progressed into the neck of the face, had diabetes mellitus, hypertension and gout, and her family history had already been diagnosed with colon carcinoma. The patient's tomography revealed multiple multicentric cysts in both lung parenchyma and hypodense lesions consistent with multiple cysts in bilateral kidneys. Genetic analysis revealed heterozygous c.1285dupC (p.His429Pro fs) variation in the 11th exon of FLCN gene of the patient. The patient also had a SNV in exon 7 (c.653G> A) (p.Arg258His) with no clinical significance (VUS). Case 2; A 76-year-old woman had a 50-year history of generalized moles in the face, who had colon cancer 10 years ago and a cystic lung disease of 2 months. In the family history; Her son had clear-cell renal carcinoma, and her daughter also our third case had spontaneous pneumothorax, and parotid parietal oncocytoma and similar moles. Tomography revealed bilateral cysts and ground-glass opacities in bilateral lung parenchyma. Abdominal ultrasound of the patient showed hypodense area compatible with cyst in the liver. Genetic analysis revealed a change in 11th position in FLCN gene in Case 1. Case 3; A 54-year-old woman who was the daughter of Case 2, in addition to her complaint about facial and neck mole for 30 years; she had a spontaneous pneumothorax 15 years ago and a history of oncocytoma of the parotist 10 years ago. Genetic analysis revealed the same genetic change in the mother. In addition to familial Cases 2-3, the first patient had a change in the 11th exon of FLCN. In a study conducted in the Japanese population, the FLCN gene c.1285dupC (p.His429Pro fs) variation was found in the majority of cases and the FLCN gene of this variation was thought to be a hotspot mutation.Although they were independent of each other, the same variation was observed. It can be shown that this change may be a hotspot variation for Turkish society. Although skin involvement is the most common symptom of the disease, lung and renal involvement is life threatening. This autosomal dominant disease is considered to be among the syndromes predisposing to cancer in some sources and the diagnosis of the disease at optimal time is of vital importance.

Key Words: Birt-Hogg-Dube Syndrome, rare

S-080 - Long QT Syndrome: Two Case Reports

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Congenital Long QT syndrome (LQTS) is a disorder of ventricular myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG). It can lead to syncopes, ventricular arrhythmias known as torsades de pointes and sudden cardiac death, especially after increased sympathetic activity. It is the result of defects in the genes encoding the ion channels in the myocard cell membrane. Type 1 LQTS is caused by KCNQ1 gene mutation and it accounts for 30 to 35 percent of cases of the LQTS. And type 2 LQTS is caused by KCNH2 gene mutation and it accounts for 25 to 40 % of LQTS. The clinical manifestations are variable. Patients may have no symptoms. It can be life-saving for the patients and their asymptomatic relatives when clinician question the family history and ask for a genetic consultation if necessary. We described two cases that we diagnosed type 1 and 2 LQTS in this report.
First case was 40 years old female. She appealed our clinic after she had a cardiac arrest during anestesia. 12 lead elektrocardiography showed presence of long corrected QT interval and presence of negative U waves. She has family history of sudden deaths. Her sister, her mother and her mother's sister had dead suddenly at the age of 30, 44 and 39, respectively. Our other case is 51 years old male patient. He has been followed for septal hyperthrophic cardiomyopathy by a cardiology clinic. He has family history of sudden cardiac death.
In a next generation sequencing analysis, we detected patogenic, heterozygote, c.172G>A (E58K) variation on the KCNH2 gene of our first case and patogenic, heterozygote c.1768G>A (A590T) variation on the KCNQ1 gene of our second case. We called family members for genetic councelling and testing.
After detection of pathogenic variations in two patients, ß-blocker therapy was prescribed and implantable cardioverter-defibrillator (ICD) was applied to prevent sudden cardiac deaths by cardiology clinic. Also family screening was initiated for detection of symptomatic and asymptomatic family members. In conclusion, the importance of genetic diagnosis in UQTS patients and their families has been demonstrated and two new cases have been presented.

Key Words: Long QT Syndrome, Sudden Death, Genetic Counseling, KCNQ1, KCNH2

S-081 - Early Onset Retinitis Pigmentosa Case Detected to Have Mutations in CRB1 and C2ORF71 Genes

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Homozygous mutations in the CRB1 gene are effective in a group of hereditary retinal dystrophies range from Leber congenital amaurosis to autosomal recessive retinitis pigmentosa. Homozygous mutations in C2ORF71 gene also cause to retinitis pigmentosa. A case with both CRB1 and C2ORF71 gene mutations and his family will be discussed with clinical findings.
A 10 years old boy diagnosed with bilateral corneal dystrophy and bilateral chorioretinal dystophy was referred by ophtalmology clinics. It had been realized that he coudn't see in the dark at 9th months. Also he had hyperopia. There were no additional features in the history of our case whose motor and mental development were consistent with his age. His parents were distant relatives. His grandmother was said to have nyctalopia since she had been 6-7 years old and started to lose her sight in the daylight since 1-2 years. Two sisters and a brother of the grandmother had also ophthalmologic problems started after age 30 and couldn't be well described.
A gene panel including 58 retinitis pigmentosa related genes was performed to our case by next generation sequencing method. Likely pathogenic, novel, heterozygous I1003S (c.3008T>G) and likely pathogenic heterozygous A161V (c.482C>T) mutations were detected in CRB1 gene. A pathogenic, heterozygous 2756_2768del mutation was also found in C2ORF71 gene. Blood samples were taken from parents, brother, grandmother and one of her sisters for the gene analysis. His parents were carriers for the CRB1 mutations. His grandmother and her sister were detected to have homozygous C2ORF71 mutation.
In this report we wanted to discuss the segregation of two different retinitis pigmentosa causative gene (CRB1 and C2ORF71) variations in the same family and to evaluate the phenotypic consequences.

Key Words: CRB1, C2ORF71, Retinitis Pigmentosa

S-082 - Three Novel Mutation in Twenty Patients with Hereditary Spastic Paraparesis

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Hereditary spastic paraparesis (HSP) constitutes both genetic and clinically heterogeneous group of upper motor neuron diseases. To date, more than 76 genes have been reported that associated with HSP and 50% of individuals with autosomal dominant (AD) HSP have mutations in SPAST, ATL1 and REEP1 genes. This study was conducted to elucidate genetic etiology of patients with pure type AD-HSP diagnosis.
The patient group consisted of 23 individuals from 6 families. In first phase of work, Sanger sequencing (SS) was performed in ATL1, SPAST and REEP1 genes and in second phase, whole exome sequencing (WES) was performed patients with no mutation in these genes.
In ATL1; 6 patients have previously reported c.776C>A mutation and 6 patients have novel c.470T>C mutation and in SPAST; 3 patients have novel c.1072G>C mutation and 2 patients have novel c.1099-1G>C mutation. WES was performed in three patient, who had no mutation these genes, previously reported c.1859 T>C mutation in KIAA0196 was detected and it was confirmed in relatives by SS. In three of patients, any HSP associated variant could not be identified in SS and WES. Molecular genetic etiology was elucidated 20 of 23 (87%) individuals included study with utilization SS and WES.
Since HSP is a heterogeneous disease, all mutations can not be detected by SS and WES. Advanced genetic methods are needed to show other mutations that are thought to cause disease. Utilization of SS and WES methods have enabled identification of genetic etiology of HSP, and provision of appropriate genetic counseling.

Key Words: Hereditary Spastic Paraparesis, Novel Mutation, Whole Exome Sequencing, Genetic Heterogeneity

S-083 - First Noonan Patient with Glomuvenous Malformations with GLMN Mutation

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Noonan syndrome is a common autosomal dominant disorder characterized by clinical findings of facial dysmorphism, congenital heart disease, and short stature. This syndrome is caused by some genes encoding proteins of the RAS-MAPK (mitogen-activated protein kinase) signaling pathway. Glomuvenous malformations (OMIM 138000) are hamartomas presenting in childhood as multiple, bluish, soft papules and nodules. This syndrome is caused by autosomal dominant mutations in Glomulin (GLMN) gene. Herein we present the first Noonan patient with Glomuvenous malformations.
Nine years old girl was reffered to us for short stature. She was the second child of non-consanguineous Turkish parents. Her developmental milestones were normal. At the age of 9, her height was 122 cm (3-10th centile), weight 23000g (10th centile) and head circumference 52,5 cm. Physical examination, pectus excavatus, 10 cafe-au-lait spots and 6-8 venous malformations (bluish, soft papules) were noted. Additionally her father had multipl venous malformations on his legs. Routine blood tests, echocardiography and abdominal ultrasonography were normal. On the basis of the observed clinical findings, she was diagnosed as Noonan Syndrome and Venous malformations.
De-novo heterozygous c.836A>G (p.Y279C) mutation of PTPN11 and heterozygous c.108C>A (p.C36X) mutation of GLMN were detected in the patient. GLMN mutation was also detected in her father.
Our patient is the first Noonan patient with Glomuvenous malformations. Additionally, this patient and her father are the first Turkish patients with GLMN mutation.

Key Words: Glomuvenous Malformations,GLMN, Noonan

S-084 - Genetic Analyses of Patients with Lateral Temporal Lobe Epilepsy

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Autosomal dominant lateral temporal lobe epilepsy (ADTLE) is an inherited epileptic syndrome that characterized by focal seizures with auditory aura. Mutations in LGI1 (Leucine rich glioma inactived 1) gene known to cause %50 of ADTLE families yet different genes have also been identified. In the first part of the study 26 ADTLE (13 female, 13 male) patients follow-up by epilepsy clinic was evaluated in terms of LGI1 gene. Patients that were found negative for LGI1 gene mutation were studied within international Epi25 project (http://epi-25.org) with whole exome sequencing (WES) method for comprehensive genetic analyses. Epi25 project's main goal is to investigate genetic underpinnings of rare and common epilepsies. In this study we aim to identify genetic reasons of ADTLE cases.
All patients underwent clinical, neuroradiological and EEG examinations by Istanbul Faculty of Medicine, Department of Neurology. A cohort of 26 LTLE patients with focal epilepsy with auditory aura and non-lesional in MRI enrolled to the study. All exons and exon-intron boundaries of LGI1 gene was screened with sanger sequencing. LGI1 gene mutation negative patients were studied in Epi25 project with whole exome sequencing and data analysis performed with our in-house bioinformatic approaches.
Sequence analysis of LGI1 in the cohort revealed a novel heterozygous variant (NM_032013.3:c.1013T>C, p.Phe338Ser) only in a single case with a negative family history of epilepsy (Kesim et al., 2015, PMID: 26773249). In data analysis we have identified novel RELN gene variant in a patient with a negative family history of epilepsy. In another independent patient we have found heterozygous TBC1D24 gene variant (rs545689324). WES data and segregation analysis of findings are still ongoing.
Identification of new gene/gene variants with whole genome approaches for rare diseases such as clinically well analyzed ADTLE cases are crucial. In our study identification of new variants in LGI1 and RELN genes supports diagnosis and bring up genetic counseling options for the patients and also shed a light on new treatment targets and pathogenesis of the disease.

Key Words: Neurogenetics, Lateral Temporal Lobe Epilepsy, Whole Exome Sequencing

S-085 - Homozygous NPHP1 Gene Deletion of Two Patients with Joubert Syndrome

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Joubert Syndrome is a rare genetic disease that has multiple subtypes and can be caused by more than 34 genes. Though most of the subtypes develop due to biallelic point mutations, JBTS4, an extremely rare subtype consists of neuromotor developmental delay, renal symptoms and pathognomonic Molar Tooth Sign detected by Cranial MRI, develop due to homozygous deletion of NPHP1 gene. Here we present, two unrelated patients who have similar clinical findings and microarray results.
First case, 7 year old male, was referred to our clinics for neuromotor developmental delay, chronic kidney disease, gait ataxia, intentional tremor, mirror image movement disorder and oculomotor apraxia. He has gained his head control around 1 year of age, he could sit without support at around 3 years old and he could walk and pronounce simple words at around 4 years old. At physical examination mild synophrys, long eyelashes, downslanted palpebral fissures, mild hypertelorism, broad nasal bridge, tubular nose, multiple cafe-au-lait spots on his back and hindfoot deformity was noted. Molar Tooth Sign(MTS) was reported at his Cranial MRI. The second case is a 10 years old male who was reffered to our clinics for profound neuromotor developmental delay and gait ataxia. He has gained his head control at around 3 years, pronounce simple words at 6 years and he was not able to walk. At physical examination, mild synophrys, long eyelashes, mild hypertelorism, upslanted palpebral fissures, broad nasal bridge, hypoplastic ala nasi, thin upper lip vermillion, hypermobile joints, dysmetria, dysdiadochokinesia and hindfoot deformity was noted. Molar Tooth Sign was reported at Cranial MRI.
Microarray analysis to both patients revealed the same 102.261 kb homozygous deletion including MALL and NPHP1 genes and was reported as arr2q13(110862477-110964737)x0.
JBTS4 is a rare subtype which constitutes approximately 1-2% of JS spectrum. To best of our knowledge, our patients are the first Turkish patients that have homozygous NPHP1 gene deletions and diagnosed as JBTS4. For elucidating the underlying molecular pathogenesis of the disease, further analyses are necessary to detect epigenetic factors and possible modifier genes in patients with the same deletion but with clinical heterogeneity.

Key Words: Joubert Syndrome, NPHP1, Microarray Analysis, Renal Involvement, Clinical Heterogeneity

S-086 - Screening of Common and Novel Variants in the MEFV Gene in Patients with Familial Mediterranean Fever (FMF) Symptoms by Using Next Generation Sequencing

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The MEFV gene encodes pyrin protein of 781 amino acid known to be involved in the inflammation process and found in leukocytes, monocytes and fibroblasts. The function of the pyrin has not been fully clarified yet studies have shown that this protein plays a role as a chemotactic inhibitor. The majority of patients with symptoms of Familial Mediterranean Fever (FMF) have variants affecting the function of pyrin protein in MEFV. In addition to the classical FMF phenotype, patients with atypical or additional findings are thought to have rare and novel variants that are unclassified (UVs). Thus, MEFV gene sequencing was performed in patients with FMF symptoms and screened common and novel variants in order to associate phenotype to genotype.
DNA isolated from the blood of 1514 patients (673 males, 841 females) who admitted to our clinic and all exons of MEFV gene (1-10) consist of 23 amplicons were amplified, gene sequence analysis was performed by using MASTR Dx Assay kit as well as compatible agents in Illumina MiSeq. The raw data was analyzed on the Sophia DDM and Sophia Genetics MOKA was used for variant annotation. Variant classification was perfomed by in silico algorithms, multiple bioinformatics databases and ACMG variant pathogenicity classification and allele frequencies were calculated by Haploview.
We found 105 variants of which 14 were novel, 75 were exonic (7 novel) and 30 were intronic (7 novel). Of these variants, 86 were rare (MAF<0.01), 4 were non-common (0.01≤MAF<0.05) and 15 were common (MAF≥0.05) variants. Of 7 exonic novel variants, 5 were VUS missense, 1 was likely bening synonymous and 1 was was likely pathogenic missense variants. The patient who had likely pathogenic variant had early-onset of FMF symptoms (at 2 years) and did not present classical FMF phenotype so he is being followed up. The symptoms show a wide spectrum from atypical phenotype to classical AAA phenotype in patients with VUS and likely bening variant.
In our study, several variants were identified that were not previously reported and not associated with FMF. Functional studies will be conducted to elucidate the role of these variants in the pathogenesis of the disease.

Key Words: Familial Mediterranean Fever (FMF), MEFV Gene, Novel Variant, Next Generation Sequencing, FMF Symptoms

S-087 - Rare and Specific Group Skeletal Dysplasia: Desbuquois Dysplasia

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Desbuquois dysplasia (DBQD, OMIM # 251450) is a recessively inherited dysplasia with multiple joints dislocations characterized by severe prenatal and postnatal growth retardation (below -5SD), joint laxity, short extremities and progressive scoliosis. Main radiographic findings are; short long bones with metaphyseal enlargement, 'Swedish key' appearance in the proximal femur (large trochanter) and advanced carpal-tarsal bone age with delta phalanx. Desbuquois dysplasia is a heterogeneous group with clinical and radiographic findings, and had been classified into two main groups depending on the presence (type 1) or absence (type 2) of characteristic hand findings. In addition, 'Kim variant' type which is a milder phenotype has been defined in patients with Korean and Japanese origin. Type 1 and 'Kim variant' type are caused by mutations in the CANT1 gene. Type 2 is caused by mutations in the XYLT1 gene. However genetic etiology is unknown in some patients.
Ten patients with DBQD from nine unrelated families were investigated clinically and molecularly. The patients were examined for CANT1 mutations by direct sequencing of all coding exons and their flanking introns.
CANT1 mutation was found in all patients. Nine patients had missense and one patient had a new nonsense mutation that was not previously reported. p.W125C in exon 2 found in three individuals from two different families and the p.R300C in exon 4 detected in five individuals from five different families were thought to be hotspot regions for the Turkish population. In our case series, only one patient had exon 3 mutation. In addition, exon 2 and 3 mutations were associated with severe osteoporosis.
Desbuquois dysplasia should be kept in mind in patients with severe growth retardation, advanced bone age, and joint laxity-dislocation, especially in consanguineous marriages. While the presence or absence of hand anomalies have been used to distinguish subtypes of DBQD, this finding is not distinctive to predict the molecular basis. This autosomal recessive disease, which has no clear clinical and genetic heterogeneity, is an easily recognizable phenotype in patients with congenital dislocations.

Key Words: Desbuquois Dysplasia, CANT1, DNA Sequencing Analysis, Dislocation

S-088 - Clinical and Molecular Characterization of Stuve-Wiedemann Syndrome in Six Cases

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Stuve-Wiedemann syndrome (SWS) is a rare, autosomal recessive skeletal disorder characterized by feeding difficulties, and congenital bowing of long bones. Mortality rate is high, due to respiratory insufficiency, hyperthermia and autonomic dysfunction. It is caused by biallelic mutations in LIFR. Here, we present 6 cases from 5 families with a definitive clinical and molecular diagnosis of SWS. The 6 cases are expected to contribute to the clinical and molecular diagnosis of SWS.
In this study, we report of fetal and postnatal 6 cases. We detected a femur-curvature in the antenatal ultrasonography in five patients. Prenatal and postnatal skeletal findings of all cases except one case were broadly consistent with SWS. Autonomic dysfunction was present in all cases.2 cases died due to respiratory failure.
All cases were born to consanguineous unions, prominent bowing of the femora in antenatal ultrasound was noted in five cases. Four different mutations were identified, one being a novel deletion leading to frame shift (p.Phe26Profs*16), and the remaining (p.Arg597Ter, p.Thr541Asnfs*6, p.Arg692*) being disease-causing. Two patients died due to respiratory insufficiency. One patient was initially being evaluated for Hereditary sensory and autonomic neuropathies due to reduced perioral pain sensation and self injurious behaviour, and lacking prominent skeletal findings, a diagnosis of SWS was possible through clinical exome analysis. Prenatal and postnatal clinical findings in all cases were broadly consistent with SWS
SWS should be considered in all cases with femoral bowing in antenatal ultrasound, especially when parents are consanguineous. Skeletal findings may be mild in some patients, even in juvenile age. p.Arg692*, previously reported as spesific in Turkish population, was observed in three of our cases, ascertaining it as a founder mutation.

Key Words: SWS, Stuve-Wiedemann, Antenatal, Founder, Clinical

S-089 - Mutation Spectrum and Genotype–Phenotype Correlation In 7 Hemophilia B Patients

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Hemophilia B (HB) is an X-linked recessive bleeding disorder with a prevalence of 1 in 30,000 live male births. Bleeding symptoms vary depending on the level of coagulation factor IX (FIX) activity. To date more than 1200 mutations have been reported in F9 gene, and approximately 70% of those are point mutations. The aims of this preliminary study are to identify F9 gene mutation spectrum and to investigate phenoptype-genotype correlation in patients with HB from Turkey.
Seven HB patients, molecularly analyzed in Ege University, were evaluated. Clinical and laboratory findings of all patients were obtained from their hospital records. Direct sequencing of the F9 gene was performed to identify the mutations responsible for HB. The identified mutations were searched in the Factor IX Gene Variant Database (FIXVDB) and Human Gene Mutation Database. Pathogenicity of all the variants (novel and previously known) detected was classified according to ACMG 2015 criteria.
Four of 7 HB patients molecularly analyzed had moderate phenotypes, whereas 3 of them had severe phenotypic findings. Missense variants were found in 3 (42.8%) of the patients, nonsense in 2 (28.6%) and splice site in 2 (28.6%). Two of 7 mutations (c.521-1G>A and c. 89-2_89-1insT) were novel.
This is a preliminary study investigating F9 mutation spectrum in HB patients from Turkey. Two mutations have been defined for the first time in this study.

Key Words: Hemophilia B, F9 Gene, Mutation Spectrum

S-090 - Prenatal Diagnosis Experience in a Family of Pathogenic Variants in the MTM1 Gene

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The incidence of myotubular myopathy is estimated at 1/50,000 male births. The disease, which is caused by mutations in the MTM1 gene, is characterized by significant weakness, hypotonia, respiratory failure and a severe phenotype in male infants. Signs of antenatal onset are frequent and comprise reduced fetal movements and polyhydramnios.
The couple who had consanguineous marriages and died in the neonatal period had a history of 2 boys. Hypotonia and respiratory failure were reported in the children they lost. When questioned, no apparent dysmorphic signs were found in children. Parental inherited panel was studied with an autosomal recessive or X linked inherited entity.
As a result of the inherited panel study, we identified previously unreported heteozygous variant in maternal MTM1 gene c.1493delT (p.Leu498TyrfsTer4) (NM_000252). Clinical findings were consistent and a previously defined non-sense mutation was reported in the same region. In addition, this variant created a premature stop codon with frameshift effect. Therefore, the variant was thought to be pathogenic. Prenatal diagnosis was planned by providing detailed genetic counseling.
The aim of presenting this study is to emphasize the possibility of genetic diagnosis with the application of comprehensive molecular tests to the parents, although there are no materials of clinically affected individuals.

Key Words: MTM1, Prenatal Diagnosis, Myotubular Myopathy

S-091 - Immun Deficıency to Glycosylation Defect Diagnosis: WES Effect

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Diagnosis of diseases by clinical findings has been applied as the basic principle of classical medicine for many years. In recent years, access to increased genetic information and tests has an impact on the diagnosis process. Instead of determining the genetic mutation after clinical diagnosis, in some cases first find genetic mutation to reach the clinical diagnosis ie the phenomenon of reverse phenotyping has entered our lives after whole exome sequencing(WES).

Key Words: WES, Sequencing, Reverse Phenotyping

S-092 - A Rare Spastic Paraplegia Family Diagnosed Via Reverse Genetics

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SPPRS(Spastic Paraplegia and Psychomotor Retardation with or without Seizures, OMIM:#616756) is a very rare autosomal recessive neurodevelopmental syndrome. Biallelic loss-of-function mutations in HACE1, which is an E3 ubiquitin ligase, underlie in this disease. In this study, we aimed to determine the genetic etiology and figure out the phenotype/genotype relationship of two brothers who suffered from spasticity, psychomotor retardation with or without seizures.
Two brothers who suffered from an intellectual disability, spasticity and abnormal gait referred to the genetics department for etiology. Both patients have hypotonia in early childhood, spasticity especially in upper limb, developmental delay. They both have dysmorphic features like brachycephaly, microcephaly, long eyelashes, prominent nose and smooth philtrum. Six years old patient also has pes equinovalgus, tapering fingers. Sixteen years old patient has epilepsy but his brother has no seizures yet.
Because of the consanguinity and two affected child in one family, an autosomal recessive inheritance was suspected. Their karyotype analysis and Array CGH (Comparative Genomic Hybridization) were normal. The affected individual which is 16 years old was analyzed by whole exome sequencing (WES). We determined homozygous novel c.2581G>C(p.Ala861Pro) mutation in HACE1 gene. Sanger sequencing of patient and other family members was performed after PCR of genomic DNA derived from whole blood. Heterozygous mutation in parents and homozygous mutation in other affected 6 years old child was found in Sanger sequencing.
Genetic etiology of two brothers who suffered from spasticity, psychomotor retardation find out with reverse phenotyping. Further molecular study of HACE1 should permit a better understanding of its genotype-phenotype relationships.

Key Words: Whole Exome Sequencing, Spasticity, Epilepsy, HACE1

S-093 - Can PDE11A Mutations Cause Benign Bone Tumors through the CAMP/PKA/PCREB Signaling Pathway?

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Whole exome sequencing (WES) may not uncover any causal variant in genes analyzed based on patients' clinical findings. However, variants on other genes bearing enough pathogenic criterion should be appraised with respect to how much it can explain clinical findings. Bone scintigraphy revealed osteopoikilosis in a 23-year-old woman. LEMD3 sequence analysis for Buschke-Ollendorff syndrome (multiple subcutaneous nevi or nodules, osteopoikilosis) did not find any causal variant. Since a benign bone tumor may be a shared finding of different conditions WES analysis was performed in peripheral blood DNA.
SureSelect Human All Exon V6 capture kit (Agilent) and Novaseq 6000 platform (Illumina) was used. The analysis was performed by the Verita Trekker® Variation Site Detection System and the Enliven® Variation Site Annotation Interpretation System (BGI). Variants with an allele frequency below 5% were obtained. American College of Medical Genetics and Genomics recommendations and guidelines were used for variant classification.
A causal variant was not found in "dense bone dysplasia" panel (14 genes). Heterozygous c.1829delA alteration in PDE11A was classified as likely pathogenic. Her mother was a carrier of the same mutation. PDE11A mutations cause "Pigmented nodular adrenocortical disease (PNAD), primary, 2". However, the ultrasonographic investigation did not indicate any solid mass in adrenal glands. Plasma renin, aldosterone, metanephrine or normetanephrine measures were normal. PRKAR1A, a tumor suppressor gene, is related to PNAD type 1. PRKAR1A also causes Carney complex, in which osteochondromyxomas may accompany with a frequency of 1%. PRKAR1A mutations render PKA hyperresponsive to cAMP, a suggested mechanism of how parathormone (PTH) stimulates tumor growth. PTH regulates osteoblasts via the cAMP/PKA pathway and leads to CREB phosphorylation and subsequent promoter binding of pCREB and gene transcription. Horvart et al. (2006) showed that PDE11A inactivating mutations beget high cellular cGMP, cAMP, and pCREB. Both PRKAR1A and PDE11A proteins exist in the same signaling pathway.
Bone tumors may be triggered via excessive promoter binding of the pCREB as enforced by high cellular cAMP. Structural reevaluation of the adrenal glands is required using computed tomography. A 24-hour urine cortisol measurement is needed for functional evaluation. PDE11A mutations may exhibit incomplete penetrance.

Key Words: Osteopoikilosis, PDE11A, CAMP/PKA/PCREB

S-094 - Two Variants Associated with Phenotype in TECPR2 and NKX6-2 Genes; Think Twice: In-Silico Prediction Tools or Family Screening?

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Interpretation of two variants that may be related to phenotype observed as a result of WES analysis by means of in-silico prediction tools and family screening.
Healthy-consanguineous parents's (23 year-old mother and 25-year-old father) second child were consulted to our unit for microcephaly, hypotonia and feeding difficulties.
Two variants were identified as a result of WES analysis; homozygous c.715 G>A in TECPR2 gene and homozygous c.771 G>C in NKX6-2. According to in-silico prediction tools, these variants were evaluated as probably pathogenic. Parents were heterozygous for both variants. The result of the analysis from other healthy sibling; heterozygous c.715 G>A in TECPR2 and homozygous c.771 G>C in NKX6-2.
Because of the chance of family screening, the patient was diagnosed as spastic paraplegia type 49. In a case sample, we aimed to illustrate the approach of detecting more than one variant associated with phenotype in WES analysis.

Key Words: Family Screening, Prediction Tools, NKX6-2, TECPR2, Variant

S-095 - Primary COQ10 Deficiency in Two Sibs Due to a Novel Mutation COQ4

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Primary coenzyme Q10 (CoQ10) deficiency is a group of mitochondrial diseases characterized by a phenotypic variability ranging from neonatal fatal encephalopathy to late-onset slowly progressive form including seizures,ataxia, dystonia, spasticity that may manifest at any age. Till date mutations in COQ2(MIM 609825),COQ4 (MIM 612898),COQ6(MIM 614647),COQ8A(MIM 606980),COQ8B (MIM 615567), COQ9(MIM 612837),PDSS1(MIM 607429), PDSS2(MIM 610564) were reported in primary COQ10 deficiencies. Among those genes, COQ4 was reported in 12 patients from 9 families. Herein, we report on two sibs with a novel homozygous missense mutation in COQ4 in order to further contribute to the delineation of the phenotypic spectrum.
Patient1 was the second child of healthy, consanguineous parents. She was born at 36 weeks of gestation with a birth weight of 3190g(25-50thcentiles). She was hospitalized in the neonatal intensive care unit for 6 days because of feeding difficulty. At 1month of age, rapid eye blinking and staring were noticed and anti-epileptic treatment was initiated. Profound developmental delay,growth retardation and increase in seizure frequency were noted despite the antiepileptic therapy in her following visits. She died at 2 years of age due to status epilepticus. Patient2,the younger brother,was born at 39 weeks of gestation with a birth weight of 3350g(10-25thcentiles). He was hospitalized in the neonatal intensive care unit for 6 days because of feeding difficulty and seizures beginning in third day of life. Progressive axial hypotonicity,swallowing dysfunction,global developmental delay,increased number and frequency of seizures despite anti-epileptic treatment were noticed in his following visits. Urine,blood amino acid,and urine organic acid examinations were normal in both patients. Brain MRI examinations and EGG studies revealed cerebellar atrophy and large-amplitude irregular slow wave pattern in both,respectively.
WES analysis was performed due to consanguinity and similarly affected siblings. A homozygous missense pathogenic variant was identified in the COQ4 gene. The patients were diagnosed with primary CoQ10 deficiency.
The differential diagnosis list is quite extensive and challenging in patients with epilepsy, hypotonia,and global growth retardation. In this group of patients with the history of consanguinity and affected siblings, WES analysis has a great importance in the enabling diagnosis,initiating possible treatments in the early stages and providing appropriate genetic counseling to families.

Key Words: Coenzyme Q10,COQ4,Neonatal Epilepsy

S-096 - Melatonin Inhıbits Angiogenesis and Wound Healing on Adult Fibroblasts and HUVECS

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Melatonin secreted by the pineal gland has a regulatuar role in body's circadian ritm. Melatonin has oncostatic effects on some tumor types. It inhibits the proliferation and metastatic behavior of human breast cancer cells. Melatonin also has antioxidant, antiinflammatory, antiapoptotic and antiageing roles. Angiogenesis is an important process in wound healing. Melatonin has angiogenic effect during repair of bone defects. Melatonin inhibits angiogenesis in human neuroblastoma cells by downregulation of VEGF. So, melatonin's role is not clear on angiogenesis and wound healing. Here, the possible role of melatonin on angiogenesis and wound healing was tried to explain on fibroblasts and HUVECs.
Human normal dermal fibroblast (ATCC/PCS-201-010) and human umbilical vein endothelial cells-HUVEC (ATCC/PCS-100-010) were used for cell culture studies. LD 50 dosages were found for melatonin in both cell types in MTT assay (10-3M, 10-6M). Melatonin solutions were added on fibroblast/HUVEC cell cultures for “cell viability assay” and “cell migration assay” studies. RT-PCR analyses were performed for gene expression studies. The genes which have angiogenic roles (VEGFA, VEGFB, VEGFC, FGF2, FGF3, FGF6, FGF11, IGF, PDGFA, PDGFD) were studied in this panel. Melatonin solutions in different concentrations were added on chick chorio-allantioc membrane (CAM) in fertilized eggs for finding angiogenesis with melatonin. “Tube formation assay” which represents the angiogenic roles of molecules was performed. Melatonin solutions were applied on HUVECs and the results were analyzed.
Melatonin decreased cell viability in 10-3M and 10-6M concentrations on both cell types. Melatonin decreased the cell proliferation on fibroblasts/HUVECs in the same concentrations. CAM model results revealed the antiangiogenic role of melatonin on only 10-3M concentration. Melatonin decreased the expression of VEGF gene family including VEGFA, VEGFB, VEGFC genes on fibroblasts/HUVECs. “Tube formation assay” results which represent angiogenic role of methionin revealed no change in cell proliferation in HUVECs in 10-3M and 10-6M melatonin concentrations.
Melatonin inhibits cell viability/proliferation/migration processes on both cell types. Angiogenesis are inhibited by melatonin as observed on CAM experiments. In its antiangiogenic affect the genes in VEGF family are used. Our results represents that melatonin can be used as an antiangiogenic agent in possible future clinical applications on certain conditions.

Key Words: Melatonin, Cell Viability, Cell Migration, Tube Formation Assay, Chorio-Allantoic Membrane

S-097 - Expression Levels of Inflammasome Complexes in Experimental Autoimmune Myasthenia Gravis Mouse Model(EAMG)

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The aim of this research is to determine the importance of inflammatory complexes in pathogenesis of Myasthenia Gravis (MG).
METHOD 1- EAMG(Experimental Autoimmune Myasthenia Gravis) induction in mice 2- RNA isolation 3- cDNA synthesis 4- Q-PCR
In the sera of AChR-CFA (patient) and CFA (control group) mice, the anti-AChR IgG antibody was measured by ELISA. 1/100 and 1/1000 antibody concentrations were determined and the DOMG model was confirmed. RNA isolation was performed on total lymph node from DOMG model and control group and caspase-1, NLRP3, IL-1B, GADPH, P2X7R and Akt-1 gene expression levels were examined with qPCR. The expression of NLRP3, IL-1β, P2X7R and caspase-1 was higher in the DOMG model group than in the control group, but no significant difference was observed in the expression of Akt gene.
Inflammasomes are multimeric protein complexes that regulate the activation of caspase-1 and form an inflammatory response. In our study, NLRP3 infiltration and increase in expression of caspase-1 in the DOMG model group of mice clearly reveals the role of inflammasomes in MG disease. P2X receptors are an important signal that activates inflammasomes. We confirm this finding in our study with the increase in the expression of P2X7R gene observed in the DOMG model mouse group.

Key Words: Myasthenia Gravis (MG), Inflammasomes, EAMG, Autoimmunity, NLRP3

S-098 - Proliferative and Differential Effects of Lentivirus-Mediated GLP-1 Gene Delivery on Pancreatic Beta Cells in Type 2 Diabetes

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Glucagon-like peptide-1 (GLP-1), which has been evaluated as a therapeutic agent for Type 2 Diabetes, stimulates glucose-induced insulin secretion (GSIS), and suspected to increase beta-cell mass through proliferation, neogenesis, and trans-differentiation. Additionally, reduced gastric emptying and food intake result in weight loss in the long run. Inhibition of glucagon release from the pancreatic alpha cells is another beneficial effect of GLP-1 relevant to diabetes therapy. Unfortunately, the incretin response to glucose is reduced in type 2 diabetes which is accompanied by a moderate degree of GLP-1 hypo-secretion.
In order to produce stable GLP-1 synthesis and secretion to compensate the reduced incretin effect, a GLP-1 encoding lentiviral vector (LentiGLP-1) was generated and its therapeutic efficacy was tested in experimental animal models of Type 2 Diabetes. Immunohistochemical analyses were performed on pancreatic sections dissected from LentiGLP-1 administrated rats to reveal the mechanism of beta cell expansion.
Intraperitoneal injection of LentiGLP-1 into obese diabetic rats broke-down insulin resistance, improved glucose tolerance, reduced plasma glucose levels and decreased plasma triglyceride levels. Reduced plasma glucose level was correlated with increased pancreatic beta cell mass. In addition to appearance of small insulin positive cell clusters on pancreatic sections, Ki67 (+) cells were observed in the acinar regions of pancreatic tissue.
Based on these findings, it is safe to claim that LentiGLP-1 vector should be assessed as a novel gene therapy modality for the treatment of patients with T2DM. Our findings also suggest that GLP-1 gene delivery promotes cellular proliferation of pancreatic cells. Grant Support: TUBITAK-112S114 References: Tasyurek, H. M., Altunbas, H. A., Balci, M. K., Griffith, T. S., & Sanlioglu, S. Therapeutic potential of lentivirus-mediated glucagon-like peptide-1 (glp-1) gene therapy for diabetes. Human gene therapy. 2018.

Key Words: Beta Cells, Gene Therapy, GLP-1, Lentıvırus, Type 2 Dıabetes

S-099 - Mutation Frequency of APP, PSEN1 and PSEN2 Genes in Turkish Early Onset Alzheimer Patients

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In this study, APP, PSEN1 and PSEN2 genes analysis were performed and mutations detected in 11 cases with early onset Alzheimer diagnosis. Mutational frequency and prognosis differences between patients with similar or different mutations were investigated and compared with the literature.
In this study, we retrospectively analysed genotypic and phenotypic data (APP, PSEN1 and PSEN2 sequencing analyses; disease onset age, family history and prognosis) from individuals who were referred to our outpatient clinic between January 2014 and January 2017 with early onset Alzheimer's disease diagnosis. We classified patients as mutated and non-mutated and determined the differences between in two groups and then compared with the literature.
In this study, we found mutation rate in early-onset Alzheimer's patients as 13.58% (11 of 81 patients), mutation rate in PSEN1 gene as 63% (7 of 11) and 36% in PSEN2 gene. There were no APP mutations in the study group. In our study, when we compared the age of onset in mutated and non-mutated patients we found a statistically significant difference (p: 0.038). However, no significant difference was found between in the patients with PSEN1 and PSEN2 mutation (p: 0.06).
In the literature, disease causing mutations have been reported mostly in PSEN1 gene and then in APP and PSEN2 genes, respectively. The PSEN1 mutations rate in our study is consistent with the literature, but APP and PSEN2 mutations frequency is not compatible with the literature. This result may be explained by the small number of patients or APP mutations may not be common in Turkish population. When we compare the age of onset, the results are consistent with the literature.

Key Words:PSEN1, PSEN2, Early Onset Alzheimer Disease

S-100 - The Effect of Genetic Factors which are Related with Vitamin D Metabolism to Obstructive Sleep Apnea Syndrome

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Obstructive sleep apnea syndrome (OSAS) is a common disorder characterized by repetitive episodes of decrease or cessation in nocturnal breathing due to upper airway collapse. OSAS causes excessive daytime sleepiness and low blood oxygen saturation, as well as it is associated with a significant cardiovascular morbidity and mortality. Since vitamin D deficiency and some variations in the genes which are related with vitamin D metabolism have found in an association with some disorders hence it may also be related with OSAS progression. Therefore the aim of this study is to investigate the association between vitamin D level, vitamin D receptor (VDR), vitamin D binding protein (VDBP) gene variations, and some other risk factors with OSAS.
Fifty patients who were diagnosed as OSAS were selected as patients and 50 healthy volunteers without any disease were selected as controls. First of all, DNA was isolated from peripheral blood. Then BsmI (rs1544410) and FokI (rs2228570) variations in VDR; rs7041 and rs4588 variations in VDBP were investigated with real-time polymerase chain reaction (RT-PCR). Other risk factors such as vitamin D level, smoking, alcohol intake, body mass index (BMI) etc. were also obtained from individuals. Results were evaluated by using statistical methods.
Statistically significant differences were observed between groups such as gender, BMI, vitamin D, total cholesterol, LDL, HDL, trigliseride levels; current smoker status, epworth sleepiness scale, excessive daytime sleepiness (EDS), apnea-hypopnea index (AHI) and waist circumference. Also AA genotype in BsmI, CA genotype in rs4588, CC genotype in FokI were found statistically significant in patients whereas TC genotype in FokI and GA genotype in BsmI were found statistically significant in controls. When the relation between risk factors and genotypes were investigated, statistically significant associations were detected for BMI, waist circumference, AHI, EDS, vitamin D and triglyceride levels.
In conclusion; VDR,VDBP polymorphisms, vitamin D deficiency and some other risk factors were found to be related with OSAS. Possible tracking of these variations and risk factors with some other studies may help to clarify the mechanism of OSAS.

Key Words:OSAS, VDR, VDBP,Vıtamin D, RT-PCR

S-101 - Association of TOMM40 (Rs1160985 and Rs157581) Polymorphisms with Alzehimer Disease

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Alzheimer's disease (AD), a neurodegenerative disease characterized by progressive mental deterioration, is becoming increasingly prevalent as the population ages. An early defect in the pathogenesis of late-onset Alzheimer's disease (LOAD) is determined by mitochondrial dysfunction. The translocase of outer mitochondrial membrane 40 homolog (TOMM40) gene is one of the candidate genes that has attracted interest from researchers for mitochondrial dysfunction in LOAD. The latest studies demonstrated that the amyloid precursor protein (APP) in brains of AD patients aggregates in the import channel of TOM40 and in this way hinders the entry of numerous nuclear-encoded proteins. The aim of this work was to investigate TOMM40 polymorphisms (rs1160985 and rs157581) with AD in Turkish population.
DNA samples was taken from the blood of 38 AD patients and 100 healthy individuals. Analysis of the polymorphisms was done by using PCR/RFLP method. For the analysis of rs1160985 C>T polymorphism, F5'-GTACCCTGCTAGGCTCGAAA-3' and R5'-GCTGGCATCATCTCTCTGTG-3' primers were synthesized. The amplified 225bp region was digested by using ACCI restriction enzyme. For the rs157581 T>C region polymorphism, F5'-GGGTGGTAGGGAAGGAAGAG-3' and R5' GAGTAATTGGGCCGAGTGTG-3' primers were synthesized. The 224bp amplified region was digested by EcoRII restriction enzyme. Products were run in 3% agarose jel electrophoresis from which genotypes were determined.
As a result of this study, T minor allele in C/T heterozygote genotype of rs1160985 polymorphism of TOMM40 gene was higher in patient groups compared with healthy control groups. However the obtained results were not statistically significant (OR:1.19, P=0.553). Meanwhile TOMM40 polymorphism rs157581, genotype and allele frequencies in patients and control groups were compared but significant difference was not detected (OR: 0.75, P=0.432).
The obtained results doesn't approve the association of TOMM40 polymorphisms with AD. Yet we cannot say that TOMM40 is not a risk factor for AD. One of the reasons in which the results were not significant because of not having sufficient patient numbers. Especially in order to OR ratio of rs116085 polymorphism to be relevant we need larger number of patient groups. In future, to get more valuable results measuring the factors that affect the expression of polymorphisms especially the promoter region and TOMM40 expression in the blood is planned.

Key Words: Alzheimer's Disease, TOMM40, Polymorphism, Mitochondria, Memory

S-102 - Micro RNA Expression in Ankylosing Spondylitis

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We aimed to determine the expression levels of micro RNAs associated with T and B cell differentiation / stimulation in peripheral blood mononuclear cells and their relationship with the etiology of the disease in ankylosing spondylitis patients and healty controls. So the potential to be a biomarker and a target molecule for diagnosis of the disease and in the treatment respectively.
Fifty patients with AS and 50 healthy controls were included in the study. After considering the inclusion and exclusion criteria, first, peripheral blood mononuclear cells were isolated and RNA isolation, cDNA synthesis and quantitative real-time PCR expression analysis were performed. Then clinical findings and levels of disease activity were recorded using appropriate laboratory and measurement parameters.
At the patient and healthy control group, after detection of micro-RNAs associated with T and B cell differentiation / stimulation, the expression level of miR-142-5p and miR-143 was found significantly different ($p<0.05$). When compared to BASDAI, BASMI, BASFI scores, ESR level, HLA-B27 status, extraspinal signs and symptom duration, the level of expression of miRNAs was not statistically correlated. The expression of miR-143 was significantly higher in patients with high CRP levels ($p<0.05$).
At the current literature although there is limited data about miRNA expression associated to AS itself, miR-142-5p and miR-143 expressions were found important for the diseases sharing similar etiology with it. We think that miR-142-5p and miR-143 may play a role in the etiology of disease, especially miR-142-5p may be a diagnostic biomarker and a target molecule for the treatment. It might be an opportunity for the treatment if further researches using mRNA expression assays and cell culture analysis could be done.

Key Words: Micro RNA, Ankylosing Spondylitis, Epigenetics, Anti-MIR Treatment

S-103 - The Frequency of Mutations in Major Genes Associated with Fronto-Temporal Dementia in Turkish Dementia Patients

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Prolongation of life expectancy in the world and Turkey, and consequently with the increase of the elderly population, makes dementia a common health problem.Mutations in a growing number of genes in the most common types of dementia (Alzheimer's Disease, Fronto-temporal dementia, etc.) are responsible for the hereditary forms of the disease. The major known genetic causes of Fronto-temporal dementia are the mutations in the 'Microtubule-associated protein tau' (MAPT), the 'granulin' (GRN) and the 'chromosome 9 open reading frame72' (C9ORF72) genes. Recent studies suggest that mutations in these genes may also be associated with other forms of dementia. The main goal of this comprehensive study in the Turkish dementia patients was to identify pathogenic mutations and new variants in MAPT, GRN, C9ORF72 genes as well as other FTD related genes (such as CHMP2B, FUS, TARDBP, SQSTM1, VCP).
A combination of whole exome sequencing, genome wide association study and Sanger sequencing was performed for molecular screening of our study cohort consisting of 93 index patients with different types of dementia.
We determined one pathogenic mutation (c.1907C>T, p.P301L) and one novel missense variant (c.38A>G, p.D13G) in MAPT, a probably pathogenic TGAG deletion in the splice donor site of GRN exon 6. Three patients were found to carry the GGGGCC expansions in the C9ORF72 gene.
In summary, our results revealed a frequency of 5.2% of pathogenic mutations in the MAPT, GRN and C9ORF72 genes. Given the frequency of variants identified in these genes, a standardized molecular screening procedure for these genes should be implemented in Turkey.

Key Words: Dementia, MAPT, GRN, C9ORF72, Mutation, Exome Sequencing

S-104 - Polymorphisms of Growth Hormone and Growth Hormone Receptor Genes in Turkish Children with Idiopathıc Short Stature and Idiopathic Growth Hormone Deficiency

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In many endocrine disorders, polymorphisms of relevant human genes have been reported to be associated with polygenic diseases. Polymorphisms of genes taking part in hypothalamo-pituitary growth axis are also related to growth and height.An intronic single nucleotide polymorphism (SNP) of growth hormone gene (GH1), IVS4+90A>T,c.1663A>T, was reported to be associated with short stature in some populations, and a common polymorphism of growth hormone receptor (GHR), exon 3 deletion (GHRd3), associated with increased responsiveness to growth hormone (GH) was reported in various articles. We aimed to investigate the frequency and effects of these polymorphisms in our pediatric population.
We analyzed the frequency and distribution of this SNP in GH1, and its correlation to height in Turkish population. We also studied the association of GHRd3 polymorphism with normal height distribution, and with 1st year response to GH therapy. A total of 39 children with idiopathic isolated growth hormone deficiency (IGHD), 10 children with idiopathic short stature (ISS) and 50 control subjects were recruited in the study. All short stature subjects were receiving GH treatment.
The frequency of 'T' allel in GH1 polymorphism was higher in all groups; and the frequency of genotypes carrying 'A' allel was significantly higher (p:0.027) in IGHD group than ISS and control groups (57.9%, 20%, 34% respectively). The frequency of homozygous d3d3 genotype of GHRd3 polymorphism in the control group was 6%, reflecting its relation with height distribution in the normal population. The GHRd3 polymorphism, did not affect the 1st year response to GH therapy in any group.
In conclusion, significant correlation was found between 'A' allel of GH1 IVS4+90A>T polymorphism and short stature. Similarly, we identified the association of GHRd3 polymorphism with height distribution in normal population and in study groups; though, it had no effect on response to GH therapy. This is the first study, analyzing both of these polymorphisms in Turkish population. We aimed to compare results of a section of our population with previous series and to inform the clinicians about the importance and relevance of gene polymorphisms with short stature and GH treatment.

Key Words: Short Stature, Growth Hormone, Polymorphısm, GHRD3,Growth Hormone Therapy

S-105 - Allelic Determination of Interleukin-1 A Rs1143634 and Interleukin-1 B Rs1800587 Polymorphisms in Patients with Chronic Periodontitis

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Periodontitis is a complex disease, mainly characterized with gingival inflammation and alveolar resorption. Chronic periodontitis (CP) is a common disease characterized by a painless, slow progression. Verified markers of any disease suggest causative variants exist in the gene and, if the causative variants can be identified, such variants also will be informative about inclination of periodontitis. The aim of this study was to examine IL1-A rs1143634 and IL1-B rs1800587 polymorphisms in Turkish patients with CP.
29 periodontitis patients and 15 healthy controls were enrolled for the study. Peripheral blood samples were used for DNA isolation. Commercially available Invitrogen (Van Allen Way Carlsbad, CA, USA) DNA isolation kit was used. Genotypes of IL1B and IL1A gene (rs1143634, rs1800587) were determined using RT-PCR method.
In the patients with CP the numbers and percentages of CC and CT genotypes for IL1-B rs1143634 polymorphism were 12 (41%) and 16 (55%), respectively, and one TT (4%) genotype was detected. C and T alleles were counted as 40 (69%) and 18 (31%). The numbers and percentages of CC, CT and TT genotypes for rs1800587 polymorphism were 9 (31%), 17 (59%) and 3 (10%), respectively. The distributions of C and T alleles were as 35 (60%) and 23 (40%).In healthy control group the numbers and percentages of CC genotypes for IL1-B rs1143634 polymorphism were 15 (%100). CT and TT genotypes were not detected. Allele distribution was %100 C. For IL1-A rs1800587 polymorphism scores were for CC 7(%47), CT 7(%47), TT 1 (%6). Allele frequencies of alleles were C allele %70, T allele %30, respectively.
When rs1143634 and rs1800587 polymorphisms of IL-1A were examined, it was observed that CC, CT and TT genotypes and also C and T allele for rs1143634 and for rs1800587 polymorphism were found to be similar. C allele was found to be superior to T allele for both examined polymorphism. These two SNPs were associated with risk for chronic periodontitis. We believe that these data add further studies support for the clinical validity of IL-1 genetic variants as a predictor also chronic periodontitis. Our study will proceed with increasing number of periodontitis and healthy groups.

Key Words: Genetic Risk, Chronicperiodontitis, Interleukin-1, Polymorphism,

S-106 - The Relationship between Myocardıal Infarction and the Expression Level of MİR-142-5P

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Myocardial Infarction (MI) which is one of the leading causes of death around the world is a pathophysiological process that is regulated by different mechanisms. miRNAs are in the non-coding RNA group and have regulatory roles on gene expression. Determination of miRNA expression changes in inflammatory blood cells involved in the development of atheromatous plaques is important for diagnosis and follow-up of disease. In this study, it was aimed to determine the association of miR-142-5p expression levels with atherosclerosis and MI. For this purpose, the expression levels of miR-142-5p associated with inflammation were researched with MI and atherosclerosis severity in the study population, which was evaluated according to the cardiological assessment scores.
miR-142-5p expression levels in leukocytes derived from the patients with MI (n=76) who had RELATIONSHIP with MI and control cases without MI (n=102) who were operated due to aortic or mitral valve defect and non-lesion according to coronary angiography in the Cardiology Institute were determined by the quantitative RT-PCR method. In all cases, GENSINI and SYNTAX scores determined the severity of atherosclerosis by using coronary angiography. The associations between miRNA expression level and clinical data were analyzed statistically. Furthermore, the target genes of miR142-5p were determined using bioinformatics tools and their possible role in atherosclerosis was investigated.
It was observed that miR-142-5p expression levels (8.03 ± 8.9) in patients with MI had a statistically significant decrease compared to the control group (14.2 ± 19.4) ($p = 0.048$). In logistic regression analysis performed by age and sex, it was found that the decrease in miR-142-5p expression level was more significant in myocardial infarction ($p = 0.022$). There was no correlation between the severity of atherosclerosis and the level of expression. In addition, according to bioinformatics analyzes, miR-142-5p was found to regulate TGFBR2 and SMAD3 genes in the TGF-signaling pathway induced with MI.
In conclusion, it was found that miR-142-5p which have a regulatory role in TGF- pathway, is related to MI. Further studies are needed to understand the function of miR-142-5p in the pathogenesis of MI. This study was supported by Scientific Research Projects Coordination Unit of Istanbul University (Project number: TSA-2017-25306)

Key Words: MİR-142-5P, Expression Level, Myocardial Infarction, Atherosclerosis

S-107 – X-Linked OHDO Syndrome: A Case Diagnosed by Clinical Exome Sequencing

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Intellectual disability (ID) affects 1-3% of population and X'linked ID accounts for 5-10% of ID in males. Mutations in MED12 gene are related to several X'linked ID phenotypes with overlapping features such as Lujan syndrome, FG syndrome, and X'linked Ohdo syndrome. In this presentation, a boy with no distinctive clinical diagnosis and a mutation in MED12 gene detected by clinical exome sequencing will be discussed with clinical features.
2 5/12 year-old boy with no parental consanguinity, moderate/severe psychomotor retardation, microcephaly, facial dysmorphic features (mild blepharophimosis, epichantal folds, synophrys, medially flared eyebrows, wide and depressed nasal bridge, broad nasal tip, anteverted nares, small mouth), micropenis and sex chromosome abnormality (47,XYY).
A hemizygous c.4147G>A (p.Ala1383Thr) mutation was detected in MED12 gene by clinical exome sequencing in the case with 47,XYY karyotype in whom microdeletion / microduplications were excluded by SNP array analysis. Carrier state of the mother was confirmed for the same mutation by Sanger sequencing.
Clinical exome sequencing revealed a mutation in MED12 gene which is related to several phenotypes in the case with psychomotor retardation and dysmorphic features with no clinical diagnosis. The mutation was reported in an another case with X'linked Ohdo syndrome. Clinical findings were consistent with X'linked Ohdo syndrome when the case was reevaluated after molecular results. X'linked Ohdo syndrome was ascertained by clinical exome sequencing (CES) and reverse phenotyping.

Key Words: MED12, OHDO Syndrome, Clinical Exome Sequencing

S-107 - The Effect of UCMA-GST Fusion Protein on Expression of IL-6 in Human Osteoblasts

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UCMA (Upper Zone of Growth Plate and Cartilage Matrix-Associated) is one of the newest members of vitamin K-dependent protein family. It has been reported in recent studies that UCMA is related with some pathological conditions such as osteoarthritis and inflammation. OA is the most common chronic articular disease in the world. There is no effective treatment against OA yet despite recent developments regarding OA pathophysiology and current treatment options are limited with unpleasant side effects. In OA pathogenesis in which inflammatory mediators such as IL-6, IL-1β involve, osteoblasts play effective role besides chondrocytes. In addition, molecular pathophysiology of UCMA with respect to several disorders including OA has not been yet fully understood. We aimed in the present study to analyze the effect of UCMA-GST (UCMA-Glutathione S-transferase) fusion protein on the expression levels of IL-6 in human osteoblast cell line.
In our study MTT assay was used to assess the effect of UCMA-GST on the cell viability. Then osteoblast cells were exposed to UCMA-GST (500 ng/ml, 1000 ng/ml, 48 hour). Thereafter, total RNA isolation and cDNA synthesis were performed subsequently. mRNA expression levels of GAPDH, UCMA, TNFSF11, and IL-6 were analyzed with real time PCR (qRT-PCR) method. Qiagen online web site was used to analyze gene expression data.
Our results revealed that, UCMA-GST fusion protein augmented the mRNA expression levels of IL-6 while it had no significant effect on the mRNA expression levels of TNFSF11 and UCMA. Moreover, we observed that UCMA-GST had no significant effect on the cell viability in a duration and dose dependent manner.
In conclusion, our results demonstrated for the first time that UCMA-GST fusion protein had a significant effect on the mRNA expression levels of IL-6 in osteoblasts. Additionally, further studies conducted with different duration and dosages of UCMA treatment will provide a better understanding about the association of this protein with OA pathogenesis.

Key Words: UCMA, Osteoarthritis, UCMA-GST Fusion Protein, Osteoblast

S-108 - Investigation of RASD1 Gene Mutations in Schizophrenia Patients

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Schizophrenia is a chronic psychiatric disorder characterized by recurrent psychotic attacks. The incidence of schizophrenia in the population is reported as about 1%. Currently, there are no biological markers routinely used in the diagnosis of schizophrenia, so the diagnosis is based on clinical assessments. Despite numerous anatomical and histochemical/pathological examinations of post-mortem brain tissues and functional neuroimaging studies, pathogenesis of schizophrenia is still unknown. Dexras1 (Dexamethasone-induced Ras-related protein 1) is a small GTPase encoded by the RASD1 gene and belongs to the Ras superfamily. The Dexras1 is a component of the Dexras1-NOS1AP-NOS1 ternary complex in the glutaminergic post-synaptic terminal. NOS1 is activated by NMDAR-mediated calcium influx so that nitric oxide is produced. Dexras1 is activated by S-Nitrosylation caused by NO. Active Dexras1 inhibits adenylyl cyclase through Gαi activation; as a result of this interaction, ERK/MAPK and CREB signal pathways are indirectly inhibited.
In this study; sequence analysis of RASD1 was performed in the DNA samples of 200 schizophrenia patients which were obtained from Ankara University Brain Research Application and Research Centre (AUBAUM). We aimed to contribute to the literature by examining the RASD1, which is closely associated with molecules such as NOS1, NOS1AP, NMDAR, which were associated with schizophrenia, and which has not been investigated in schizophrenia patients before.
In this study; we performed sequence analysis (promoter, 5'UTR, both exons, intron and 3'UTR) of RASD1 in DNA sample of 200 schizophrenia patients and nine variants in different regions of the gene were found. At least one variant was detected in 87% of cases. Distribution of these variants was as follows: one in 5'UTR, one in the intronic region, one in exon 2 and six in the 3'UTR. While eight of nine variants was defined in the dbSNP database; NM_016084.4:c*32G>A variant, located in 3'UTR, was described in this study for the first time.
In this study; RASD1 was investigated by Sanger sequence analysis in DNA samples of 200 schizophrenia patients. Nine variants in different regions of the gene were found. None of the variants detected in this study was found to be associated with schizophrenia by in-silico analysis.

Key Words: RASD1, DEXRAS1, Schizophrenia, NOS1, NOS1AP

S-109 - The Effect of Estrogen on B-Catenin, DUX4 and PAX3 / 7 Levels in Fasioscapulohumeral Muscular Dystrophy (FSHD)

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FSHD is one of the most common muscular dystrophies and is an autosomal dominant disorder. The onset age and symptoms of this disease vary among individuals. Clinical findings are more severe in males than females, but it is noteworthy that in postmenopausal female patients symptoms aggravate. In this study, it is aimed to determine the possible relationship between FSHD and estrogen.
Two male and two female individuals, a total of 4 cell lines with FSHD, were used. Expression levels of DUX4, PAX3 / 7 and B-catenin proteins were determined both without estrogen treatment and after 30 minutes, after 4 hours of treatments at 10 nM dose with estrogen.
After estrogen treatment, both increasing and decreasing expression level of B-catenin was reached. DUX4 protein showed an increase of 30 minutes after estrogen treatment and a decrease of 4 hours after estrogen treatment. When PAX3 / 7 protein was examined, both increase and decrease were observed after estrogen treatment in smaller and larger variants of 56 kDa variant. In the 56 kDa variant, only the samples obtained after 4 hours of estrogen application exihibited a band; no band was observed both in the group of 30 minutes after estrogen treatment and in the group of without estrogen treatment.
This study demonstrates that estrogen has an effect on DUX4, PAX3 / 7, B-catenin protein levels that play a key role in the pathophysiology of FSHD. This is the first study revealing the effect of estrogen on B-catenin and PAX3/7 levels at FSHD cells.

Key Words: Facioscapulohumeral Muscular Dystrophy(FSHD), Estrogen, DUX4, B-Catenin , PAX3/PAX7

S-110 - Is PGRN Rs5848 Polymorphism a Risk Factor for FTLD in a Turkish Cohort?

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Frontotemporal lobar degeneration (FTLD); describes a group of progressive brain disorders that are clinically, pathologically, and genetically heterogeneous. The rs5848 (c.*78C> T) polymorphism is thought to be a binding point for miR-659 and is caused to increase the translational suppression of Progranulin (PGRN) due to its more efficient binding to the T allele. Progranulin is the precursor of granulins, and its downregulation may lead to neurodegeneration. In this context, it was aimed to determine the relationship of the FTLD with the rs5848 polymorphism in this study.
Following the sequencing of MAPT, PGRN, CHMP2B, VCP, TARDBP and FUS genes by NGS method, 100 FTLD patients (71 bvFTD, 6 svFTD, 10 PPNA, 6 FTD-MND, 4 CBD, 2 PSP ve 1 FTD-park) without pathogenic mutation in these genes and 100 age-matched control cases without neurological/psychiatric pathological findings were included in the study.
TT genotype was found to be 18% in the patient group and 12% in the control group for the rs5848. There was a significant difference between the patient and control groups in terms of genotype distribution and this difference was statistically significant ($p<0,01$). Although it was not statistically significant, patients carrying the T allele in rs5848 showed an increased risk for FTLD (OR= 1.286, % 95 CI: 0.556-2.974, $p >0.05$).
There are contradictory data about the polymorphism rs5848 in studies for different dementia groups. Although some studies have considered this polymorphism as a risk factor for dementia, others have not confirmed this.The main reason for this difference may be population based differences as seen in other polymorphism studies or other genetic factors may have a dominant effect on the disease. To our knowledge, this study is the first study to evaluate rs5848 polymorphism in Turkish FTLD cohort. As a result of our study, we concluded that this polymorphism is not a risk factor for Turkish FTD cases, but may act as a predisposing factor. We think that it would be more informative if serum PGRN levels of FTLD patients with CC and TT genotypes in rs5848 polymorphism are evaluated. This study was supported by TUBITAK 1001, Project No: 114S346

Key Words: RS5848, Polymorphism, FTLD

S-111 - The Investigation of Epigenetic Changes of RANK/RANKL Signaling Pathway in Post-Menopause Women

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The first menstrual period and onset of menopause are the key milestones of female reproductive ageing. Genetic and environmental factors have effects of the timing of ending and starting periods. Decreased level of estrogen associated with osteoporosis and RANK/RANKL pathway is important during the osteoclastogenesis. MS-HRM used for identification of promotor methylation of ESRRA, RANKL, NFATC1, C-FOS genes in 30 pre-menopausal and 35 post-menopausal women. The statistical analyses and their associations with patient characteristics were performed by Pearson Chi-Square and Fisher's Exact Test ($p<0.05$). RANKL and ESRRA gene were unmethylated in %82,1 of the post-menopause cases, so there was a direct interaction between RANKL and ESRRA gene unmethylation ($P=0,032$). In %31,4 of the post-menopause cases, NFATC1 gene was methylated and %68,8 of the cases were unmethylated ($p= 0,010$). There were a statistically significant association between RANKL and C-FOS; where C-FOS gene was unmethylated in %100 of cases but RANKL gene was methylated in these cases ($p= 0,022$). C-FOS is a down-target of RANKL pathway and RANKL regulates C-FOS activity and this is concordant with our results. There were a significant association between NFATC1 unmethylation and unmethylation of RANKL and C-FOS genes ($p<0.005$) which was another target gene in RANK/RANKL pathway. Based on literature knowledge, this was the first study which investigate the relationship between methylation of RANK/RANKL pathway and post-menopause.

Key Words: Menopause, Methylation, ESRRA, RANKL, NFATC1, C-FOS

Poster Presentation Abstracts

P-001 - Prenatal Genetıc Applications in Pregnant Women with Non Syndromic Mental Retardation in the Family: Next Generation Sequencing

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In recent years, new generation sequencing methods are preferred due to the ability of providing high quality data rather than old, time consuming and expensive methods in order to detect responsible genes in mental retardation which cannot be explained by clinical and laboratory examinations and high heterogeneity.
A 11-week pregnant woman who had a high risk for Down syndrome in double screening test was referred to our clinic from a pediatric gynecology clinic. According to the anamnesis, the couple's families had patients with undiagnosed mental retardation. It was learned that the father's 13-year-old brother has no feature in prenatal and natal period, however his motor development was at borderline, he had retardation in psychosocial and language development.In the neurological examination of the patient; it was observed that his cranial nerves were intact, muscle strength and tonus were in full, his walking was normal. No atrophy or pseudohypertrophy was detected in the muscles. His sensory examination was normal, deep tendon reflexes in bilaterally were normoactive and no pathological reflexes were detected. Exome analysis was planned for this case due to the nonsyndromic mental retardations are genetically very heterogeneous and limited time for prenatal diagnosis in the index case. It was observed that the other patient had an encephalitis sequel.
A hemizygous likely pathogenic variant was identified in the DMD gene.The DMD variant c.10247G>A;p.(Trp3416*) creates a premature stop codon. ClinVar lists this variant as likely pathogenic (Variation ID: 374132). It's classified as likely pathogenic (class2) according to the recommendations of ACMG. This variant has been confirmed by Sanger sequencing.
Over the past few decades there has been increasing attention to neurodevelopmental dysfunction in Duchenne muscular dystrophy (DMD), on the other hands research in cognition, learning, and behavior in Becker muscular dystrophy is even scarcer, being limited to only few study. DMD gene analysis should be considered in patients with unexplained mental retardation. However, if there are individuals with mental retardation who do not have any clues for the muscle involvement in the family that applied for prenatal diagnosis; an exom analysis can be planned because of providing high data in shorter time.

Key Words: Nonsyndromic Mental Retardation, DMD, NGS

P-002 - Different Genes, Different Mutations, Do They Cause Phenotypic Difference ?: Alport Syndrome

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Herein our aim is to figure out the phenotype/genotype relationship of the cases diagnosed as Alport Syndrome referred with hematuria/proteinuria.
Patients were analyzed with their history, physical examination, pedigree and COL4A3, COL4A4, COL4A5 genetic results. DNA isolation was performed using QIAamp DNA Mini Kit(Hilden,Germany) and Multiplicom ALPORT MastrDx kit was used for mutation analysis. The bioinformatic analysis of the data was analyzed with Sophia version(5.0.13.2) software and up-to-date databases (HGMD/MutationTaster/Exac/Polyphen).
Thirty seven patients with Alport Syndrome admitted between September 2017- September 2018 were analyzed for COL4A3, COL4A4, COL4A5 gene mutations. Twelve patients that had one or more defined mutations of the COL4A3, COL4A4, COL4A5 genes; the five of the six COL4A5 gene mutations were; [Patient 1, c.4732 A>T (p.Ser1578Cys); Patient 2, c.286 G>A (p.Gly96Arg); Patient 3, c.2692A>G (p.Met898Val) and c.1957 G>A(p. Gly653Arg) ; Patient 4, c.3554 G>A (p.Gly1185Asp); Patient 5 c.3071 G>A (p.Gly1024Gly)]. One patient had frame shift mutation at COL4A5 gene [Patient 6, c.2870delC (p.Pro957Glnfs*39]. All but one of the six patients had seeing and hearing abnormalities typical for Alport Syndrome as extra-renal findings. Three of the COL4A3 gene mutations, 2 of them were missense [Patient 7, c.364G>A (p.Gly1216Arg) ; Patient 8, c.1015G>A (p.Gly339Arg)], and one causing RNA splicing defect was [Patient 9, c.87+1G>A]. There were no extra-renal finding at these 3 patients. At one patient there were mutations at both COL4A5 and COL4A3 genes. Seven nucleotide deletion at COL4A3 and nonsense mutation at COL4A5 gene were detected. [Patient 10, COL4A3 c.4347_4353delCCGACAC ve COL4A5 c.1102G>T (p.Gly368*)]. The patient had no abnormalities at ENT examination but the spot like opacities detected at lens were Alport Syndrome" associated. There were 2 patients with COL4A4 gene mutations; one of the mutations was missense [Patient 11 COL4A4 c.4263 C>T (p.Gly1421Gly)] and the other was a frameshift mutation [Patient 12 COL4A4 c.4444delC]. Neither of the patients had eye and ENT findings.
Genetic etiology was detailed for twelve of our patients and the family members who are at risk were determined, the genotype-phenotype relationship could better understood.

Key Words: Alport Syndrome, Hematuria/Proteinuria, Extrarenal Findings, COL4A3/ COL4A4/ COL4A5 Mutations

P-003 - An in-Silico Study to Identify miRNA's Effective in Tyrosine Kinase Inhibitor Resistance Chronic Myeloid Leukemia

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MicroRNAs (miRNA) are short RNA sequences of 21-24 nucleotides, that post-transcriptionally regulate gene expression. miRNAs play an important role in cancer, in processes such as metastasis, apoptosis and proliferation. Bioinformatics is the examination, processing and the storage of biological information with the help of computer software. Our aim is to identify miRNAs that play a role in primary tyrosine kinase inhibitor resistance in chronic myeloid leukemia. The first step of our work comprises of data mining and in-silico studies. Microarray and database scans define hundreds of possible miRNAs. In aim to verify and proceed with wet laboratory investigations, this number must be reduced. Based on mRNA and miRNA microarray data in a primary resistant KML cell line, in-silico methodology was used to narrow the miRNA pool to be investigated prior to in-vitro experiments. KML cell line K562 was grown under selective imatinib pressure, resulting in a imatinib resistant subclone: K562-IR. K562-IR cells are resistance to apoptosis, have altered adhesion properties, and phenotypic changes. mRNA and miRNA microarray expression analyses were performed on K562 and K562-IR (Germany / Berlin ATLAS Biolabs GmbH). miRNA potential target genes generated as a result of database research were compared with mRNA expressions (transcriptomes). miRNAs that displayed increased expression in K562-IR, were compared with the mRNA microarray expression levels of their target genes. Microarray mRNA results of the K562-IR subclone revealed differential gene expression especially for genes functioning in differentiation pathways, gene ontologies that focus on cell differentiation were studied using bioinformatics databases: • miRDB (http://mirdb.org/miRDB/, Release: 03 Nisan 2012) • WebGestalt: http://www.webgestalt.org/option.php, Organism:hsapiens; Method of interest: ORA analysis; Functional database: Gene Ontology/Biological Process; Gene ID type: Gene symbol; Reference Set for Enrichment Analysis: illumina humanht 12 v4. Our initial pool of 196 miRNAs has been reduced by our data mining and in-silico studies. The number of miRNAs associated with phenotypic changes and differentiation in imatinib resistance has been reduced to only four : hsa-miR-202-3p, hsa-miR-495-3p, hsa-miR-610, hsa-miR-1273h-3p. Microarrays results indicate hundreds of genes which need to be reduced to a workable level. The in-silico methodology presented here provides guidance for wet laboratory studies.

Key Words: Chronic Myeloid Leukemia, Imatinib, Micro Rna, Bioinformatics

P-004 - Evaluation of BRCA1 and BRCA2 Gene Mutations in Breast Cancer Patients

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Breast cancer in women is the most common type of cancer in the world and in our country. It is one of the most leading cause of death among cancer types. In this study, BRCA1/BRCA2 results were evaluated retrospectively in 31 patients who were referred Yeni Yuzyil University Medical Faculty from oncology service to Genetic Diseases and Diagnosis Center in between September2017 and September 2018. These patients were diagnosed with breast cancer before the age of 45 years and includes breast cancer patient in one or more close relatives at any age.
Preparation of the targeted sequences library using Nextera XT (Illumina). Paired-end Sequencing 2X151bp using MiSeq sequencer (Illumina) with a mean coverage in the analyzed regions of 244.88X, and 24.27% of bases are > 20X covered. The variants were generated by alignment against reference genome (UCSC hg19) using BWA aligner and GATK variant caller. Annotation of the variants according to reference sequence mentioned in Human Gene Mutation Database (HGMD).
In one of the cases of BRCA1 gene, heterozygote p.Cys61Gly (c.181T>G) variation was detected and it was identified in HGMD. In another case, heterozygote p.Pro977Ala (c.2929C>G) variation was detected but it was not found previously in HGMD. The benign variations; p.Ser1613Gly(c.4837A>G), p.Pro871Leu, p.Glu1038Gly, p.Gln356Arg, p.Lys1183Arg, p.Ser1040Asn, p.His1746Asn(c.5236C>A), p.Met1628Thr(c.4883T>C), p.Asp693Asn. No variation was found in the BRCA1 gene of 23 cases. In one of the cases of BRCA2 gene, heterozygote p.Thr1251Asnfs*14(c.3751dupA) variation was detected and it was identified in HGMD. 4 different heterozygote variations detected in 3 patients as follows; p.Ile3224Val(c.9670 A>G), p.Thr1653Ala(c.4957A>G), p.Leu667*(c.1998delT), p.Thr2097Met(c.6290C>T). But they were not identified in HGMD. Benign variations;p.Asn372His(c.1114A>C), p.Val2466Ala(c.7397C>T), p.Asp1420Tyr(c.4258G>T). No other variation was found in the BRCA2 gene of the other 27 cases.
It is very difficult to develop effective strategies to reduce the incidence of breast cancer because, only a few of the existing risk factors are interchangeable. If there is a known variation in the family, other family members should be inspected for relevant gene variations. If a pathogenic variation is found in the BRCA1 or BRCA2 gene, genetic counseling should be given to the patient about the various options to manage the risk of cancer.

Key Words: BRCA1, BRCA2, NGS

P-005 - Targeted Gene Panel Analysis of 67 Patients with Early-Onset Epileptic Encephalopathy

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Epileptic Encephalopathy (EE) is the most common and severe heterogeneous disease in infancy and early childhood. Genetic and phenotypic heterogeneity of EE make diagnosis difficult and affect treatment adversely. Targeted gene panel sequencing are used to identify causative genomic defects in clinical settings. We aim to report our experience of targeted gene panel testing in children with EE.
We performed a custom designed gene panel sequencing with 55 known EE genes to asses 67 probands (31 males /36 females) who underwent clinical triage by neurologists between October 2017 and September 2018. Nineteen patients were West syndrome, 2 patients were malignant migrating partial seizures of infancy (MMPSI) , 2 patients were Dravet syndrome and 44 had unclear classification. We used parental testing, segregation analysis and in silico tools for the assessment of variant pathogenicity. We classified the variants according to the American College of Medical Genetics (ACMG) guidelines.
Pathogenic (P) or likely pathogenic (LP) variants were identified in 18 patients (26.87 %). Among these P/LP variants 5 were de novo. Nine P and 3 LP variants were novel, 2 P and 4 LP variants were reported. Variants of uncertain significance (VUS) were found in 17 patients (25.37 %). P/LP variants were found in SCN1A (4), PCDH19 (2), PLCB1 (2), STXBP1 (2), WWOX (1), SCN8A (1), KCNQ2 (1), SCN2A (1), SPTAN1 (1), NECAP1 (1), FGF12 (1) and SLC35A2 (1) genes. Main findings were identified in SCN1A gene in West syndrome and in Dravet syndrome, PLCB1 gene in MMPSI. Vigabatrin treatment was found effective in patients with STXBP1 gene mutation.
The diagnostic rate (26.87 %) of P and LP variants was similar to previous studies of early-onset EE. Functional analysis could be performed to clarify the pathogenicity of variants classified in VUS. Targeted gene panel sequencing is an efficient tool to identify the genetic causes of EE and to recommend gene-spesific antiepileptic drugs.

Key Words: Early Onset Epileptic Encephalopathy, Targeted Next Generation Sequencing, Antiepileptic Drugs

P-006 - The Management of Heart Transplant Requirement Associated with Dilated Cardiomyopathy in Multiple Family Members by Exome Sequencing

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In the literature, it was observed that the cases who were evaluated with exome analysis were selected from cases that could not be mostly diagnosed. Thus, the detected pathogenic variant can be investigated in the preimplantation/prenatal period and the family can be prevented from encountering a similar situation. Although exom is mostly used in healthy pregnancy planning, it has also vital importance for predicting the processes that may be experienced before and after transplantation in such patients who are planned to have solid organ or bone marrow transplantation.
A 13-year-old male case in the cardiovascular surgery service who was in wait listed for cardiac transplantation was asked to evaluate genetically due to vitiligo and learning disabilities in addition to cardiomyopathy. When the patient, whose parents had the 3rd child cousin marriage is third child of the family, were evaluated with the physical examination it was observed that our patient had vitiligo, mental retardation (mild-moderate), epilepsy, limitation of the joint movements and cardiomyopathy. It was learned that our patient's older sister had similar complaints and was also receiving dialysis treatment for three years due to renal failure. Re-evaluation of our patient's renal functions and an exome analysis for both siblings were recommended in order not to adversely affect the schedule of transplantation. Genomic DNA is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted against coding regions of ~6700 genes. A homozygous pathogenic variant was identified in the XPNPEP3 gene. This finding is consistent with a genetic diagnosis of autosomal recessive nephronophthisis-like nephropathy type 1. NPHP, a recessive cystic kidney disease, is the most frequent genetic cause of CKD in the first three decades of life.
Two children weren't diagnosed with any disorder until 13 year olds. The treatment algorithms have been rearranged when both siblings were diagnosed Nephronophthisis with exome analysis. However, our male patient was ex during this period. It is recommended that cases should be also evaluated with a multidispliner approach by a specialist in genetics, from the point of problems that patients with syndromic features who are candidate for transplantation may encounter.

Key Words: Cardiac Transplantation,Nephronophthisis,Exome

P-007 - The Importance of Whole Exome Sequencing in Clinical Heterogeneity

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Fanconi anemia is a rare autosomal recessive syndrome with early onset bone marrow failure, congenital anomalies (café-au-lait spots, pigmentation abnormalities, short stature, thumb anomalies, microcephaly, ear deformities, hypogenitalism, kidney abnormalities) and susceptibility to malignancy. It is the most common cause of hereditary aplastic anemia with extensive genetic heterogeneity. Clinical presentation may vary within a wide spectrum. Therefore, there may be diagnostic difficulties in some cases. The most important condition in differential diagnosis is VATER/VACTERL association due to variable clinical presentations. In addition, TAR syndrome (thrombocytopenia- absence of radius), t(11;22) and deletion of 22q11.2 are included in differential diagnosis.
A 6-day-old female patient was referred to our clinic for anal atresia, duodenal atresia, renal agenesis, ectopic kidney and radius agenesis. Parents were third degree cousins. She was born at 39th gestational week with a birth weight of 2100 g by C/S. A double-bubble appearance was detected in the prenatal USG. Radiographs revealed absence of thumb and radius, costa and also vertebral abnormalities. Renal ultrasonography demonstrated right kidney agenesis and the left kidney was ectopic. Echocardiography revealed ductus patency and secundum atrial septal defect.
A homozygous mutation was detected in the FANCC gene (OMİM #227645) as a result of whole exome sequencing (WES) analysis.
The most important condition in differential diagnosis in Fanconi anemia is VACTERL association because of high variability of clinical presentations. When vertebral anomalies, anal atresia, cardiac anomaly, radial and renal agenesis are considered together, VACTERL association should be considered in the differential diagnosis. TAR syndrome is another condition with varying degrees of agenesis or hypoplasia in the upper extremity bones, but presence of thumb is the rule. 22q11.2 microdeletion is considered because of the vertebral and cardiac findings. Although in Fanconi anemia the age of onset of hematological findings is variable, the mean age is 8 years and early diagnosis is important to determine the need of stem cell transplantation. In presence of multiple congenital anomalies and a long list of differential diagnosies, diagnosis can be achieved more quickly by WES analysis to determine the patient's priorities and treatment strategies.

Key Words: Fanconi Anemia, FANCC, Multiple Congenital Anomalies, Bone Marrow Failure

P-008 - Genetic Analysis Results of a Patient Cohort Diagnosed with Arrhythmia

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Arrhythmia is a group of heart disorder which may cause sudden cardiac death especially in young people. It is important to reveal underlying molecular genetic defect to prevent morbidity and mortality from arrhythmias other at-risk asymptomatic family members. The aim of our study is to define the responsible genetic etiology in patients who are referred to our clinic due to arrhythmia and to explain its relationship with phenotype.

Key Words: Arrhythmia, Catecholaminergic Polymorphic VT, Arrhythmogenic Right Ventricular Dysplasia, Long QT Syndrome

P-009 - Genetic Analysis Results of the Patient Cohort Diagnosed with Cardiomyopathy

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Hypertrophic cardiomyopathy is typically defined by the presence of unexplained left ventricular hypertrophy. Dilated cardiomyopathy is characterized by the dilation of ventricles and progressively impairing of systolic ventricular function. The aim of our study is to define the responsible genetic etiology in patients who are referred to our clinic due to cardiomyopathy and to explain relationship between genotype and phenotype.

Key Words: Cardiomyopathy, MYH7, Troponin, Sarcomer

P-010 - New Mutations in the Autoinflammatory Disease Panel with NGS

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Autoinflammatory diseases, also known as hereditary periodic fever syndromes, are characterized by symptoms such as recurrent fever attacks, rash, serositis, lymphadenopathy and arthritis. The absence of autoantibody in the pathogenesis and the absence of autoreactive T cells result in a proinflammatory condition resulting in non-inflammatory activation. Some of the autoinflammatory syndromes with similar clinical findings are inherited as autosomal dominant, while others show an autosomal recessive transition. With genetic tests, understanding of diseases at the molecular level and clinical diagnosis are important. In the light of this aim, variation / mutation analysis was performed on the responsible gene regions in 128 individuals with autoinflammatory disease findings.
This study was carried out on the next generation of sequencing technologies in the Ion Torrent Personal Genome Machine® (PGM ™) sequencing device.The basis of this sequencing system is the transfer of the pH caused by hydrogen ion release during DNA polymerization to the digital system by semiconductor sensors.Genes analyzed in the Next Generation Sequencing panel;NLRP3, NLRC4, IL1RN, PSMB8, TNFRSF1A, MVK, PSTPIP1, MEFV, NOD2, PLCG2, NLRP1, CARD8, NLRP12, CARD14, CECR1, TNFRSF11A, TMEM173, TNFAIP3, LACC1, OTULIN, IL23R, TREX1, IL12RB1, PRF1, DNASE1, UNC13D, STX11, STXBP2, USP43, RIPK1
As a result of the evaluation of all data, unique variant was identified as 262. Of the 262 variants, 144 were exonic, splice, frameshift, and 118 of them were found in the synonym, intronic, utr, downstrteam and upstrem regions.When samples are obtained; a total of 3,205,386 total reading, 744 total base, 260 bp, 81% chip loading, 100% Enrichment, 80% clonal, 95% Final library was obtained.
As a result of the analysis; In the MEFV gene Met53Thr missense and in the NLRP3 gene Ser599Cys missense mutations were detected. These mutations have not been previously reported in the literature and have been evaluated as new mutations.

Key Words: Autoinflammatory, Next Generation Sequencing

P-011 - In Silico and in vitro Analysis of the Missense Mutations Causing PRKAG2 Cardiomyopathy

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Missense mutations in PRKAG2, the gene for the gamma subunit of adenosine monophosphate-activated protein kinase (AMPK), cause glycogen-storage cardiomyopathy associated with cardiac hypertrophy and progressive cardiac conduction system disease. In our previous study, PRKAG2 p.E506K mutation was determined in an index case with PRKAG2 cardiomyopathy. Although the pathogenic role of this mutation was supported in the segregation analysis of her family, the aim was to determine the effect of three missense variants in the fourth CBS (cystathionine b-synthase) domain of PRKAG2 with both in silico and in vitro analyzes.
In silico analysis, the p.E506K, p.E506Q and p.R531G missense variants were searched using different bioinformatics tools: MutationTester, PolyPhen-2 and SIFT. For in vitro experiments, each variant was constructed by site-directed mutagenesis technique in full RPKAG2b transcript ligated pcDNA3.1/V5-His-TOPO expression vector and then transfected into HEK293 cells by lipofectamine system. The PRKAG2 protein was determined by immunofluorescence staining and the gene transcripts of AMPK pathway was determined by quantitative RT-PCR in wild-type and mutated cells. Intracellular glycogen deposits were examined by PAS staining in light microscope.
The follow-up of family members with E506K mutation and treatment of symptomatic individuals continue. However, the index case diagnosed at the age of 19 died 8 years later due to advanced cardiac insufficiency. In silico analysis of these three missense variants using the bioinformatics tools predicted a pathogenic alteration causing disease. The differential expression levels of PRKAG2, PRKAA2, PRKAB2 encoding AMPK isoforms and also PFKM, SLCA5A1, SLCA2A4 and PFKFB3 in AMPK pathway were showed in PRKAG2b p.E506K, p.E506Q and p.R531G mutated cells compared to wild-type cells. PRKAG2 protein was localized in the cytoplasm of the mutated cells by immunofluorescence. Glycogen deposits were also observed in all cells stained with PAS.
In this study, it was shown that single nucleotide variants that cause amino acid change in the PRKAG2 gene are associated with AMPK-related glycogen-storage cardiomyopathy. This study was supported by Scientific Research Projects Coordination Unit of Istanbul University (Project number: TDP-2017-22581) and The Scientific And Technological Research Council Of Turkey (Project number: 115S137).

Key Words: PRKAG2 Cardıomypathy, Single Nucleotide Variants, AMPK, In Silico, In Vitro

P-012 - The Role of NGS in Molecular Classification of Steroid Resistant Nephrotic Syndrome

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Nephrotic syndrome is a disease characterized by edema, massive proteinuria and hypoalbuminemia. NGS plays a role in the clinical field, both in basic and experimental studies, as well as in the diagnosis of innate genetic diseases. In this study; Nephrotic Syndrome panel aims to provide a precise diagnosis and classification of common diseases of kidneys and urinary tract. The NGS system we use in the study is mainly based on the measurement of the level of H + ions released when the bases are bound by DNA polymerase. This measurement is done extremely fast on a semiconductor chip. Our aim in this study was to improve SRNS genetic diagnosis by sequencing all gene coding regions and all intron regions of twenty genes at the same time.
Seventy patients (41 males and 29 females) were included in the study. These patients were selected from patients with steroid resistant nephrotic syndrome.The genes analyzed in our NGS panel are NPHS1, NPHS2, NPHS3, NPHS6, WT1, LAMB2, DGKE, ARHGDIA, ADCK4, EMP2, COQ2, COQ6, CD2AP, ACTN4, CRB2, INF2, PAX2, MYO1E, APOL1 ve TRPC6.
661 variants were detected in 70 patients. Of these 285 variants are intronic, UTR and up-down stream; 90 variants were missense, nonsense, frameshift, 98 variants were synonymous and 188 variants were considered low quality. Among the 90 variants identified, 75 variants were previously reported in the database; 15 variants were evaluated as new. In these 15 variants, 7 variants were evaluated as pathogens and 3 variants were evaluated as possible pathogens. The remaining 5 variants were accepted as benign.
The target NGS can be successfully applied in the molecular diagnosis of NS, which is a genetically very heterogeneous group of diseases.

Key Words: Steroid Resistant Nephrotic Syndrome, Variant, Next Generation DNA Sequencing

P-013 - A Rare Case who had Variants in CEP290 and RARS Genes with Whole Exome Sequencing

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A 25-month-old girl was referred to us for suspicion of metabolic disease due to deep hypotonia, lack of walking and speech.The patient, who had seizures and was thought to have a neurotransmitter defect, was consulted.She had consanguinity between her parents and at the moment she had 1 male and 1 female brother, who had no similar clinical problems. Families did not have a history of similar disease. The patient was bed-dependent and mentally affected.
Routine biochemical tests, electrophysiological studies and radiological examinations were done. The DNA was isolated from the peripheral blood sample and necessary preparations were made and Whole Exom Sequencing (WES) was performed with Illumina-Miseq platform by NGS (next generation sequencing) method.
Kranial MRI.abdomen USG, array-CGH analaysis were normal and metabolic tests were nonspecific.Whole exome sequencing(WES) was performed in the patient. WES method involves approximately 2% of the genome, and 85% of the mutations causing this disease can be detected by this method. As a result of the analysis, a heterozygous variant in exon 15 (c.1517G>A (p.Arg506His)) and a heterozygous variant (c.3709C>T(p.Arg1237Cys)) variant in exon 31 of the the CEP290 gene were found. In addition,a homozygous variant (c.875A>G(p.Gln292Arg)) in exon 8 of the RARS gene was found.Along with bioinformatics and in-silico analysis data, all variants were classified as “VUS" and segregation analyzes containing family members were ongoing.
Although the function of the CEP290 protein is not well understood, it suggests that it plays an important role in the structure of centrosome and silia in the cell.It has been reported in the literature that homozygous mutations in the RARS gene can lead to hypomyelinization, leukodystrophy and ataxia associated neurodegenerative disorders.The determined molecular results are expected to lead to the clinic in the patient and genetic counseling was given to the family with the clinical follow-up plan regarding the results.

Key Words: CEP290, RARS, Leukodystrophy, Hypotonia

P-014 - Ataxia Telangiectasia: Case Report

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Ataxia telangiectasia (AT) is an autosomal recessively inherited rare disease which is the most common reason of progressive cerebellar ataxia. It is characterized with conjunctival telangiectasia, oculomotor apraxia, choreoathetosis, immune deficiency, and increased risk of cancer. The prevalence of the disease varies between 1/40.000 and 1/100.000. ATM gene responsible for the disease, is localized at 11q22.3, it has 62 exons and it encodes a serine tyrosine kinase which includes 3056 amino acids. When protein is phosphorized, it functions as an important cell cycle control kinase and DNA repair by activating repair enzymes at double chain DNA fragmentation. In this study, a case with pathogenic variant in the ATM gene was examined.
12-year-old male case whose parents were fourth degree relatives referred with a complaint of abasia. Due to progressive ataxia that started at the age of 2, the patient became wheelchair-bound at the age of 7. The patient's cranial MR showed atrophy at both hemispheres. Anthropometric measurements, height, weight and head circumference percentile values were found to be normal. Physical examination showed conjunctival telangiectasia, choreoathetoid movements.
ATM whole gene sequencing analysis of the patient showed that he carried pathogenically defined p.Lys1192Lys (c.3576 G>A) homozygous change at 25th exon and ClinVar. The patient's parents were found to be the carriers of the same mutation. The patient was diagnosed as AT according to clinical and genetic test result.
Ataxia telangiectasia diagnosis can be made with molecular genetic tests for ATM gene which will be performed on cases whose clinical findings bring to mind AT following a family history of at least three generations and after a detailed family tree is drawn. After the diagnosis is made, tests for carriers can be conducted. Since it is an autosomal recessive disease, carrier parents have 25% risk of disease, 50% risk of carrier and 25% having a completely healthy pregnancy. After the affected individual is diagnosed, it is possible to have prenatal diagnosis and preimplantation genetic diagnosis. It is very important to avoid sunlight and radiation. As a conclusion, for definitive diagnosis of AT, pathological variants of ATM gene should be examined with molecular genetic tests.

Key Words: Ataxia, Telangiectasia, ATM, Cancer

P-015 - Caytaxin Appears as a Regulating Element in Breast Cancer Metastasis

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Breast cancer is the second most common cancer in the World and the most common and deadliest cancer in women. Despite all advances in diagnosis and treatment, advanced disease and drug resistance are still the major problems. Understanding the pathogenesis of breast cancer will have a great impact to cure. Aim of this study is to elucidate the role of caytaxin protein in breast cancer pathogenesis.
An immortalized breast epithelial cell and 4 breast cancer cell lines were used in this study. An MTS assay for proliferation, PI staining for cell cycle, annexin V staining for apoptosis and invasion assay for detection of metastasis were used. Western blotting was largely used for detection of molecular events and protein changes.
Alterations in caytaxin expressions led to change in expressions of metastasis related proteins including src and fak therefore the metastatic potential of the cells.
Our study suggests that caytaxin may regulate migration of breast cancer cells. This study has been supported by TUBITAK with a project number 115S286.

Key Words: Caytaxin, Breast Cancer, Metastasis

P-016 - Investigation of Genetic and Biological Properties of Different Tumor Cell Populations in an in-vitro Tumor Heterogeneity Model

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Genetic/phenotypic heterogeneity observed in cancer cell populations, are areas of intense research. Intratumoral cancer cell populations have different susceptibility to treatment modalities. It is essential to identify resistant subclones and to develop effective treatment methods. Near-diploid and near-tetraploid subclones from the DLD1 colon cancer cell line were isolated and clone-specific genetic anomalies were identified. Clones were evaluated for cell viability, migration, invasion, proliferation, tumor spheroid formation and resistance to chemotherapeutic drugs.
Main methods used in evaluation of cellular behavior are: crystalline violet and trypan blue staining, BrdU incooperation analyses, scratch test, tumor spheroid formation and MTT viability tests. Biological behavior and genetic differences of subclones were compared and evaluated.
4n clones isolated from the DLD1 colon cancer cell line are: C28, B9, B12; 2n clones are C34, C3. Higher viability is observed in 4n clones (B9>C28>B12>C3>C34, 4n>2n). In BrdU incorporation assays, 2n clones proliferate faster than 4n clones with the exception of B9 (C34> B9> C3> B12> C28). Scratch assays revealed that 4n clones have higher migration ability (B9>C28>C3=B12>C34, 4n>2n). To determine invasive properties, inserts (8µm-por) treated with matrijel were placed in Boyden chambers; 4n clones were observed to be more invasive (B9>B12>C28>C3>C34, 4n>2n). Aneuploidy did not play a decisive role in terms of tumor spheroid formation: B9>C34>B12>C3=C28. 5-Fluorouracil, Oxaliplatin, Irinotecan, Paclitaxel and Gemcitabine were used to evaluate the response of DLD1 subclones to chemotherapeutics. The most resistant clone for all chemotherapeutics with the exception of paclitaxel is B9. C3 is the most resistant clone to paclitaxel.
The genetic characteristics and cellular behavior of the different clones constituting a tumor were investigated. 4n clones were found to be more resistant and aggressive but had slower proliferation rates when compared to 2n clones. In terms of all the features investigated, the B9 clone is prominent. The identification of genetic/epigenetic differences between intratumoral clones and examining their inter-population behaviors will allow new expansions in the field of tumor heterogeneity. This research was supported by TUBITAK1001, 116Z300.

Key Words: Clonal Evolution, Intra-Tumoral Heterogeneity, Treatment Resistance, Colon Cancer, Chemotherapeutic, DLD1

P-017 - Comparison of VUS and Pathogenic Mutatıons in BRCA Genes at Breast and Ovarian Cancer Patients

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BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. These proteins help to repair damaged DNA and, therefore, play a role in ensuring the stability of each cell's genetic material. Specific inherited mutations in BRCA1/2 most notably increase the risk of female breast and ovarian cancers, but they have also been associated with increased risks of several additional types of cancer. People who have inherited mutations in BRCA1/2 tend to develop breast and ovarian cancers at younger ages than people who doesn't have these mutations. BRCA1/2 gene mutation testing can give several possible results: positive result, negative result, or an uncertain result. In this study, we wanted to compare the patients with mutations in BRCA1/2.
A total of 38 patients with breast cancer, ovarian cancer or individuals who have positive family history came to our clinics. BRCA1 and BRCA2 testing was performed by next gene sequencing. The variants were evaluated according to ACMG2015* criteria.
In 9 patients (23,6%), pathogenic, likely pathogenic and VUS (variants of unknown significance) had been found. A pathogenic variant at BRCA1 and another one at BRCA2 were found in two different young breast cancer patients, a likely pathogenic variants in BRCA1 was found at an ovarian cancer patient. Two different VUS at BRCA1 were found in two breast cancer patients, in two patients with fibroadenoma and positive family history. Pathogenic variants were mostly seen in breast cancer patients, especially in BRCA1. One of the patients with early onset ovarian cancer had VUS in BRCA2, another patient with early onset breast cancer had VUS in BRCA1. Different types of variants for BRCA genes were detected at our patients. BRCA1 mutations were mostly related with early onset breast/ovary cancer or positive family history. This was compatible with the literature. BRCA1/2 mutations confer a lifetime risk of breast cancer of 60-80%. Healthcare providers counsel patients according to their personal and family histories of cancer. Many studies attempt to re-classify VUS according to their pathogenicity. It is reported that half of the assessed VUS in both BRCA1 (49%) and BRCA2 (45%) resulted as pathogenic.

Key Words: BRCA; Breast Cancer; VUS; Ovarian Cancer

P-018 - Apoptotic DNA Fragmentation Triggered by Combination Theraphy of Gallic Acid and Tecamen in SKBR3 Cell Line

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Anthocyanin-rich nutrition, which is highly concentrated in some plants and foods, is effective in the inhibition of some types of cancer. Tecamen (Irinotecan-HCl) is an antineoplastic enzyme inhibitor especially used in the treatment of colorectal cancer. It is a semi-synthetic variant of camptothecin that inhibits topoisomerase I action. By binding to the DNA-topoisomerase I complex, DNA can cause double-strand fractures to cause cell death. The aim of this study is to investigate the effect of combined treatment of anthocyanin metabolite galice acid and antineoplastic enzyme inhibitor Tekamen (Irinotecan-Hcl) on apoptotic DNA fragmentation.
Cells were cultured in DMEM in a humidified atmosphere of 5%CO2 at 37°C. Cell viability was determined by MTT assay. The IC50 values were detected for gallic acid, tecamen and combined treatment by 250 µM, 75 µM ve 62,5/18,75 µM respectively; cell viabilities were detected 48,29%, 49,96% ve 50,103% respectively. Cells were treated with determined concentration for 48 hours. After treatment, cells were isolated according to DNA fragmentation protocol and DNA fragments showed on 2% agarose gel.
IC50 were detected for gallic acid, tecamen and combine theraphy, treated with ¼ rates, 250 µM, 75 µM and 62,5/18,75 µM; cell viabilities were detected 48,29%, 49,96% ve 50,103% respectively. We determined that DNA fragmentation, is a marker for induction of apoptosis, increased with combine treatment at 48 hours.
These results suggest that induced apoptosis with combine treatment .This study is a basic qualitative study for the investigate of the apoptosis pathway triggered by gallic acid and tecamen combine treatment.

Key Words: Gallic Acid, Tecamen, Apoptosis, Breast Cancer

P-019 - Integration of Global miRNA and mRNA Expression Profiles in Sporadic Colorectal Cancer

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Colorectal cancer (CRC), a disease with high incidence and mortality rates, has been studied for decades. Due to the heterogeneous nature of the disease, novel biomarkers are needed for its diagnosis, prognosis and treatment of the disease. In this study, we aim to determine miRNA's responsible of CRC development and pathogenesis via integration of meta analysis of previous CRC miRNA profiling datasets with transcriptome profiling data from our CRC patient group.
Herein, for a mechanistic understanding of differential gene expression in CRC tissue, we analyzed miRNA expression profiles of 78 CRC tumors against 62 normal colorectal mucosa samples, using raw data from E-MTAB-752, E-GEOD-35834 (Affymetrix), GSE35982 and E-MTAB-813 (Agilent) datasets obtained from Gene Expression Omnibus and ArrayExpress. Raw samples were normalized using quartile normalization in BRB-ArrayTools. Differential expression of miRNAs was identified using cut-off values of $p \leq 0.05$, fold change ≥ 1.5 and stringent false discovery rates. miRTarBase and miRWalk2.0 databases were explored to identify validated targets. hsa-miR-182, hsa-miR-183, hsa-miR-145, hsa-miR-195 from aforementioned analysis, with potential targets belonging to cancer related pathways, were chosen for further qPCR analysis (n=20 paired tumor normal samples). For statistical analysis, Ln (2^-ΔΔCT expression value) transformation and one sample t-test were used.
We found thirty and thirteen miRNAs commonly upregulated and downregulated respectively, in both Affymetrix and Agilent microarray results. Predicted targets of these miRNAs frequently belong to pathways related to cancer like β-catenin, Phosphoinositol-3Kinase, and TGF-β, to name few. Moreover, the target genes were significantly enriched in clusters related to cell cycle, cell differentiation and regulation of apoptosis. These miRNAs were quantified using qPCR among the same Turkish cohort. Interestingly, miR-182-5p and 183-5p were upregulated in both meta-data analyses and our samples from Turkish cohort. Similarly, miR-145-5p and miR-195-5p were downregulated in meta-data as well as our colorectal cancer samples.
The expression of miR-195-5p and miR-145-5p is significantly correlated. This correlation points out a possible common upstream regulatory event engaged in carcinogenesis. These findings validate that a disrupted miRNA expression profile has a strong likely role to play for aberrant regulation of cancer related genes, both tumor suppressors and oncogenes.

Key Words: Sporadic Colorectal Cancer, mirRNA, Epigenetics, FFPE, Meta-Analysis

P-020 - BRCA2 Pathogenic Genotype in the Monozygotic Triplets and Breast Cancer Phenotype Discordance

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BRCA1 and BRCA2 associated hereditary breast and ovarian cancer. It is the most common cause of familial breast and ovarian cancers in all race and ethnic populations. Women with BRCA2 pathogenic variants have a 38% -78% risk of developing breast cancer for life. In this study, we have defined a pathogenic variant of the BRCA2 gene splice region for the first time in the monozygotic triplets and discussed its importance.
At the age of 44, she was diagnosed with invasive ductal breast carcinoma at 30 years of age. No malignancy was detected in one of the triplet sisters. In his pedigree analysis, his father had been diagnosed with pancreatic cancer and his aunt was diagnosed with lung cancer.
In this study, BRCA1 and BRCA2 gene analysis were performed by Sanger sequencing method. A pathogenic variant of c.7008-1G> C was observed in the intron 13 region of the patient's BRCA2 gene. The other two of the triplet siblings had the same change. It was confirmed by the chimerism analysis .The co-segregation analyzes of the individuals who were likely to be affected in the family were performed and genotyping of the pathogenic region was performed.
BRCA2 c.7008-1G>C pathogenic changes previously unspecified at literature and observed for the first time at identical triplets in our case. Because of the fact that we observed breast cancer genotype phenotype discordance; we suggest that environmental factors and life style might affect expected result of genetic changes and contribute to clinical result variations.

Key Words: Monozygotic Triplets, BRCA2, Pathogenic Variant, Breast Cancer

P-021 - Investigating the Effects of TNFRSF11A Gene Variations on the Risk of the Breast Cancer Development on Patients Carrying BRCA1 and BRCA2 Mutations

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In our research, the aim was to investigate the effects of TNFRSF11A gene rs9646629, rs4485469, rs34739845, rs4941129, rs17069904, rs884205 single nucleotide polymorphisms on breast cancer development in BRCA1 or BRCA2 pathogenic variation carrier phenomenon with breast cancer.
The research was conducted on 23 patients diagnosed with BRCA1 or BRCA2 pathogenic variation and 28 patients that didn't have any trace of BRCA1 or BRCA2 pathogenic variation, and 55 healthy people included as a control group. Genotypes were determined on patients and control group included in the research by isolating the DNA from peripheral venous blood, using the polymerases chain reaction system in accordance with the protocol of the kit used, and by allelic discrimination for single nucleotide polymorphisms.
In the light of the analyses performed, no statistically significant differences were found between TNFRSF11A gene rs9646629, rs4485469, rs34739845, rs4941129, rs17069904, rs884205 single nucleotide polymorphisms and breast cancer patients carrying BRCA1 or BRCA2 pathogenic variation
The differences between the results of the genetic study can be caused by ethnic differences among the populations. In this context BRCA1 / 2 in the etiology of occurring breast cancer mutations reason that there may be a role for TNFRSF11 variations, increasing the number of samples to be held in different centers in Turkey, we öngörüsünd it should be supported by new studies.

Key Words: TNFRSF11A, Breast Cancer, BRCA1, BRCA2, Single Nucleotide Polymorphism

P-022 - Epigenetic Approach in Forensic Age Estimation

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In this study, it is aimed to determine the recent developments in the epigenetic field and to evaluate the forensic use of epigenetic-based age estimates.
The use of genetic analysis in forensic science began with RFLP (Restriction Fragment Length Polymorphism) analyzes in the late 1980s. Later, Alec Jeffrey began working in the forensic field with STR (Short Tandem Repeat) sequences, a molecular genetic technique that revealed genetic differences between humans. The use of STR loci in forensic science has begun to create DNA fingerprints belonging to suspicious and victim. However, even though STR studies have a very high discrimination power, they can not be used to solve all kinds of justice cases. In forensic science, it is possible to study DNA with SNP (Single Nucleotide Polymorphisms) method of all kinds of samples (blood, hair, swab). Together with molecular genetic developments, SNP analyzes, which also allow the detection of an unknown sample hair, eye and skin color and geographical sub-structure in the forensic case, have started to be used over time.
Recent studies on epigenetic mechanisms have shown that DNA methylation can be used in case of studies for the prediction of forensic age. Using different methodological approaches and DNA methylation markers (CpG sites) tested to date, results were obtained with an accuracy of ± 3-4 years. Thus, the progress of genetic and epigenetic studies in forensic sciences has begun to predict phenotypic properties from the DNA of evidence samples. Because DNA base sequences are the same, discrimination of single twins for forensic cases is one of the most troublesome aspects of forensic science. In a study of DNA methylation levels in monozygotic twins; there was little difference between the twins in the early stages of life, but there were significant differences between twins over 28 years of age.
For the estimation of age in forensic sciences in recent years; Significantly reduced error rates in the discovery age estimates of new multiple CpG regions with the linear correlation between DNA methylation levels and biological age.

Key Words: Forensic Sciences, Epigenetics, Age Estimation

P-023 - Silencing of CERS5 (Ceramide Synthase 5) Alters the Protein and Gene Expression of Atherosclerosis Related Genes in Endothelial Cells

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Ceramide is a secondary messenger in sphingomyelin pathway, which can be produced from sphingomyelins or synthesized de novo by ceramide synthase. CERS5 (LASS5) which is crucial for the de novo synthesis of ceramide was found to be indirectly related with the AMPK. Since, the association between AMPK and atherosclerosis and hypertension was already known, in this study we aimed to investigate the relation between atherosclerosis and CERS5.
In order to investigate the differential expression of CERS5, AMPK, and AMPK target genes, CERS5 gene-specific small interfering RNA (siRNA)-mediated gene silencing was performed in human umbilical vein endothelial cells (HUVEC). Then HUVEC cells were treated with AMPK activator and inhibitor to examine the relationship between AMPK activity and the expression levels of CERS5. Quantitative real time polymerase chain reaction (qRT-PCR) and western blot testing were performed for the determination of expression levels.
Downregulation of CERS5 and activation of AMPK by AICAR was found to increase expression of some AMPK target genes in HUVEC, in both mRNA and protein levels. HUVECs that were incubated with AICAR which is the activator of AMPK, increased both KLF2 and eNOS expression. Silencing of CERS5 with gene-specific siRNA showed an increase in expression of KLF2 and eNOS. On the other hand, in the culture conditions which contain Compound C, a decrease in the expression levels of eNOS and KLF2 was observed.
In this study, with the silencing of CERS5 gene, it was observed that expression and protein levels of AMPK and AMPK target genes altered and these findings demonstrate CERS5 might be playing role in pathogenesis of atherosclerosis.

Key Words: CERS5, AMPK, Atherosclerosis, siRNA, Western Blot

P-024 - Computational Modelling Approaches as a Potential Platform to Understand the Molecular Genetics Association between Parkinson's and Gaucher Diseases

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To computationally characterize the shared mutations between Gaucher disease (GD) and Parkinson's disease (PD)
We used different in silico tools and molecular dynamics, in silico tools for both pathogenicity and stability of the GBA protein enzyme shared mutations between PD and GD. We found that the L444P is the most damaging shared mutation. The GBA mutations that were reported to be associated with the development of PD (L444P, N370S, K198 T, T369M, V394L, R496H, and E326K). The L444P mutation was found to be highly pathogenic and was possessed destabilizing properties compared to the other mutations. The structural analysis and molecular dynamics approach were utilized to compare most frequent deleterious mutations N370S and L444P with the mild mutation E326K. The structural analysis showed that the E326K and N370S mutations are least pathogenic that were positioned in the alpha helix region of the protein, whereas the pathogenic L444P mutation was positioned in the starting point of the beta-sheet. This positioning of L444P mutation might be the reason for the potential pathogenicity of the mutation. Finally, molecular dynamics simulations demonstrated a higher deviation and fluctuation with a lower number of intramolecular hydrogen bonds and compactness in the L444P mutant protein. These computational findings were supported with the previously published in vitro and in vivo data, emphasizing the usefulness of computational tools in variants interpretation. This suggests that the mutation L444P could be a potential target for therapeutic development for patients with GD and PD. This study will shed light on the structural and functional role of GD mutations that are involved in PD pathogenesis.

Key Words: Gaucher's Disease; L444P; N370S; Parkinson Disease; Variant Classification

P-025 - Expression Levels of Inflammasome Complexes in Experimental Autoimmune Myasthenia Gravis Mouse Model(EAMG)

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Myasthenia gravis (MG) is an autoimmune neuromuscular disease characterized by abnormal muscle weakness, fatigue, and the development of anti-acetylcholine receptor (AchR) antibodies against nicotinic acetylcholine receptors and receptor damage as a result. It is known that antibodies developped against AchR cause postsynaptic membrane destruction via complement system and decrease the number of receptors by cross-linking of these antibodies. However, how the autoimmune response begin is still not known. Current treatment of the disease is aimed at relieving the symptoms and there is need for treatment with more specific mechanism of action and lower side effects. Our aim is to determine the relationship between the genes involved in the inflammasome complex and the inflammatory response in MG disease.
Induction of experimental autoimmune myasthenia gravsis(EAMG) is done by immunizing C57BL/6 mice three times in total by one-month intervals using torpedo AchR which is specific to MG disease and Freund's Complete Adjuvant(CFA) as an adjuvant. Blood was collected from tail of mice before immunization and total IgG levels against AchR were determined by ELISA. Lymph node cells are isolated and caspase-1, NLRP3, IL-1B, P2X7R, and Akt-1 gene expression levels were determined by RT-PCR.
Mice are monitored for signs of muscle weakness by performing clinical scoring, paw-grip test and motor activity tests. Anti-AChR Ig isotype levels in the serum is determined by ELISA. Mice that developed antibodies against AchR is included in the EAMG group. Incresement in caspase-1, NLRP3 and P2X7R gene expression, and a decreasement in Akt-1 gene level is determined in EAMG group compared to the control group. The increasement in IL-1β gene was significant ($p = 0.01$) in EAMG group. There was no correlation between serum antibody levels and gene expression levels.
The reason why the difference in the gene expression was not significant is due to the low number of mice included in the study. However, significant increase in the level of IL-1B expression indicates the importance of inflammation response. We believe that this study will be able to determine the importance of inflammasome complexes in the pathogenesis of MG and contribute to finding inflammasome-based treatments.

Key Words: Myasthenia Gravis, Inflammasome, EAMG

P-026 - Determination of IL-28B Polymorphism and IL-28B Serum Levels in Turkish Patients with Hepatitis B and Hepatitis C

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It is important to determine the factors that lead to chronicity in hepatitis B virus (HBV) and hepatitis C virus (HCV) infection so that we can take measures to prevent chronic infection. In this study, we aimed to investigate the frequency of Interleukin-28B (IL-28B) rs12979860, rs8099917 and rs12980275 single nucleotide polymorphisms (SNP) and to detect IL-28B serum levels among Turkish patients with HBV and HCV infection.
A total of 64 patients with HBV infection, 76 patients with HCV infection, and 70 healthy control were included in the study. IL-28B SNPs were investigated by real time PCR. Plasma levels of IL-28B were measured by ELISA.
The rs12979860CT genotype and T allele and the rs12980275AG genotype and A allele were significantly lower in patients with HBV infection when compared with controls. However, the TG genotype and G allele frequencies of the rs8099917 in patients with HCV infection were significantly higher than that in controls. The plasma IL-28B levels were lower in patients with HBV or HCV infection compared to controls.
rs12979860CT and rs12980275AG genotypes may play a role in preventing the chronicization of HBV infection. In the HCV infection, the rs8099917TG genotype may be contributing to the chronicity of HCV infection. Considering the results, we believe that these SNPs could be used as biomarkers for predicting clinical outcomes and be useful to take precautions to prevent progression of hepatitis infection and to improve new molecular targeted therapies with further investigations.

Key Words: IL-28B Polymorphism, Hepatitis B, Hepatitis C

P-027 - Investigation the Serum Total Antioxidant and Total Oxidant Status in Diabetic and Non-Diabetic Acute Ischemic Stroke

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Free radicals formed during tissue damage, depending on various factors, cause oxidative stress, which is dangerous to all organs and tissues in the organism. Free radicals cause changes in nucleic acid, lipid and DNA, degradation of protein and cell structure, and alteration of enzyme responses. Determination of Total Antioxidant Status (TAS) and Total Oxidant Status (TOS) are useful markers to understand the oxidative damage and defence of body to free radicals. Several studies have shown that oxidative stress is associated with stroke and diabetes. The aim our study is to investigate the oxidative-antioxidative status in acute ischemic stroke.
In this case-control study 50 patients who had a stroke for the first time in their life and 30 healthy controls, a total of 80 individual were included. The 50 stroke patients were divided into two groups as 27 diabetic and 23 non-diabetic. Serum levels of TAS and TOS were measured by using commercial kits.Serum TAS values were 1.68±0.29 mmol/l in diabetic stroke patients, 1.72±0.33 mmol/l in non diabetic stroke patients and 2.04±0.22 mmol/l in control group ($p<0.01$). Serum TOS values were measured as 33.08±20.95 mmol/l in diabetic stroke cases, 23.98±18.34 mmol/l in non diabetic stroke cases and 9.26±4.17 mmol/l in the control group ($p<0.01$). Compared controls with ischemic stroke, serum TAS levels were significantly lower and TOS levels were significantly higher in patients with ischemic stroke than controls. Also, diabetic patients had lower TAS levels and higher TOS levels when compared other groups ($p<0.01$).
A significant association between diabetes mellitus and oxidative stress has been established in patients with ischemic stroke, a proven risk factor. This study suggests that patients with diabetic ischemic stroke have a higher risk of exposure to oxidative stress than non-diabetic ischemic stroke patients.

Key Words: Total Antioxidant Status, Total Oxidant Status, Ischemic Stroke, Oxidative Stress, Diabetes Mellitus

P-028 - Evaluation of the Association of MTHFR Gene Polymorphism with the Family History of Fibromyalgia Syndrome (FMS)

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Fibromyalgia syndrome (FMS); etiology is unknown and is characterized by chronic diffuse pain, usually accompanied by fatigue, sleep problems, cognitive disorders, and somatic complaints. Causes of the disease are multifactorial. In individuals with genetic predisposition; environmental, immunological, traumatic, hormonal factors, central and peripheral sensitization trigger the formation of FMS. FMS is more common in family history. Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme in folate metabolism. In MTHFR C677T polymorphism, there is a point mutation resulting from the change of C (Cytosine) to T (Thymine) which is the nucleotide 677 in the gene encoding MTHFR enzyme. In our study, we investigated the relationship between clinical status and MTHFR gene polymorphism (C677T) in the family history of FMS patients.
The study included 50 patients with FMS and 35 healthy control subjects. The MTHFR C677T polymorphism of the patients and the control group were analyzed by the real time-PCR method and homozygous mutant, heterozygous mutant and homozygote were divided into 3 groups. Visual analog pain scale (VAS), Back depression scale (BDI), sensitive point number, SF-36 and fibromyalgia effect questioning (FES) were used in the clinical evaluation of the patient group.
Patients in the patient group had 15 (30%) were history. 7 (46.7%) of the patients had a heterozygous mutant, 6 (40%) had a homozygous mutant and 2 (13%) had a homozygous normal genotype ($p <0.05$). There were 35 (70%) patients with no family history, 14 (40%) had heterozygous mutants, 5 (14.3%) had homozygous mutants and 16 (45.7%) had homozygous normal genotypes ($p <0.05$). . 10 (31.3%) of the subjects in the control group were heterozygous mutants and 22 (68.8%) were homozygous normal genotypes ($p> 0.05$). No homozygous mutant genotype was found in the control group. We couldn't analog any significant difference in heterozygous mutant patient group when we compared VAS pain, BDI, FES and SF-36 values with other genotypic groups ($p> 0.05$).
216/5000 The results of our study showed that MTHR C677T homozygous mutant genotype was more common in patients with FMS, but this genotype, with the clay status of the disease.

Key Words: Fibromyalgia Syndrome, Methylenetetrahydrofolate Reductase, Polymorphism

P-029 - The Role of Nurses in Genetics and Genomics Health Care

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Advances in genetics, genomics and pharmacogenomics play an important role in the treatment of genetic diseases such as cancer, Marfan syndrome, sickle cell anemia. After the completion of the human genome project in 2003, the need for nurses to understand genetics information has attracted more attention and genetics has become a part of all aspects of nursing today. This study focuses on the potential role of nurses in genetics and genomic health care.
We conducted a PUBMED literature review on the potential role of nursing in genetics and genome health services.
Recent advances in pharmacogenomics of the treatment of diseases such as cancer and cardiovascular illness emphasize genetic linkage. Therefore, the genetic aspect of the abnormality in current treatments has been targeted. In addition, as nurses have a major impact on the care and treatment of patients, they need to be informed about the conditions of treatment affected by genetic factors. Nurses can contribute to treatment when they provide training to patients or their relatives about a genetic mutation specific treatment. As an example of this practice, Marfan syndrome is an autosomal dominant disease caused by the mutation of the FBN1 gene. Nurses can show their genetic competencies by evaluating a patient's knowledge of this disease and by explaining the heredity pattern and treatment plan. Due to the development of genetic tests and targeting of genetic changes of drugs, it obliges critical care nurses to share information about the genetic and genomics with the patients and their relatives. Nurses function as educators and help patients to understand the science of genetics behind the treatment plan.
In conclusion, in critical care nursing, genetic becomes increasingly important. The training of all nurses in the field of genetics and genomics is an important need in order to provide the best practices in the treatment, identification and prevention of the disease.

Key Words: Genetics, Genomics, Nursing

P-030 - Chitin Molecule Increases the Angiogenesis in Chorioallantoic Membrane Model in the Presence of Testosterone and Progesterone

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Angiogenesis is a process of generating new blood vessels from preexisting vessels. In adults, it is activated in only pathologic conditions. Chitin is an organic molecule which is used in scaffold technology in tissue engineering. Growth hormones such as testosterone and progesterone are used in scaffold structure for induction of angiogenesis. No literature was found about the angiogenic roles of chitin/testosterone/progesterone. In this study, chitin was analyzed in the presence of testosterone/progesterone to find out its' possible role on angiogenesis.
Chitin used in our study was obtained from shrimp shells in our laboratory. The angiogenic effects of chitin/testosterone/progesterone were analyzed on chick embryo chorioallontoic membrane (CAM) model. Six different study groups were prepared (control group-Group 1, testosterone applied group-Group 2, progesterone applied group-Group 3, chitin/testosterone applied group-Group 4, chitin/progesterone applied group-Group 5, chitin/testosterone/progesterone applied group-Group 6). Hormones were used in different concentrations. The angiogenic role of selected molecules was clarified according to the total differentiation score of angiogenesis (TDSA) results in all groups. In obtaining of TDSA results, Knighton's protocol was applied.
TDSA was 6±0.1 in testosterone applied group, 5±0.2 in progesterone applied group, 7±0.1 in chitin/testosterone applied group, 5±0.1 in chitin/progesterone applied group, 7±0.1 in chitin/testosterone/progesterone applied group. In all groups, TDSA results were statistically significant. These results represented the angiogenic role of chitin in the presence of testosterone and progesterone ($p<0.05$).
Our results support the angiogenic roles of chitin in the presence of testosterone and progesterone. Chitin, testosterone and progesterone can be used in scaffold technology together.

Key Words: Chitin, Testosterone, Progesterone, Chorioallantoic Membrane, Angiogenesis

P-031 - Effects of VDBP, VDR Mutations and other Factors to the Development of Stent Thrombosis in Coronary Artery Disease Patients

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Coronary artery disease (CAD) is associated with functional and structural changes of the coronary arteries, resulting in ischemia or plaque rupture, and is highly associated with endothelial. In some CAD patients, stent trombosis (ST) occur after stent implantation. vitamin D deficiency and some mutations in the genes which are related with vitamin D metabolism have found in an association with some disorders therefore it may also be related with ST development. Therefore the aim of this study is to investigate the association between vitamin D level, vitamin D receptor (VDR), vitamin D binding protein (VDBP) gene mutations, and some other risk factors with ST in CAD patients after stent implantation.
Seventy-three CAD patients who were implanted with stents by surgical intervention were enrolled. Thirty-seven patients with ST were included in the patient group, and 36 patients without ST were included in the control group. After obtaining necessary information from the patients, DNA was isolated from blood. Rs2228570 and rs1544410 mutations in the vitamin D receptor (VDR) gene as well as rs4588 and rs7041 mutations in the vitamin D-binding protein (VDBP) gene were investigated by performing real-time polymerase chain reaction. Biochemical measurements, such as those of vitamin D and lipid levels, were performed using appropriate kits. Results were evaluated using statistical methods.
The number of individuals who carry homozygous or heterozygous alleles of the rs4588 mutation in the VDBP gene was found to be statistically high in the patient group ($p=0.027$). Vitamin D and hemoglobin levels were significantly low and C-reactive protein levels were significantly high, while the occurrence of vitamin D deficiency, hypertension, and familial history of CAD as well as the current status of smoking were significantly high in the patient group ($p<0.05$). Additionally, the presence of a homozygous rs1544410 mutation in the VDR gene of individuals who have diabetes mellitus was statistically high ($p=0.035$). According to genotype distribution, statistical significance was observed between HbA1c levels and the rs1544410 mutation ($p<0.05$).
The rs4588 mutation in the VDBP gene, which plays a role in vitamin D metabolism, vitamin D deficiency, and some other risk factors may cause ST.

Key Words: CAD, Stent Thrombosis, VDR, VDBP, Vitamin D Deficiency

P-032 - miRNA Expression Levels in Patients with Chronic Venous Insufficiency

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Chronic venous insufficiency (CVI) is a common health problem with various symptoms such as cramps, skin changes, venous ulcers due to venous hypertension caused by venous obstruction or pathological valve failure in lower extremity veins. Various candidate miRNAs have been identified in endothelial cells, vascular smooth muscle cells and great saphenous veins, which are involved in the regulation of vascular rearrangement, collagen metabolism, and matrix metalloproteinases in studies investigating mechanisms of pathogenesis of CVI. The aim of this study is to compare the expression levels of miR-155 and miR-146a which expressed in immune cells that are effective in formation and regulation of inflammation in the blood was taken from antecubital vein and varicose saphenous vein.
Peripheral blood samples were collected from antecubital vein and varicose saphenous vein from 22 male CVI patients with mean age 45,5±10,6 years. For control group, peripheral blood samples were collected from antecubital vein from 5 male with mean age 43±13,5 years. Once cDNA was synthesized from appropriate quality and quantity of isolated RNAs, expression levels of candidate miRNAs were determined by qRT-PCR in the LC480 device. The statistic analyses were performed by SPSS. The miR-155 and miR-146a expression levels in the blood from varicose saphenous vein and the blood from antecubital vein were found to be increased compared to control group (respectively, p=0,028 and p=0,087). The increasing of miR-146a expression level was 1.9 fold in varicose blood according to antecubital blood. However, miR-155 expression level was not changed in varicose blood according to antecubital blood. The expression levels of miR-155 were found as mean: 1.56 ± 1.11 in control group, 21.83 ± 28.22 in antecubital blood and 23.68 ± 43.16 in varicose blood. And also, the expression levels of miR-146a were found as mean: 1,34±1,20 in control group, 18,89±33,95 in antecubital blood and 35,25±109,43 in varicose blood. As there were significant differences in the expression levels of miRNAs among the patients' samples, it was planned to increase the number of cases and perform subgroup analyses.
The miRNAs involved in the formation and regulation of inflammatory responses may have local effects in the etiopathogenesis of CVI and venous valve dysfunction.

Key Words: Chronic Venous Insufficiency, Varicose Veins, Micro RNA, Expression Level

P-033 - The Investigation of Relationship between Hot Flashes and Epigenetic Changes in Menopause Cases

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The decreased level of estrogen causes physiological problems and hormonal changes in menopause. Reduction of estrogen also has an effects the catecholamine metabolism and decreased the catecholamine synthesis. This leads the lower catecholamine concentration in hypothalamus and imbalances in body temperature. This study was carried out on 30 pre-menopausal and 35 post-menopausal women. Methylation status of RANKL and FSHR genes was studied by MS-HRM. The statistical analyses and their associations with patient characteristics were performed by Pearson Chi-Square and Fisher's Exact Test ($p<0.05$). The mean age of 30 pre-menopause patients was 33.5 ± 6.9 and 56.7± 4.9 was the post-menopause patients. RANKL gene was detected as a methylated in 16 post-menopausal cases and 10 pre-menopause cases. There we no statistically significant association detected between two group ($p>0.05$). But in 12 (%75) of the 16 RANKL methylated cases had hot flashes and there were statistically significant association detected between methylation and hot flashes ($p=0.024$). FSHR gene was detected as a methylated in 18 post-menopausal cases and 20 pre-menopause cases. There were no statistically significant association detected between two group ($p>0.05$). In 13 (%75) of the 18 FSHR methylated cases had hot flashes and there were statistically significant association detected between FSHR gene methylation and hot flashes ($p=0.028$). The association between RANKL gene abnormalities, fluctuation of FSH level and thermoregulation has been identified by researchers. This was the first study which showed the association between epigenetic changes of RANKL and FSHR genes and hot flashes in menopause.

Key Words: FSHR, RANKL, Menopause, Hot Flashes, Epigenetics

P-034 - Epigenetic Mechanisms in Osteoarthritis

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Osteoarthritis (OA) is the most common joint disease and is the leading cause of physical disability in the elderly population. OA is characterized by degeneration in the articular cartilage, synovial inflammation and anormal changes in the subchondral bone. OA causes a tremendous socioeconomic burden and its etiology is not fully understood. A better understanding of the molecular mechanisms underlying the pathophysiology of OA is needed to identify new therapeutic targets or biomarkers. OA is a complex and multifactorial disease in which genetic and environmental factors are effective. Expression of OA related specific genes are regulated by epigenetic mechanisms including DNA methylation, histone modification, non-coding RNAs. This study focuses on epigenetic mechanisms of genes associated with the pathogenesis of OA. A PUBMED literature review was performed to investigate the original papers on epigenetic mechanisms in OA.
Recently, epigenetic studies have developed as a new field of OA research. OA-related risk factors such as obesity, age, gender, injury trigger epigenetic mechanisms. This may lead to abnormal gene expression of transcription factors (SOX9, Nfat1), collagen (COL2A1, COL9A1), cytokines (IL-1β, TNF-α) and matrix proteinases (MMP13, ADAMTS4) in articular Cartilage. Abnormal expression of these OA-specific genes disrupts the anabolic and catabolic balance of articular tissues (cartilage, synovium, subchondral bone). Consequently, joint homeostasis is disrupted and cartilage degeneration occurs as a major finding of OA.
Recent advances in epigenetic studies concerning the pathogenesis of OA contribute to a better understanding of the cellular and molecular mechanisms underlying the development of OA. Furthermore, these studies will promote the development of new potential drugs or strategies for the treatment of OA.

Key Words: Osteoarthritis, Epigenetic, Regulation

P-035 - VDBP, VDR Variatıons and other Factors Related with Vitamin D Metabolism may be Associated with Type 1 Diabetes Mellitus

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Type 1 diabetes mellitus (T1DM) is an insulin dependent autoimmune disorder resulting the progressive destruction of pancreatic beta cells. It has known that both genetic and environmental factors effect development of the disease. Another possible factor considered to be related with T1DM is vitamin D deficiency. In this study, it was aimed to investigate the associations between vitamin D binding protein (VDBP) and vitamin D receptor (VDR) gene mutations, vitamin D deficiency which are related with vitamin D metabolism and some other factors with T1DM.
Fifty five T1DM paitents and 40 healthy volunteers were recruited to the study. FokI (rs2228570), BsmI (rs1544410) mutations in VDR; rs4588 and rs7041 polymorphisms in VDBP were investigated with real-time polymerase chain reaction (RT-PCR). Other risk factors related with T1DM were also investigated. Results were evaluated statistically.
Statistically significant relations were found in glucose, HbA1c, thyroid-stimulating hormone (TSH), higher 25[OH]D, free vitamin D, calcium, albumin, log25[OH]D, retinopathy, higher than 30 mg/day microalbuminuria in T1DM patients. Also statistically significant association was found between C allele in FokI and T1DM in patients. When the relation between the risk factors and mutations were investigated, it was found that VDBP, free vitamin D and bioactive vitamin D were significantly associated with rs7041 mutation in VDBP whereas HDL was significantly associated with rs2228570 mutation in VDR.
In conclusion; VDBP, VDR variations and other factors related with vitamin D metabolism may be associated with type 1 diabetes mellitus. Other studies with larger data sets may demonstrate more reliable statistical results to rule out genotype-phenotype correlations of the disease.

Key Words: Type 1 Diabetes Mellitus, Vitamin D Deficiency, VDR, VDBP, RT-PCR

P-036 - A Prenatal Case of Mosaic i(20)(q10) Presenting with Multiple Fetal Anomalies

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The isochromosome 20q is formed by the loss of the short arm and joining of the two long arms. In the prenatal period, it is usually seen as confined to the placenta and is rarely associated with anomalies. In the literature, a few cases of mosaic i(20)(q10) with anomalies in prenatal period have been described. Diaphragmatic hernia, ventricular dilatation, anophtalmia, dysmorphism, segmentation disorders of the thoracic vertebrae, single umbilical artery, artrogriposis and clubfoot were described. Here we present a rare antenatally diagnosed case of i(20)(q10) with FUSG anomalies.
Amniocentesis was performed to a 21-year-old mother in her first pregnancy with the indication of cystic hygroma and elevated risk for trisomy 18 in the the first trimester screening test. Detailed F-USG was performed at 22 + 3 weeks and revealed cystic hygroma, hyperechogenic bowel, lower thoracic hemivertebrae, left isomerism and complete AVSD . In addition, the inferior vena cava could not be observed and the stomach was replaced towards the midline. Fetus had single umbilical artery.
Cytogenetic analysis of amniocentesis revealed mosaic 46,XY[6]/46,XY,i(20)(q10)[34] in two seperate cultures. FISH analysis with both uncultured and cultured amniocytes confirmed the presence of i(20)(q10) mosaicism. Karyotypes of the patient and her husband were normal. Cordocentesis was recommended to the patient, but the patient reject. The baby was born at 34 weeks of pregnancy in another hospital and after 1 month of neonatal intensive care, the baby died.
The mosaicism of i(20)(q10) which is detected in prenatal period is very rare. Most of the patients have placental mosaism and no anomalies can be detected and are born normally. Fetal anomalies were found only in true mosaic cases. Cystic hygroma, thoracic hemivertebra and single umbilical artery were well-defined anomalies in these cases and our patients had them too. However, it was noteworthy that the patient had a cardiac anomaly and left isomerism which were not previously described in the literature. In the prenatal period, mosaic i(20)(q10) cases should be considered carefully and it should be differentiated from placental mosaism and followed up with F-USG for anomalies. Cordocentesis or second amniocentesis should be recommended all the cases.

Key Words: Multiple Fetal Anomaly, Isochromosome 20q, Left Isomerısm

P-037 - A Case with 48,XXYY Syndrome Diagnosed at Prenatal Period

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A 28-year old G3P1A1 woman underwent amniocentesis at 19-weeks-3-day of gestation due to detection of single umbilical artery in fetal ultrasonography (USG) and presence of maternal anxiety.
Fluorescence in situ hybridization (FISH) analysis of direct amnion cell preparation revealed aneuploid signals of sex chromosomes. After long-term tissue culture of amniocytes, FISH result was confirmed in conventional cytogenetic analysis with 48,XXYY karyotype. The family who was informed about the syndrome and given genetic counseling, requested termination of the pregnancy due to the expected severe neuropsychiatric findings.
48,XXYY syndrome which is seen in 1/18.000-50.000 in male births is rarely diagnosed in prenatal period due to lack of specific fetal USG findings. Although the syndrome which has been adopted as a variant of Klinefelter syndrome in the past, in addition to nonspecific minor dysmorphic symptoms, congenital heart defects and skeletal anomalies may be associated, it is now defined as a syndrome different from Klinefelter syndrome with anxiety, aggression, severe mental retardation and taller stature. In the literature, four prenatal cases have been described so far, and for review of prenatal diagnosis indication in the presence of minor USG findings in fetuses who do not have a significant finding for aneuploidies the fact that in terms of presented our case make it valuable.

Key Words: 48,XXYY Syndrome; Prenatal Diagnosis; Single Umbilical Artery

P-038 - The Investigation of the Relationship between Spermatogonial Stem Cell Biomarker ITGA6 with Spermatogenic Defects

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Integrins act as surface membrane receptor that provide calcium-dependent cell-cell and cell-matrix interactions. Integrins are cell surface glycoproteins and integrated between the extracellular matrix and the intracellular environment. The junction of the SSCs to the laminin of the basal lamina occurs with glycoprotein receptors on the surface of the SSC. Two receptors are known to bind to the laminin: integrinα6 (ITGA6) and integrinβ1 (ITGB1), these receptors have been reported to be necessary for the proliferation, differentiation, survival and migration of cells. Our aim was to investigate both ITGA6 gene and protein expressions in testis tissues of non-obstructive azoospermia (NOA) patients
Gene expression and protein expession were performed by qPCR and western blot analysis. NOA group consisted of hypospermatogenesis (HS), maturation arrest (MA), Sertoli Cell Only syndrome (SCO) patients. All groups were compared with OA groups (n=10).
It was showed that ITGA6 gene expressions decreased 0.65±0.15 and 0.22±0.03 fold ($p < 0.05$) in the HS (n=20) and MA (n=20) groups, respectively. In the SCO (n=20) group, ITGA6 gene expression increased 1.67±0.37 fold ($p > 0.05$). It was determined that ITGA6 protein expressions decreased 0.70±0.18 fold in the HS (n=5), while increasing 2.18±0.87 ($p < 0.05$) and 1.21±0.11, ($p > 0.05$) folds in the MA (n=5) and SCO (n=5) groups, respectively.
In many experiments, ITGA6 has been used as a surface marker in the purification of human spermatogonia. Our results showed that the ITGA6 gene was differently expressed in NOA patients. The significant decreases in ITGA6 gene expression may be related with spermatogenesis defect as a result of effecting dynamism of tight junctions. On the other hand, significant increase in ITGA6 might induce germ cell aplasia, causing germ cell death with the activation of apoptosis pathway which is NF-KB and caspase-dependent by ITGB1/ITGA6 complex. It is planned to study protein expression levels in more patients. The results we obtained contribute to understanding the etiology of the spermatogenesis defect and has the capacity of helping to develop spermatogonial stem cell treatments.

Key Words: Spermatogonial Stem Cell, ITGA6, Non-Obstructive Azoospermia, Male Infertility

P-039 - A Case with Recurrent Fetal Loss, 46,XX,T(2;6) (q33pP25) Karyotype and Her Thrombophilia Panel

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Chromosomal translocations occupy an important place in terms of spontaneous pregnancy losses and anomaly infant birth. The frequency of thrombophilia can be as high as 60% in families with TFK (recurrent fetal loss). The risk of TFK and pregnancy complications is significantly increased by chromosomal anomalies, thrombophilic disorders and placental vascular thrombosis due to antiphospholipid antibodies. Chromosome analysis was performed on the metaphase plaque obtained from the our case's peripheral blood cell culture. In our case, factor V leiden, Factor II (G20210A), (MTHFR) (C677T), (MTHFR) (A1298C) mutations were screened by Real Time PCR method and the mutations of PAI (4G/5G), Factor V Cambridge (G1091C) were screened by RFLP method.
Our case was 29 years old woman who had 3 pregnancies resulted in intrauterin fetal loss and she had a family history of abortion. Her pregnancies were lost at 7 weeks of age.
Anticardiolipin and lupus anticoagulant screening were negative. In karyotype analysis, she was 46,XX, t(2;6) (q33;p25) and .her partner was 46, XY karyotype. Her thrombophilia panel result was found as PAI 4G/5G, FVLeiden G1691A and MTHFR A1298C heterozygote. Conventional cytogenetic analysis planned from the third abortion material. The karyotype of the abortion material was found as 46, XY, der(17) t(10:17) (p11.1; q11.1).
Thrombosis risk factors and balanced translocation carrier are very important in habitual abortions.

Key Words: Chromosomal Translocations, Recurrent Fetal Loss, Thrombophilia Panel

P-040 - Frequency of Chromosomal Abnormalities in Cases with Recurrent Pregnancy Loss

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To determine the frequency of chromosomal aberrations in cases with recurrent pregnancy losses in the first trimester of pregnancy using conventional cytogenetic analyses
Chromosomal results of 3424 cases (1638 male,1786 female) presented with recurrent pregnancy losses to our department between 2007 and 2017 were analyzed retrospectively.
In addition to the 1409 couples, there were 229 males and 377 females who presented without their partners. Means of age were 34.21±5.81 and 31.26±5.66 among men and women respectively. Chromosomal abnormality was found in 64 out of 3424 individuals (1.87%). Cytogenetic abnormalities were found 2.18% for women and 1.52% for men. The most frequently observed chromosomal abnormality type in both genders was reciprocal translocations (50%). The most frequently translocated chromosome was chromosome 1 (17.18%). While isodicentric chromosomes constituted 12% of abnormalities in men, there was only one woman with dicentric chromosome and no women had isodicentric chromosome. Balanced complex chromosomal rearrangements were found in two females with four chromosomal breaks involving two (chromosomes 1 and 21) and three (chromosomes 7, 8, and 12) chromosomes. In one of these causes the abnormality was observed to be familial. There were inversions in both groups involving chromosome 3 (in the female case) and 12 (in the male case). We observed that female patient with der(X)t(X;Y)(p22;p11)SRY- had a healthy baby after being diagnosed. Karyotype of the baby was normal.
Unbalanced gametes in the carriers with balanced chromosome abnormality can lead to early pregnancy losses. Although gamete possibilities due to new chromosomal rearrangements have been known theoretically, empiric risk may be different than expected. Therefore the couples who have recurrent pregnancy losses should receive genetic counselling and be referred for cytogenetic analyses. Follow up of couples after being diagnosed may provide important data on the risks of individuals with the same abnormalities.

Key Words: Recurrent Pregnancy Loss, Chromosomal Abnormality

P-041 - Associating the Number of Copy Number Changes Detected in the 1st Chromosome to the Phenotype as a Result of Array CGH Analysis

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This study is a review of cases of different genomic magnitudes between the 605 patients who applied to the Department of Medical Genetics of Trakya University Medical Faculty between 2015-2018 and analyzed for peripheral blood and amniocentesis materials.
This study included pregnant women with prenatal ultrasound findings and patients with dysmorphic findings (including their parents). Karyotype analysis was performed to the patients within the clinical findings of the patients. As a result of the karyotypes evaluated, SNP + CNV array (single nucleotide polymorphism, copy number variation) method was used to determine the number of copy changes that could be associated with the patients' clinics. Since SNP arrays are prepared using the original probe, the polymorphic allele allows for the detection of copy number changes as well as genotyping and UPD detection. Array based methods provide a higher resolution analysis than conventional cytogenetic methods and FISH analysis. In some centers, the first step in the detection of chromosomal anomalies was used as a diagnostic method.
The array applications of SurePrint G3 4x180K Human Kit (Agilent Technologies, Santa Clara, CA, USA), and slide scans Agilent Feature Extraction software is used. The data were analyzed by human genome reference sequence hg19. The data were analyzed by human genome reference sequence hg19.
In all patients presenting to our outpatient clinic with different clinical pictures (605 patients), as a result of arrayCGH analysis, changes in the number of copies of different sizes of p and q arms of the chromosome 1 were detected in 13 patients.

Key Words: Chromosome, Array-CGH, Phenotype, Dysmorphology

P-042 - A Case Wİth Del15q11.2: Interpretatıon of a Neurosusceptibility Locus

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Proximal part of long arm of chromosome 15 is rich for segmental duplications and five break point defined in that region. 15q11.2 microdeletion (OMIM#615656) is located between break point 1 and 2. Del15q11.2 is one of the copy number variants which creates risk for neurodevelopmental disorders. Besides, congenital heart defects and obesity were shown to accompany in some patients. It is often inherited from phenotypically normal parent. Deleted region is characterized by reduced penetrance and variable expressivity. Phenotypic variability creates challenge for counselling (Vanlerberghe et al., 2015; Wolf et al., 2013). The aim of this presentation is to discuss interpretation and genetic counseling process of a neurosusceptibility locus over a patient with del15q11.2.
Genetic etiology of moderate intellectual disability and obesity was investigated in a 8 year old patient.
Methylation pattern of Prader Willi-Angelman Syndrome locus was normal and 908 kb loss at chromosome 15q11.2 region was detected with microarray (Affymetrix CytoScan 750K) analysis. Detailed genetic counseling provided to parents. Analysis of same region with RT-PCR for confirmation and after that microarray analysis of parents were also planned.
Del15q11.2 is defined as neurosusceptibility locus namely a risk factor for various neurodevelopmental disorders. Phenotypic variability creates a real challenge for counselling. Variable genetic and environmental factors probably associated with more severe phenotypes. Detailed medical and family history, inheritance pattern could help medical professionals for interpretation process. Further genetic studies in families with del15q11.2 will eliminate unknowns of this condition.

Key Words: Del15q11.2, BP1-BP2, Neurosusceptibility Locus, Interpretation, Genetic Counseling

P-043 - Clinical Findings of 16p13.11 Copy Number Variations

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Chromosome 16 harbors ‘‘low copy repeat’’ regions that result in recurrent genomic rearrangements by non-allelic homologous recombination. 16p13.11 deletions are implicated in epilepsy and cognitive impairments whereas duplications are associated with various neurodevelopmental and neuropsychiatric disorders such as autism spectrum disorder, attention-deficit/hyperactivity disorder, intellectual disability and schizophrenia. 16p13.11 duplication is also implicated in cardiac and skeletal manifestations like joint hypermobility, craniosynostosis and polydactyly. Here we report on 5 patients harboring 16p13.11 duplications and 2 patients with 16p13.11 deletions with diverse clical findings.
The ages of the patients varied between 5.5 years and 31 years(Median age: 7.5 years), six of the patients were males and one was female. All of the patients exhibited varying degrees of neurodevelopmental and neuropsychiatric findings. Although the patients didn’t have common dysmorphic findings, brachycephaly, microcephaly, wide and high forehead, frontotemporal baldness, hypotelorism, synophrys, anteverted ears, ear lobule crease, tubular nose, bulbous nasal tip, prominent nasal bridge, long philtrum, micrognathia, prominent jaw and prominent upper central incisors were observed amongst patients. Evaluation of associated anomalies revealed urinary tract dilatation in one patient with duplication, scoliosis in two older patients with duplications and in one patient with deletion. Also two patients with duplication had epilepsy while three other patients with duplications exhibited central nervous system abnormalities. Asperger syndrome, aggressiveness and language delay was observed in one patient with deletion while the other patient with deletion had global developmental delay, hyperactivity and stereotypic movements.
Patients were screened for CNVs using the Affymetrix Optima Microarray and analysis revealed partially overlapping CNVs in 16p13.11. The sizes of the rearrangements varied between 752kb and 1.929kb. Parental studies were performed for three patients with clinically unaffected parents and demonstrated paternal and maternal inheritance.
Our report supports that CNVs of 16p13.11 region have broad clinical spectrum. Also, there might be pleiotropic effects of the CNVs in this region within the observation of both neurodevelopmental and skeletal findings. Furthermore patients with 16p13.11 CNVs should be evaluated for scoliosis during the follow up. Additionally, epilepsy was observed only in patients with duplications. However, this finding is considered as not generalizable to all CNVs in 16p13.11.

Key Words: 16p13.11 Copy Number Variations, Developmental Delay, Pleitropy, Scoliosis

P-044 - A Case Report with 18q Deletion Syndrome

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18q deletion syndrome is a disorder that occurs 1 in 40,000 newborns, due to the loss of part of the distal end of the long arm of chromosome 18. The findings of the syndrome vary according to the size of the missing area and the genes involved. The syndrome inheritance pattern is thought to be autosomal dominant, but most deletions are de novo. Usually the parents are asymptomatic,in some families, balanced translocation is observed.General features are short stature, mental retardation, hypotonia, hearing problem and foot deformities.
We first performed a karyotype test with cytogenetic methods for an 11-year-old male patient who was referred us because of epilepsy history, mental retardation and facial anomalies and Array CGH analysis was performed as a forward test.
In his neurological examination, severe motor mental retardation, total hearing loss ,hypotonia, behavior problems, eye contact difficulties and genaral tonic-clonic seizure story beginning at the age of 9 were remarkable. His cranial MR revealed hyperintensities near the bilateral occipital horn. On physical examination, there were mid-facial hypoplasia, deeply located eyes, up-slanting palpebral fissures, high-wide nasal bridge, repaired cleft palate- lip deformities, downward mouth corners, hypodontia, protuberant lower lip, prominent ears, bilateral pes ekinus, brachydactyly of the fifth finger of his hands and fourth, fifth fingers of his feet. His TSH level was high and thyroid parenchyma was heterogeneous,pseudonodular, the contours of the gland were irregular in thyroid ultrasonography .There was no consangenious marriage in his family story. We found 46,XY,del18q21.3(qter→q21.3) karyotype and in Array CGH study, we found loss at 18q21.33-q23 region and gain in 21q22.3 region. We found karyotypes 46, XX of his mother and 46, XY,t(18; 21)(q21.3; q22.3)(balanced translocation) of his father who had no clinical findings.
This result explains the findings of our patient and it is presented as a rare syndrome with the aim of contributing to the literature.

Key Words: Mental,Retardation,Chromosome,Deletion, Balanced,Translocation

P-045 - A Case Report of Mosaic Down Syndrome with 21q21q Robertsonian Translocation

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Mosaicism is clinical entity of different cell lines occur in a single zygote from different genetic origins in an organism or tissue. Mosaic conditions may occur as a result of gene, genome and chromosome mutations at any stage of embryonic development. In classic Down's syndrome, trisomy of the 21st chromosome is observed in all cells. On the other hand, trisomic and normal cell lines are seen in mosaic Down's syndrome cases. Furthermore, Down's syndrome could be result of Robertsonian translocations between acrocentric chromosomes while only a few of them have Down's syndrome as a result of Robertsonian 21q21q translocation of between chromosome 21. The aim of this study was to investigate a newborn case which were rarely seen at chromosome analysis with both 21q21q translocations and mosaicism.
A 3-day-old girl with Down syndrome stigmata and had cyanosis at her hands and feet admitted to our clinic and patent ductus arteriosus and small secundum atrial septal defect detected at echocardiography. There was no anomaly in the abdominal ultrasonography of the patient who had also no simian line.
With standart G-banding technique chromosome analysis performed. While normal chromosome structure were found in the 11 field, there were 21q21q translocation in 39 fields. 46,XX,+21,(21;21)(q10;q10)[39]/46,XX[11] karyotype was reported finally. It was planned to perform chromosome analyses from patient's parents but no samples could be taken yet.
Most mosaic Down's syndrome cases are caused by the loss of one of the 21st chromosomes during mitotic division in the early embryonic period and show a wide phenotypic variability according to the ratio of trisomy 21 cells. Some of the typical features of Down's syndrome may not be seen at mosaic forms because of the normal number of chromosomes in some cells. It's expected to have mild phenotype of mental retardation. Furhermore, only a few percent of these cases occur as a result of 21q21q translocations. While 21q21q translocations were expected to inherited from carrier parents; it is thought that our case arised from de novo due to the parents had two healthy children earlier. And it's expected to have moderate Down's syndrome stigmata because of mosaicism.

Key Words: Down Syndrome, Mosaicism, Robertsonian Translocation, 21q21q Translocation, Cytogenetics

P-046 - A Rare Presentation of 22q11.2 Deletion Syndrome: Cayler Cardio-Facial Syndrome

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Cayler cardio-facial syndrome is a rare presentation of 22q11.2 microdeletion syndrome; characterized with asymmetric face while crying and congenital heart disease. Unilateral weakness or hypoplasia of depressor anguli oris muscle leads to downward motion of the lower lip on the contralateral side and causes facial asymmetry while crying. Even though exact prevalence is unknown, it is a rare syndrome. In this case, we present a newborn who was diagnosed as Cayler cardio-facial syndrome by detection of 22q11.2 deletion in FISH analysis, referred us during neonatal period for asymmetric crying face and congenital heart disease.
A term male baby was born through normal vaginal delivery with birth weight of 2580 g and 46 cm in length. He was the first child of non-consanguineous parents and pedigree analysis was normal. During prenatal examinations, multicystic dysplastic kidney and pulmonary stenosis was detected. In neonatal period he was referred us for asymmetric crying face and multiple congenital anomalies. Baby had normal symmetric face in silent but while crying his right corner of mount deviates downward. In his abdominal and sacral ultrasonografic examination, right kidney was found as multicystic dysplastic kidney and a dermal sinus tractus was detected.
Karyotype analysis was normal and in FISH analysis 22q11.2 deletion was detected. With his clinical and genetic findings, he was diagnosed as Cayler cardio-facial syndrome. For genetic counselling, his parents' karyotype and FISH analysis also performed and reported as normal.
Generally, asymmetric crying face is an isolated finding but as in this case, we see association with congenital heart diseases. Cayler cardio-facial syndrome is a rare cause of hypoplastic depressor angular oris muscle and congenital heart disease. In 22q11.2 deletion syndrome, facial asymmetry is less frequent sign; molecular cytogenetic diagnosis generally missed so the exact prevalence is unknown. Lastly, facial asymmetry can be treated as in isolated cases (botulinum A toxin injection to contralateral side or myectomy) because of cosmetic concerns.

Key Words: Cayler Syndrome, 22q11.2 Deletion Syndrome, Asymmetric Face, Congenital Heart Disease

P-047 - 3p Deletion Syndrome with Congenital Hypothyroidism

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3p deletion syndrome is a rare contiguous gene syndrome caused by deletions in the 3p25-pter region. Clinical spectrum may vary depending on the size of deletion site. Characteristic features are low birth weight, hypotonia, mental retardation, growth retardation and dysmorphic facial findings such as ptosis, microcephaly, hypertelorism, and micrognathia. Other features include polydactyly, renal anomalies, congenital heart defects, ear anomalies and gastrointestinal system abnormalities. The aim of this study was to evaluate the findings of a 3p deletion syndrome patient with congenital hypothyroidism.
A 4.5-year-old male patient was referred to the medical genetic clinic due to abnormal facial appearance and mental motor retardation. The patient had a height of 90 cm (-3.57 SDS), weight of 14 kg (-1.55 SDS) and head circumference of 50 cm (-0.27 SDS). Her physical examination revealed ptosis, hypertelorism, synofiriz, anteverted nares, low ears, bilateral hand pituitary and pectus excavatum. The patient with normal hearing test had mild atrophy in the brain MRI and ASD in the ECO. It was learned that the patient had started to take new steps.
Chromosome analysis of the patient was reported as 46, XY, del (3) (p25). In the microarray study, a loss of 10,234 kbp was observed covering the 3p26.3p25.3 region. chromosome analysis could not be done to parents.
The findings of our patient with a rare 3p deletion syndrome were consistent with the characteristics of the syndrome. However, in our knowledge, congenital hypothyroidism was previously reported in only one case. The case is presented as it may have clinical contribution.

Key Words: 3p Deletion Syndrome, Congenital Anomaly, Hypothyroidism

P-048 - A Case with 45,X Karyotype and Male Phenotype with Deletion in SRY Region in 80% of Cells

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45, X karyotype is a rare sexual development disorder characterized by short stature, gonadal dysgenesis, renal and cardiovascular anomalies. The clinical presentation can be quite variable ranging from the female phenotype with findings of sexual infatism to ambiguous genitalia or male phenotype with hypospadias. Chromosome analysis was performed on the metaphase plaque obtained from the the patient's peripheral blood cell culture. SRY FISH analysis was performed in the interphase/metephase cells with the specific FISH probe of the SRY (Yp11.3) region. Routine biochemical tests and necessary radiological examinations were performed.
The 8-month-old male patient who was born subsequent to a term gestation from unrelated parents with a birth weight of 3305 gr, birth length 50 cm. His arm and leg length was short in antenatal ultrasonography.
Currently, the patient's weight is 7.7 kg (18 p), length is 65 cm (3 p), phallus is normal size, both testes are in scrotum and he had short stature and hypospadias. Skeletal X-ray showed no anomaly and TFT, ACTH, cortisol levels were in normal range. Karyotype analysis was determined as 45, X. Pelvic ultrasonography showed no uterine-ovary-compatible appearance. In the SRY FISH analysis, deletion was detected in the SRY region in 80% of the examined cells (100 cells) and the signal from the SRY region was detected as two in 20% of the examined cells. Abdominal ultrasonography and echocardiography were normal.
Clinical follow-up was planned because of the increased risk of gonadal tumor. SRY analysis is important in male cases with short stature and hypospadias findings.

Key Words: 45,X Karyotype, Short Stature, Gonadal Dysgenesis

P-049 - A Case of Primary Amenorrhea with 46,X,der(X)(?)(6)/45,X(23) Karyotype

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Turner syndrome is a chromosomal disorder characterized by a aneuploidy or structural change of one of the sex chromosomes, mostly affecting female. The incidence in live-born girls is approximately 1/2.500. Phenotype is highly variable in terms of mosaic status, X chromosome reduction rate and type of chromosomal structural disorder. In this paper, we aimed to present a variant Turner case with 46,X,der(X)(6)/45,X(23) karyotypes.
The patient was 157.4 cm (25p) in length, 58.90 kg in weight (97p), and in BMI 23.9 when she refered at the age of 15 years. On physical examination, her secondary sex characters were consistent with tanner stage 1 and age of bone was consistent with age 12. There was no visual and auditory pathology.
Endocrine examinations revealed isolated hypergonadotropic hypogonadism. In pelvic ultrasonography and magnetic resonance imaging of the lower abdomen, both ovaries were not visualized in normal position, the uterus was 30x14x6 mm in size. Chromosome analysis was performed on the metaphase plaque obtained from the patient's peripheral blood cell culture. Karyotype analysis revealed 46,X,der(X)(?)(6)/45,X(23) variant turner syndromes. It was planned to investigate the derivative structure of X-chromosome by microarray method. Echocardiography revealed bicuspid aortic valve and mild valvular aortic stenosis. Bone mineral densitometry showed -2 Z score. During the follow-up period of estrodiol replacement and vitamin D treatment, our patient gained excess weight (BMI 30.5). She had adenoidectomy because of sleep apnea. Our patient is now 18 years old and her weights is 88.8 kg (> 97 p), height is 168.4 cm (82p), breast development and pubic hair is consistent with tanner stage 5. There was no short stature which accepted from the stigma of Turner syndrome in our case but osteopenia was observed.
The SHOX gene (Xp22.2) identified on the short arm of the X chromosome is important for bone growth and development. Microarray method has an important place in screening DNA copy gains and losses related to chromosomal disorders

Key Words: Turner Syndrome, Chromosomal Mosaicism, Primary Amenorrhea

P-050 - Clinical and Endocrine Evaluation of 5 Infertile Patients with 47,XYY Syndrome

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47,XYY syndrome is the most common sex chromosomal abnormality after Klinefelter syndrome. The incidence is 1/1,000 men and occurs as a result of nondisjunction in meiosis-2. While most of the patients do not have a phenotypic anomaly, tall stature, behavior problems, mild learning disabilities, delayed speech and language development have been described. Sperm production can vary from normal to azoospermia, and therefore infertility could be seen in these patients.
Here, we present the clinical, laboratory and genetic results of 5 cases with 47,XYY.
All our 5 patients presented with infertility. The mean age was 29.8 years. Mean height was 180.2 cm, mean weight was 93.4 kg, and mean BMI was 28.4 kg cm2. Secondary sex characteristics were normal. The mean volume of the testes were 22 ml and were within normal limits except for one patient. The mean level of FSH was 7.9 mU/ml, LH was 7.0 mIU/ml, and the total testosterone was 4.5 ng/ml and was within normal limits. 3 of 5 patients had oligoasthenoteratozoospermia and remainig 2 had azoospermia. The karyotypes of all patients were 47,XYY. No deletions were detected in Y microdeletion analyzes. The pregnancy outcome of 2 patients could be reached and both of them had children with IVF. In 1 patient, sperm were detected with TESE and IVF was planned.
47,XYY patients are tall individuals. Most of them don't have a phenotypic anomaly and are generally fertile Spermiogram can be variable in a range from normal to azoospermia. It has been shown that 37.2-37.8% of these patients have aneuploid sperms. The errors in meiotic pairing result in the loss of germ cells and the production of aneuploid sperms, which causes oligoastenoteratozospermia and azoospermia in some of the patients. All of our patients were tall and infertile. All of them had sperm abnormalities and these findings are compatible with the literature. These patients could achive to have pregnancy with IVF and it is very important to give a true genetic counselling.

Key Words: Infertility, Oligoastenoteratozoospermia, Tall Stature

P-051 - 4p16.3 Trisomy: A Case with Genital Abnormalities and Mild Dysmorphic Findings

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4p16.3 microduplication syndrome was first described in 1977 and up to 100 cases have been reported. The main features of the disease are neuromotor delay, seizures and dysmorphic signs. In addition, anomalies of the eye, congenital heart anomalies and genital anomalies such as micropenis, hypospadias and cryptorchidism have also been reported. Co-occurences of 4p13 trisomy and 7q36 monosomy have not been reported previously, we aimed to present this case and discuss the clinical effects.
A 4-year-old male patient presented with micropenis and speech delay. The patient's anthropometric measurements were 103 cm (93p) in height, 20.8 kg in weight (40p). Physical examination revealed coarse facial appearance, outward rotated and full earlobe. Penile stretched length was 4 cm (5.0-77 cm.), and penis circumference was 4.2 (3.6-5.7 cm), glandular hypospadias, rugae of scrotum were detected. The patient was operated due to right cryptorchidism and hypospadias when he was 2 year-old. In hormone profile, free T3 was high, TSH was normal, testosterone and DHEAS were low.
In the chromosome analysis, 46,XY ad(7)(q36) was detected and the parents' chromosomal analysis were normal thus change was evaluated as de novo. A further technique, molecular karyotyping reported as arr [19] 4p16.3p15.31 (68,345-18,464,078) x3, 7q36.3 (157,473,221-159,119,707) x1.
Our patient's genital anomalies, speech delay and mild dysmorphism were thought to be related with increase in the 4p16.3 region. In the literature, patients who have dysmorphic facial features, attention deficit hyperactivity disorders, learning difficulties, speech and cognitive delays, were reported in with similar increase size at 4p16.3 localization. It is suggested that SLBP, TMEM129, TACC3, FGFR3 and LETM1 genes may be responsible from the clinical picture because these common genes duplicated in similar cases. In addition, the clinical significance of 7q36 loss is unknown. In this case report, it is aimed to contribute to the literature by discussing the effects of trisomy of 4p16.3 and monosomy of 7q36.3 which has not been previously reported.

Key Words: Chromosome Analysis, Microarray, 4p16 Duplication, Micropenis

P-052 - Further Defining the Critical Region associated with Characteristic Features in 4q21 Microdeletion Syndrome

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4q21 microdeletion syndrome (OMIM: 613509) is characterized by intellectual disability, delayed speech, growth retardation, hypotonia, CNS malformations, and facial dysmorphism. The critical region for this disorder was considered to be the recurrent overlapping region of 1.37 Mb including 5 genes; PRKG2, RASGEF1B, HNRNPD, HNRNPDL, and ENOPH1. Here we report on two unrelated female patients with 4q21 deletions and provide an opportunity to further define the critical genes associated with specific features of the 4q21 microdeletion syndrome.
Patient 1: She was born to non-consanguineous healthy parents at term. She exhibited hypotonia during infancy. Physical examination at the age of 56/12 years revealed height of 107cm (3-10p), weight of 19kg (10-25p) and head circumference of 48cm(<3p). She had prominent metopic ridge, bitemporal narrowing, synophrys, up-slanting palpebral fissures, epicanthal folds, upturned nose, long philtrum, clinodactyly and pes planus. She also had bilateral mild hearing impairment. Denver developmental screening test revealed global developmental delay. Cranial MRI demonstrated enlargement of the lateral ventricles. Patient 2: She was born to non-consanguineous healthy parents at term. Prenatal history was unremarkable except for decreased fetal movement. She had a period of fast gain of weight during infancy. Physical examination at the age of 4 years and 7 months revealed height of 92,5 cm (<3p), weight of 13.3 kg (3p) and head circumference of 50cm (25p). She had similar facial features as the first patient. She also had clinodactyly, brachydactyly and metacarpophalangeal joint hyperlaxity. EEG demonsrated epileptiform activity. She also presented with aggressive behavior and global developmental delay.
Patients were screened for copy number variation using the Affymetrix Optima Microarray Kit and analysis revealed deletions of 3,230 kb and 1,543 kb on chromosome 4q21, respectively. Three OMIM genes including HNRNPD, HNRNPDL and TMEM150C were found to be common in both deletions.
These two additional patients with 4q21 deletion further expand the clinical spectrum and narrow the critical region to 916 kb, consisting of three genes. Nevertheless further studies are required to elucidate the critical genes responsible for 4q21 microdeletion syndrome.

Key Words: 4q21 Microdeletion, HNRNPD, HNRNPDL, Global Developmental Delay

P-053 - A Case of Sotos Syndrome with 5q35 Microdeletion

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Sotos syndrome (SS, OMIM #117550) is a rare overgrowth disorder characterised by prenatal and postnatal rapid overgrowth, distinct craniofacial apperance and developmental delay. These three cardinal features are each present in over 90% of cases with SS. Haploinsufficiency of the nuclear receptor-binding SET domain protein 1 gene (NSD1), which is located at 5q35, is responsible for approximately 90% of the clinically diagnosed patients. SS in an autosomal dominant disorder, although more than 95% of cases result from de novo mutations. Among patients with classic Sotos syndrome, about 50% of Japanese origin and 10% of non-Japanese origin have a 5q35 microdeletion that encompasses NSD1.
In this report we describe a 5-year-old boy who had neonatal jaundice, seizures, tall stature (>97th percentile), macrocephaly (>97th percentile), typical facial apperance consisting of long face and high forehead, early developmental delay and corpus callosum dysgenesis. The patient had head and neck control at 3 months, sat up without support at 9 months and walked unaided at 22 months. However both receptive and expressive language were severely delayed, with a single word vocabulary achieved at the age of 4 years and 3-4-word sentences acquired at the age of 5 years.
With these clinical findings -excluding the probability of a neurological or metabolic disease- Sotos syndrome was suspected and FISH analysis from his peripheral blood revealed a heterozygous deletion encompassing NSD1 in the 5q35.3 region.
It has been suggested that patients with 5q35 microdeletions including NSD1 gene have less prominent overgrowth and more severe intellectual disability, compared to patients with intragenic mutations of NSD1. Although formal assesment of development could not be performed in the present patient, the finding of severe speech delay might further provide evidence for this hypothesis. Nevertheless, more patients are required to establish a precise genotype-phenotype correlation in SS.

Key Words: Sotos Syndrome, 5q35, Microdeletion, NSD1

P-054 - The Presentation of 6 Isodicentric Y Cases and the Results of Array-CGH Analyses

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Dicentric chromosomes are the most common aberrations of the human Y chromosome. These chromosomes are unstable during cell division, and likely to generate various types of cell lines. Most of the patients are mosaics, generally including a 45,X cell line. The phenotypic spectrum of mosaic patients may vary widely and includes healthy infertile males, females with or without Turner syndrome, ambiguous genitalia and mixed gonadal dysgenesis. Here, we present 6 infertile male cases with isodicentric Y chromosome.
All the patients were referred with infertility. The mean age was 29.8 years and the mean height was 168 cm (min-max: 160-178). 5 patients had azoospermia and 1 patient had oligoastenoteratozoospermia. Secondary sex characteristics were normal except one patient. 4 of 6 patients had testicular hypoplasia. None of the patients presents ambigous genitale or Turner Syndrome phenotype. Internal genital organs were compatible with male phenotype. Karyotypes of the patients were 45,X/46,XY/46,X,idic(Y)(q11.2), 45,X/46,XY/46,X,idic(Y)(q11.2), 45,X/46,XY/46,X,idic(Y)(p11.3), 45,X/46,X,idic(Y)(p11.2), 46,X,idic(Y)(q11.2), 45,X/46,X,idic(Y)(p11.3) and these aberrations were confirmed with FISH analysis. AZFb+c deletions were observed in 3 of 6 patients. The array-CGH was performed to all patients and break points were detected exactly. In our two patients with short stature (160 cm), SHOX gene deletion was observed in the array-CGH analysis.
The phenotypic spectrum of 45,X/46,XY,dic(Y) mosaicism varies from infertile normal male to ambigous genitalia. We didn't detecet any patient with ambigous genitalia. It has been suggested that the varying clinical phenotypes are dependent on the proportions of the different cell lines. SHOX gene is located in the PAR1 of the X and Y chromosomes (Xp22.33 and Yp11.32). The enhancer deletions of the SHOX downstream region has been related with growth failure. In our two cases with short stature, deletion was detected in SHOX gene. The combination of cytogenetic, FISH and array CGH technologies was beneficial for diagnosing the karyotype accurately, predicting the prognosis, and preparing an effective treatment plan for the patient.

Key Words: Dicentric Y Chromosome, SHOX

P-055 - Inter- and Intra-Familial Phenotypic Variability of 6q Terminal Deletion Syndrome

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6q terminal deletion syndrome is characterized by dysmorphic facial findings (prominent forehead and nasal bridge, broad nose tip, ears abnormalities), global developmental delay, mild to moderate intellectual disability, epilepsy, anomalies of the central nervous system and cardiovascular anomalies. While it is characterized by highly variable clinical symptoms that do not depend on the extension of the deletion, there is evidence that the minimal 1.2 Mb critical deletion for developmental brain abnormalities, mainly periventricular nodular heterotopia, polymicrogyria and corpus callosum dysgenesis, resides in 6q27. Familial inheritance has been observed in 15% of cases and 85% were de novo.
We here present four cases with terminal 6q deletion syndrome, one diagnosed antenatally with ultrasound findings of hydrops and brain abnormalities.
Based on clinical, cytogenetic and molecular cytogenetic findings of index cases and affected family members in two families, inter- and intra-familial phenotypic variability of the syndrome will be discussed, along with challenges in genetic counseling.

Key Words: 6q Terminal Deletion, Phenotypic Variation, Periventricular Nodular Heterotopia

P-056 - 7q Terminal Deletion: Three New Cases and Literature Comparison

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7q terminal deletion has been characterized by wide phenotypic findings, and holoprosencephaly (HPE) and sacral agenesis have frequently been associated with this deletion. Because of its rare nature, a precise genotype-phenotype correlation could not be established.
Microarray analysis (Affymetrix CytoScan Optima and Agilent 4x180K array platforms) was performed in three patients who were referred to our clinic with the complaints of microcephaly, dysmorphic findings, developmental delay and multiple congenital anomalies. A terminal deletion at bands 7q36.1 and 7q36.2 was revealed in two patients, respectively. In the third patient with the most severe phenotype, a recombinant chromosome 7 involving a duplication at 7p22.3p22.1 and a deletion at 7q35q36.3 was detected.
Dysmorphic features (hypotelorism, anteverted ears, retrognathia) of patients with only deletion were similar. However, the patient who had also a duplication had quite different dysmorphic features and additional findings such as Hirschsprung disease and ectopic kidney. The SHH gene which was involved in the deletion region was reported to be associated with holoprosencephaly. However, holoprosencephaly findings were not detected in any of the three patients. Microcephaly and developmental delay were observed in all three patients. In addition, dysgenetic changes were detected in cranial MRI of two patients. The anorectal and sacral region malformations associated with the HLXB9 gene mutations were observed in two patients. The ocular findings associated with 7q36.2 deletion previously reported in the literature were not seen in any of the patients.
7q terminal deletion is variable in terms of phenotypic features. SHH, HLXB9 (MNX1), LMBR1 genes play an important role in the embryonic development of this region. The diversity of the phenotypic findings in patients might be explained with many reasons including epigenetic regulation, polymorphisms in other regions of the genome, incomplete penetrance and environmental factors. For a complete genotype-phenotype correlation, more patient data and further genetic studies are required.

Key Words: 7q Terminal Deletion, Recombinant Chromosome 7, Microarray Analysis

P-057 - A Case Report with an Unusual Derivation between the Chromosomes 9 and 20

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Chromosomal abnormalities are responsible for 2-14% of infertile patients. These anomalies include balanced translocations, inversions and numerical sex chromosomal abnormalities. Balanced translocations were detected in 1.6-6.6% of infertile patients and inversions were found in 1-2% of them. Both of the anomalies also disrupt spermatogenesis and may produce unstable gametes. As a result, the number of sperm decreases and their structure deteriorates. Here, we present an infertile patient with a translocation between chromosomes 9 and 20, which we think is subject to a pericentric inversion.
A 27-year-old male patient presented with infertility. There was no consanguinity between the parents. Secondary sex characters were normal. The penis was 16 cm, and the testes were 30 cc bilaterally and normal. FSH, LH and total testosterone were within normal limits. Oligoastenoteratozoospermia was detected.
In the karyotype analysis, a reciprocal translocation was found between the chromosome regions 9q21.2 and 20q11.2. However, chromosome 20p was also derivative too. To understand the exact derivation, the FISH analysis with D20S108 (20q12), CDKN2A (9p21) and CEP9 were performed and this analysis revealed that the derivative chromosome 9 contained 20q12-qter. The FISH analysis with 20pter-20qter also showed that the derivative chromosome 20 contained 20pter signal at its normal locus. This results seem to be the derivative chromosome 20 had also a pericentric inversion. Parents' karyotypes were normal. Karyotype was reported as 46,XY,t(9;20)(9pter-9q21.13::20q12-20qter;20q12-?20pter::9q21.13-9qter)dn.
Chromosomal anomalies have an important place in the etiology of infertile patients. Translocations, inversions and numerical chromosomal anomalies are responsible for etiology, with creating unstable gametes in patients and disrupting sperm production. However, the coexistence of both inversion and translocation in the same chromosomes is very rare in the literature. In addition to the imbalances resulting from this translocation, considering the imbalances caused by inversion, it can be thought that sperm production will be impaired in patients with these severe anomalies. We have seen once again that karyotype analysis can provide important informations in infertile cases and it is important for genetic counseling in subsequent pregnancies.

Key Words: Infertility, Translocation, Pericentric Inversion

P-058 - Additive Chromosomes: A Case Report of Mental Retardation with 46,XY,add(5)(q35.3) Karyotype

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Mental retardation(MR) is a complex phenotype characterized by suboptimal functioning of the central nervous system and is considered as'significant limitations in mental functioning and conceptual, social and practical skills'.The frequency of MR in the general population is estimated to be1-3%. While it results from several reasons such as environmental, perinatal/postnatal reasons, infectios and psychiatric diseases;genetic causes also have an important role in etiology. Genetic causes ofMR can be classified as genomic disorders, numerical and structural chromosomal abnormalities, and monogenic diseases. In this study,we aimed to investigate the clinical status of a patient who presented with intellectual disability and speech impairment and had a rare chromosomal rearrangement as result of an additive chromosomal structure on chromosome 5 that understood arised from X chromosome.
A 4-year-old male patient,whose parents are cousins, was admitted with a pre-diagnosis of speech failure. It has been observed that the patient has retardation at all stages of developmental steps and significant intellectual disability.Large eyes, downslanting palpebral fissures, strabismus, long facial appearance and large ears were dysmorphic findings of patient. The height ofthe patient was 109cm(75-90p),and his weight was16.2kg(25-50p).
Cytogenetic banding method is applied to the metaphase plaques,which obtained from a 72-hour-cultured peripheral blood sample taken from the patient. The patient's 20 metaphase plaques were examined and the karyotype was determined as 46,XY,add(5)(q35.3).There were no chromosomal anomalies at patient's parents cytogenetic studies. DNA obtained and Affymetrix Cytoscan Optima(315K) microarray system used for the molecular karyotyping of the patient, and an increase of 17.019 kbp was observed including the Xp22.33p22.13 region. And also, arr[hg19]Xp22.33p22.13(168,546-17,187,330)x2 reported. The number of markers in Xp22.33p22.13 is1079; and there're genes associated with X-linked mental retardation in that region according to databases. Also subtelomeric FISH study showed that the Xp signal was at the terminal end of 5q. Fragile X mutation analysis revealed normal number of CGG repeats.
It's been observed that the region Xp22.33p22.13,which is duplicated as a result of cytogenetics, molecular cytogenetics and molecular karyotyping studies, added into the region 5q35.3. Additive chromosome structure of the patient's thought to be associated with the patient's mental disability and speech impairment.

Key Words: Additive Chromosome, Mental Retardation, Cytogenetics, Xp22 Duplication

P-059 - Familial Reciprocal Translocations: A Newborn Case Presentation with 46,XX,der(15)t(7;15)(p10;q10)pat Karyotype

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Translocations are one of the structural chromosomal anomalies that occur as a result of inter-chromosomal segment changes. According to gain or loss in the genetic material, it's divided into two as unbalanced or balanced translocation. Balanced reciprocal translocations are the most common structural chromosomal anomaly in humans and it's known that reciprocal translocation carriage is one in 500 people. In balanced translocation carriers, unbalanced gametes may arise because of coupling between derivative chromosomes and their normal homologs. This may cause spontaneous abortions or birth of children with anomalies. In this study, we aimed to investigate a newborn with chromosomal rearrangement because of paternal translocation.
The patient, who was known to have a balanced 46,XY,t(7,15)(p10,q10) reciprocal translocation structure in his father,was born at 35 weeks and 1,940 grams and echocardiography revealed tetralogy of fallot. In physical examination revealed blepharophimosis, ptosis, low-set and posteriorly-rotated dysmorphic ears, arachnodactyly in the hands, flexor contracture in the left wrist, overriding toes.
For cytogenetic analyses, standard peripheral blood lymphocyte was cultured in media containing phytohemagglutinin and incubated at 37°C for 72-hours. Colchicine added at the 70th hour to stop the cell division in the metaphase, which is the best step to visualize chromosomes apperantly. After cell culture and spreading of the metaphases onto slides, the chromosomes were stained with GTL (Giemsa-trypsin-Leishman)for banding. The karyotype was reported as 46,XX,der(15)t(7; 15)(p10; q10)pat according to ISCN. Molecular karyotyping was performed by using Affymetrix Cytoscan Optima(315K) microarray system from DNA obtained from the patient and analyzed in CHAS3.2.0/GRCh37/hg19 program. Molecular karyotyping revealed an increase of 57,963kbps(markers:3,360) covering 7p22.3p11.1region and arr[hg19] was reported as 7p22.3p11.1(43,360-58,006,205)x3.
People who are carriers of balanced chromosomal anomalies have a significantly increased risk of producing chromosomally unstable gametes and abnormal progeny. Fertilization with unbalanced gamete often results in embryonic loss or spontaneous abortion. In the case of the fetus survives as in our case, phenotypic abnormalities, congenital anomalies, dysmorphic findings, systemic diseases, mental motor retardation are expected. Providing detailed genetic counseling to parents with balanced chromosomal anomalies is of great importance for both balanced and unbalanced reciprocal carrier and preimplantation genetic diagnosis and prenatal diagnosis methods in subsequent pregnancies.

Key Words: Reciprocal Translocation, Derivative Chromosome, Cytogenetics, Dysmorphology

P-060 - 2q37.1-q37.3 Deletion and 16p13.11-p12.3 Duplication Detected by Arraycgh in a Patient with Dysmorphic Features

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2q37.3 deletion syndrome is considered to be a rare chromosomal disorder associated with variable clinical features, among which are intellectual disability (ID), autistic features, brachydactyly, short stature, hypotonia and obesity. The 16p13.11 microduplication has been implicated in several neurodevelopmental and behavioral disorders and is characterized by variable expressivity and incomplete penetrance. The aim of this study was to associate genotype-phenotype of a patient with a deletion in 2q37.1-q37.3 and a duplication in 16p13.11-q12.
A two years two months old female was born at 37th weeks of gestation with NSVD as weight 3000g. Her parents were nonconsanguineous and healthy. Her anterior fontanelle was closed by fifth month at age. She had dysmorphic features including low-set ears, simple ears, wide forehead, long philtrum, flat nasal bride, short and broad toes, overlapping fourth digit in left toes, hypopigmented patches at right tibia, dorsal macular rash. She had speech delay and limited walking abilities. The echocardiogram revealed mesocardia, atrial septal defect, aortic septal aneurysm and persistent left superior vena cava.
G-banding karyotype using peripheral blood was normal. Chromosomal microarray analysis was performed on the proband using Agilent Technologies 4x180K SurePrint G3 Human CGH+SNP Platform and Cytogenomics 3.0.4 software. Copy number changes arr[GRCh37]2q37.1-q37.3(234761459_243040276)x1 and arr[GRCh37]16p13.11-p12.3(15404452_18631981)x3 were identified in our patient.
To our knowledge, 2q37.1-q37.3 deletion and 16p13.1-p12.3 duplication has not been reported with together previously. We anticipate that the findings of our patient are either due to deletion of 2q37.1-q37.3, duplication of 16p13.1-p12.3, or the combined effect of these two imbalances.

Key Words: 2q37 Microdeletion Syndrome, Array-CGH, 16p13.11-p12.3 Duplication,

P-061 - Atypical Mosaic Trısomy 9: A Case Presentation with 47,XX,+9[26]/45,X[24] Karyotype

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Trisomy 9 is a rare chromosomal disorder with high neonatal mortality. It is often seen in mosaic form. Mosaic trisomy 9 may arise from errors of nondisjunctional chromosomal separation during meiosis, or may occur during mitosis cellular division after fertilization. The main features of this syndrome are bulbous nose, microphthalmia, dislocated limbs, and other anomalies of skeletal, cardiac, genitourinary, and central nervous system. In this report, we present a very rare case has trisomy 9 and monosomy X mosaicism.
An 11 year-old female patient referred to our clinic due to intellectual disability and stereotypic behaviors. In clinical examination, dysmorphic features were detected including narrow forehead, bow-shaped eyebrows, synophrys, esotropia and nystagmus in the right eye, short philtrum, small mouth, perplexed teeth and caries, high and narrow palate, pectus excavatum, and sacral hypertrichosis. Her body weigt was 15kg(<3p)and her head circumference was 52cm(<3p). Horizontal nystagmus and demyelization of left and right optic disc were noted in eye consultation.
The patient’s peripheral blood sample were cultured for 72 hours and GTL banding technic was used. 50 metaphases of 26 trisomy 9, and of 24 monosomy X detected in chromosome analysis and karyotype was reported 47,XX,+9[26]/45,X[24]. Parent's karyotype were normal. In molecular karyotyping, gain of mosaic single copy of chromosome 9 and loss of mosaic single copy of chromosome X also was detected and molecular karyotyping was reported arr(9)x3[0.5], (X)x1[0.5]. Morever, 50% of the cells analyzed in FISH analysis [100 cells] XX, 47% [94 cells] X, 3% [6 cells] XXX signal pattern were detected and there was no signal for SRY region.
Mosaic trisomy 9 is a rare anomaly in autosomal mosaic cases and often results in death at an early age, whereas our case was diagnosed at the age of 11 years. While dysmorphic findings and mental retardation are the most prominent features of mosaic trisomy 9, our patient also had mostly dysmorphic features and moderate to severe mental retardation. However, in contrast to other mosaic cases, our patient has also monosomy X. Re-evaluating of the patient in terms of Turner syndrome stigma after puberty is needed.

Key Words: Trisomy 9, Mosaic Karyotype, Monosomy X, Cytogenetics

P-062 - Clinical Findings in 20p12.3p13 Deletion including BMP2

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Short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies; (SSFSC;OMIM 617877) is a recently defined disorder caused by point mutations and microdeletions of BMP2 gene on 20p12.3. Deletions of 20p12.3p13 region are rare and associated with cleft palate, short stature, structural and electrophysiological cardiac anomalies, pituitary hormone deficiencies, craniofacial features and developmental delay. Distinctive facial features include midface retrusion, short upturned nose, long philtrum, and micrognathia.
The patient was born to non-consanguineous healthy parents with a birth weight of 2580g at term. Prenatal triple test revealed a high risk for Down syndrome. Amniocentesis was recommended however, the family declined. During the first 3 months he had feeding difficulties and failure to thrive was noted. Physical examination at the age of 2.5 years, revealed a height of 81 cm (-3.1 SD) a weight of 11 kg (-2.1 SD) and a head circumference of 48cm(-2SD). He had prominent forehead, midfacial hypoplasia, high arched palate, micrognathia, pectus carinatum, pes planus, prominent heels and sandal gap. He also had delayed teeth eruption and hypothyroidism. Echocardiography revealed hypoplastic right ventricle and double superior vena cava. The liver was palpable under costal margin. Denver developmental screening test revealed global developmental delay.
The patient was screened for copy number variation using the Affymetrix Optima Microarray Kit. Microarray analysis revealed a deletion of 5,849 kb (20: 3,746,862-9,596,287) on chromosome 20p13 that contains 31 OMIM genes including BMP2 and PROKR2.
20p12.3p13 deletion including BMP2 results mainly in growth and developmental delay. Additionally, endocrine evaluation is recommended during the follow-up of the patients. This study also demonstrates the utility of microarray studies for the evaluation of patients with short stature.

Key Words: 20p13.2 Deletion, BMP2, Growth and Developmental Delay

P-063 - A Syndromic Case with Disorder of Sexual Development; De Novo 14q31.3q32.2 Deletion

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14 q deletion syndrome is a rare genetic disorder. Microcephaly, dysmorphic face (large nasal root, long and wide filtrum, high forehead, etc.), strabismus, high palate, hydrocephalus, atrophic corpus callosum, inguinal hernia, genital abnormalities such as hypospadias and undescended testis, cognitive motor retardation are commen clinical findings. Here we present a case with a de novo deletion in 14 q deletion syndrome.

Key Words: Disorder of Sexual Development, 14q Deletion, Hydrocephalus, Corpus Callosum

P-064 - A Case Report with Cri Du Chat Syndrome: Deletion of Short Arm of Chromosome 5

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Cri du Chat Syndrome (CdCS) is caused by deletions in the short arm of chromosome 5 (5p -). In 85% of cases, deletion is de novo while in 15% of the cases there is a balanced translocation carrier in one of the parents. This syndrome estimated prevalence is 1 of 50,000. In this case report, a derivative structure detected in chromosome 5 in a patient with neuromotor retardation and hypotonia.
The 11-month-old girl presented with inability to gain weight and a low volume of voice. Anthropometric measurements are that height was 72 cm (3-10p), weight was 6.5 kg (<3p) and head circumference was 40 cm (3p). Physical examination revealed treble crying, muscle strength is natural and reduced tone. Head control started at 11 months. There is no sitting without support. Hypotonia, microcephaly and neuromotor retardation were detected.
The chromosome analysis of the patient revealed that 46,XX,5((5)(5::5p14→5qter) chromosome was established. In order to determine the possible parental origin of the change, chromosome analysis of the patient's parents was planned but could not be able to done.
CdCS is a disease characterized by microcephaly, severe psychomotor and intellectual retardation, causing dysmorphic appearance as a result of the deletion in the short arm of chromosome 5. Studies have shown that in case of deletion of SEMAF, CTNND2 and TERT genes in 5p region, cerebral development is affected and may cause intellectual disability. In addition, many clinical features specific to CdCS phenotype have been shown to be associated with TERT gene deletions. In our case, clinical findings compatible with the disease including congenital microcephaly, trembling crying and feeding problems occurred as a result of a single copy of the genes mentioned above, which caused deletion of the region causing CdCS clinic. The patient should receive genetic counseling in order to be able to plan the correct follow-up and treatment, and to inform the family about whether the next children will have similar problems.

Key Words: Chromosome Analysis, Microcephaly, Cri Du Chat

P-065 - A Very Rare Karyotype: A Case Report that has Double Aneuploidy

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Numerical chromosomal anomalies(aneuploidies) are the most common chromosomal anomalies which are Down's syndrome(47,XY,+21),Klinefelter syndrome(47,XXY), TripleX syndrome(47,XXX),Turner syndrome(45,X),Edwards syndrome(47,XY,+18) and Patau syndrome(47,XY,+13). While aneuploidies are usually seen alone in patients, rarely double aneuploidies can be seen in same patient. For example;The incidence of Klinefelter's and Down's syndrome is estimated to be approximately 1/355.000. In this study, it was aimed to investigate a case with 48,XXY,+21 chromosome analysis.
A 2-month-old male patient who presented with respiratory distress were admitted to our clinic. Ventricular septal defect and significant dysmorphic features detected at the patient. He had Down syndrome stigmata and growth retardation. His weight was 3400 g(<3p), height 51 cm(<3p) and head circumference 35 cm(<3p). Dysmorphic findings were brachycephalia, upslant palpebral fissures, simian linaes and obvious epicantial folds.
Peripheral blood sample taken from the patient was cultured in the phytohemagglutinin media. It was incubated at 37°C for 72 hours. At the end of 72 hours, the harvest stages were performed. The day before harvest, to improve quality the solutionA and 5 hours before harvest, the solutionB were added. Colsemide was added 1 hour before harvest to capture the chromosomes in metaphase stage. Harvest was started by centrifugation to separate the supernatant. A hypotonic solution was added and allowed to stand for 10minutes. Then 1cc of the fixative solution was added and centrifuged again. Separated from the supernatant. A total of 9cc fixative solution was added to the first 1cc drop by drop. Washing step performed to make ready for dripping onto slides. After slide preperation, chromosomes were stained with GTL (Giemsa-trypsin-leishman) banding technique and chromosome analysis was performed from the peripheral blood of the patient. In chromosome analysis, 2X, 1Y, and trisomy of 21 were detected in all metaphase plates. The patient's karyotype was reported as 48,XXY,+21.
Down's syndrome is seen with a frequency of about1/700, where as Klinefelter syndrome is seen with a frequency of 1/1000 seperately. It's very rarely observed that both syndromes in the same case and 48,XXY,+21 karyotype result . Our patient who has both aneuploidies; Down syndrome clinic at newborn period and it is expected to show Klinefelter syndrome characteristics after puberty.

Key Words: Down's Syndrome, Klinefelter's Syndrome, Aneuploidy, Chromosome Analysis

P-066 - A Very Rare Translocation: Case Presentation with 46,X,der(X;18)(p10;p10)+18 Karyotype

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Translocations between X and autosomal chromosomes are extremely rare,within a frequency of 1/30,000, while autosomal translocations are seen in the frequency of 1/500. In this study, a case defining an unbalanced whole arm translocation between X and 18th chromosome in the result of chromosome analysis performed due to short stature was examined. It's aimed to discuss the case in the context of X inactivation.
An 8-year-old patient with short stature,had a body weight 26kg(50-75p) and height 112cm(<3p) refered to our clinic. The patient had treatment for hypothyroidism also had somatotropin treatment due to deficiency of growth hormones. The patient who has mild scoliosis had physical therapy and swimming. In Denver test, her verbal IQ was better than the gross motor movements. Abdomen ultrasonography revealed pelvicaliectasis in kidneys.
G banding technique and the cytogenetic analysis was performed in 50 metaphases and 46,X,der(X;18)(p10;p10),+18 karyotype revealed.There were no anomalies in the karyotypes of patient's parents. Also,partial Xp deletion and partial 18 trisomy were determined at microarray analysis and reported as arr[hg19]Xp22.33p11.21(168,546-57,580,212)x1,18p11.21q23(15,124,169-78,014,123)x3.Also, SHOX deletion was in FISH analysis.
Structural and numerical changes of Xchromosome have an important role in short stature cases. The female X-inactivation mechanism significantly affects the patient's clinic with its role in Xchromosome abnormalities. While randomized X-inactivation in normal cells is observed, in most cases of X:autosomal translocation X-inactivation takes place non-randomly. In X:autosomal translocations, the normal X is inactivated preferentially to prevent deleterious monosomy of the translocated autosomal segment. However, in unbalanced X:autosome translocations, the effects of chromosome imbalance may be diminished by selective inactivation of the abnormal X. These non-random inactivation patterns do not completely eliminate the effects of the chromosomal disorder on the clinically, but have a reducing overall effect. In this the unbalanced X:18 traslocation case, having no partial trisomy effects of the 18th chromosome explains that the unbalanced X chromosome is inactivated. Lastly, the short stature in the case is thought to be caused by the Xp monosomy and SHOX deletion. Patient's findings support that X-inactivation mechanisms have a very crucial role in the autosomal translocations of unbalanced X chromosome that are very rarely observed.

Key Words: X Inactivation, X-Autosomal Translocation, Short Stature, Derivative X, Whole Arm Translocation

P-067 - A Rare Etiology in Muliıple Congenital Malformation and Global Developmental Delay: 19p13.2 Microdeletion

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Structural rearrangements of chromosome 19 are rare and difficult to detect by conventional cytogenetic analysis. In recent years, with the wide use of microarray analysis method , small deletions have been reported in the short arm of chromosome 19 in patients with multiple congenital anomalies and intellectual disability.This region is quite rich in genes, and therefore even small deletions may cause severe clinical phenotypes.
A 17-month-old boy was evaluated in our clinic for global developmental delay. In his past history, he was operated for omphalomesenteric fistula and echocardiography revealed VSD and ASD. Hand radiograph revealed shortness of phalanges. He had been taking antiepileptic medications for his seizures and receiving special training due to global developmental delay. Karyotype analysis revealed 46,XY. On his recent examination, he was 7 years old and his body weight and height were under 3rd percentile, head circumference was between 3rd-10th percentiles according to his height age. On physical examination, palpebral fissures were upslanted and nasal root was prominent.
Microarray analysis was performed, and a de novo 2,314 kb deletion was detected in 19p13.2 region.
The use of microarray technology in the investigation and diagnosis of genetic disorders has led to the discovery of several rare chromosomal anomalies. In recent years, deletions have been reported in short arm of chromosome 19 involving the regions 19p13.12, 19p13.13 and 19p13.3. The clinical phenotypes resulting from these segmentalfor deletions have not been precisely established yet. Psychomotor retardation and speech delay, hypotonia, skeletal abnormalities and dysmorphic facial features are among the frequently reported features, however multiple congenital anomalies are not. The wide utility of microarray analysis and its application to this group of patients will increase our understanding of the phenotype and will allow these patients to be clinically recognized.

Key Words: 19p13.2 Microdeletion, Intellectual Disability, Multiple Congenital Anomalies

P-068 - Case Presentation of an Adult Male Patient with 11q24.3 Deletion

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Deletions are result from losing the some part of chromosome segments. Balanced translocations occur from exchange of chromosome segments that are usually between two nonhomologous chromosomes. In cases where there is loss or gain in genetic material, translocation is considered as unbalanced. Balanced translocations with no chromosomal loss and no effect on the phenotype are the most common structural chromosomal abnormalities;the incidence is 1/500 live birth. In this study, contrary to expectations, an adult patient who has unbalanced chromosome structure, instead of the patient's balanced chromosomal rearrangement is examined. It's aimed to present a deletion case that arise from an unbalanced translocation segregation.
A patient had recurrent fetal losses at his wife, deletion of 11th chromosome's q24.3 region and distal segment were found by applying GTL chromosome banding technique in the metaphases obtained from the 72-hour-cell culture on peripheral blood lymphocytes. For molecular karyotyping, DNA obtained from the patient's peripheral blood sample was analyzed by using the Affymetrix Cytoscan Optima(315K) microarray system and the results were analyzed in the CHAS3.2.0/GRCh37/hg19 analysis program. The deletion on the 11th chromosome was confirmed in the microarray analysis of the patient and reported as arr[hg19]11q24.3q25(129,054,558-134,938,470)x1. SubtelomericFISH analysis of peripheral blood lymphocytes resulted as single signal for the terminal of chromosome 11 and three signals in the terminal region of chromosome 14.After all the studies the patient's karyotype was reported as 46,XY,del(11)(q24.3).
Unbalanced gametes may occur as a result of balanced translocations and result as spontaneous abortions and/or children with anomalies. In this case, the deletion of 11th chromosome's q24.3 region and its distally and 14th chromosome to be attached to the telomer region of the 11th chromosome are revealed after cytogenetic,molecular cytogenetic and molecular karyotyping examinations of the patient with recurrent fetal loss. This suggests that instead of the telomere region at the end of the deleted chromosomal structure,a different chromosome may be located in the telomer region and maintains chromosomal stability. This study suggests that unbalanced chromosomal changes may not have phenotypic effects in adult subjects;it has been shown that it may cause children with abnormal anomalies or miscarriages as a result of unbalanced gametes.

Key Words: Deletion, Chromosome Analysis, Habituel Abortus

P-069 - Clinical Phenotype in a Patient with Tetrasomy of Distal 15q

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Tetrasomy of distal 15q usually occurs as a result of analphoid supernumerary marker chromosome .This form of marker chromosome is derived from inverted duplication. There has been only one reported case of tetrasomy distal 15q which is due to intrachromosomal triplication.Here we report on a patient with tetrasomy of 15q distal region that is formed by intrachromosomal triplication mechanism.
The patient was full term born male who was born to nonconsangineous healthy parents.His prenatal history was unremarkable and he was born via normal spontaneous delivery.He was referred to us because of several dysmorphic features.The physical examination at the age of six months revealed a head circumference of 44 cm(75-90p),a length of 71cm(90-97p),a weight of 7500 kg(25-50p), dolichocephaly,craniosynostosis, helix anomaly and retrognathia.Urinary tract USG was normal.Also, he had a normal developmental course for his age.
A conventional karyotype analysis using GTG banding technique(550 band resolution) demonstrated mosaicism.In 42 out of 50 metaphase fields a triplicated chromosome 15 was found. Microaaray analaysis revealed mosaic pattern of duplication and triplication between 15q25.1 and 15q26.3.Parental karyotype analysis were normal.
There are common clinical features of previously reported cases with tetrasomy and trisomy of distal 15q region.Asymmetric growth,overgrowth,intellectual diasability and structural anomalies of kidney are some of the commonly reported clinical features in these patients.The previously reported case with intrachromosomal triplication of distal 15q region also presented with similar clinical findings including asymmetrical face, nephroblastoma and intellectual disability. Dysmorphic findings present in this patient were also reported in previous cases.However,because of younger age of the patient further follow-up should be done .Absence of motor mental developmental delay in this patient demonstrates that this clinical feature could be variable.

Key Words: Intrachromosomal Triplıcation,Tetrasomy of Distal 15q,Kidney Abnormalities,Asymmetrical Growth, Intellectual Disability

P-070 - Rare Robertsonian Translocation in Down Syndrome rob(21q;21q) and (14q; 21q)

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Robertsonian translocations (ROB) are common structural rearrangements in humans. Trisomy 21 is the most common chromosomal aneuploid with a frequency of approximately 1 in 700 live births (1;700). 95% of the cases are classical Down syndrome, occurs with extra chromosome 21,approximately half of the remaining occurs with rob (14q21q) translocation, the other half ocurs with robs such as rob(21q21q), rob(15q21q) and mosaic trisomes. The most common non-homologous ROB in Down's syndrome is rob (14q21q). Rob (21q; 21q) is a rare ROB. In this study, three newborns with Robertsonian translocation type Down's syndrome and parental karyotypes were identified and the prevalence of risk for subsequent pregnancies was evaluated in the light of literature information.
Phytohemagglutinin (PHA) -induced peripheral blood cell culture was used for this study. Twenty G-banded metaphases were evaluated according to the 2016 International System for Human Cytogenetic Nomenclature (ISCN).
Two newborns were diagnosed with Down syndrome with rob (21; 21) (q10: q10) as a result of cytogenetic evaluation and the karyotypes of both parents were normal. One of them is a mosaic, and the karyotype 46, XX + 21der (21; 21) (q10; q10) [6], 46, XX [14], the other is full and the karyotype is 46, XY + 21, der (21; 21) (q10; q10). The other newborn, karyotype 46, XY, t(14; 21) (p11; q11), +21, chromosome analysis showed that the mother had a balanced robertsonian translocations carrier, 45,XX, t(14;21)(p11;q11). His father's cytogenetic evaluation was normal. Although there is no phenotypic difference between Down's syndrome, one newborn had maternal carriage while other two newborns appeared de novo.
About half of the ROBs are de novo reconstructions. Rob (14q; 21q) translocations, which account for approximately 95% of de novo ROBs, have been reported to occur in maternal meiosis. It is reported that common ROBs have the same fracture points which can be formed by a random mechanism during oogenesis. Literature was reviewed and helped to explain the subject. Families, one of prenatal diagnosis method and PGD was proposed in when they want to have children again.

Key Words: Robertsonian Translocations (ROBs), Down Syndrome, De Novo, Genetics

P-071 - A Case with 46,XX,(11)ins(11;18)(q21;q12.2q23) Presented as Edwards Syndrome Like Findings

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Edwards' syndrome is the second most common autosomal trisomy and occurs in 1 in 8,000 live births. This syndrome causes severe congenital abnormalities which results in early period's mortality. Low birth weight and severe growth retardation are important features of the phenotype. Other prominent clinical features of this syndrome include cardiac abnormalities, mental and developmental retardation, dysmorphic facial appearance, skeletal dysplasias. In this case report, we presented the clinical effects of partial trisomy of 18th chromosome that inserted to chromosome 11 which was not previously reported in the literature.
A 10-month-old girl was referred for growth retardation. In clinical examination length was 108cm (-4,97 SDS), and weight was 20.9kg (-3,05 SDS). Dysmorphic features were hypotelorism, esotropia, large eye, high palate, pronounced glabella, long filtrum, thin upper lip, plump nasal arch, hypoplasic ala nigans, pectus excavatum, finger protrusions in both hands, over riding on right toes, and shortness on 5th finger. Subaortic VSD was detected in ECHO.
In chromosome analysis of the patient, 46,XX,der(11)ins(11;18)(q21;q12.2q23)pat were detected. As a result of microarray analysis revealed that arr[hg19]18q12.1q23(32,386,124-75,093,387)x3. The mother had a normal karyotype and the father's karyotype 46,XY,ins(11;18)(q21;q12.2q23).
Unbalanced transfer of 18q12.2-q23 from the father results Edwards Syndrome like phenotype. In patients with similar clinical findings to Edwards Syndrome were detected in three different studies with trisomy of 18q12.2-18q21, 18q11-qter and 18q12.2-q22.2 regions. Growth retardation, mental and developmental delays and possible seizures are common, especially in cases with trisomy of this region. On the other hand, 18q12.2q23 fragment insertion into the 11q21 region was detected in microarray where it did not cause any loss of genetic material at the insertion point. The fact that there is no additional clinical finding in phenotypic examination of our patient that supports this condition. It was observed that it was compatible with typical symptoms of Edwards syndrome compared to the patient's phenotype. Although microarray is the first tier test in congenital anomalies, karyotype analysis is still important for elucidation of complex chromosomal anomalies and detection of transition pattern.

Key Words: Chromosomal Anomaly, Microarray, Insertion, Edwards Syndrome

P-072 - Evaluation of Low Level 45,X Mosaicism by Using Cytogenetic and FISH Methods in Different Tissues

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Approximately 30-50 % of Turner syndrome (TS) patients are mosaic for X chromosome. Because the phenotype and clinical management of those cases are closely related with the karyotype, identification of chromosomal constitution and the level of mosaicism play a crucial role for genetic counselling. Clinical picture in low-level TS mosaicism is milder compared to other mosaic TS types. They are mostly recognized because of infertility. The detection of low-level mosaicism in cytogenetic analysis is therefore clinically important. It causes a challenge to laboratory because of false positive results due to cultural and technical reasons Here, we present the results of karyotype and FISH analysis of peripheral blood, and FISH analysis of buccal mucosa of 30 cases with low-level 45,X mosaicism.
A total of 30 cases with low-level 45,X mosaicism detected in peripheral blood cytogenetic analysis were included in the study. For each case, a minimum of 100 metaphase cells were counted. To further investigate the validation of mosaicism, FISH analysis from blood samples and buccal mucosa was performed. At least 500 and 200 cells were analysed for blood and buccal mucosa samples respectively. The Pearson correlation test was used in the statistical analysis.
The level of 45,X mosaicism was between 2-15% in all methods. A 70% correlation was detected between blood karyotype and blood FISH groups. No significant result was achieved when other binary groups were evaluated. A cut-off level could not be obtained because of the lack of control group.
Further studies with larger samples and the inclusion of control group may provide more accurate information concerning the relationships between those methods.

Key Words: Mosaic, Turner, Cytogenetic, Buccal Mucosa

P-073 - Investigation of FMR 1 Gene (CGG) Repeats in Patients with Different Clinical Pre-Diagnosis

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Fragile X Syndrome occurs due to the expansion of the CGG trinucleotide repeat sequences in the 5'UTR of the FMR 1 gene (Fragile X Mental Retardation 1) located at the Xq27.3. Fragile X syndrome may be presented with the moderate cognitive disabilities, significant learning disability and with premature ovarian failure (POF) in the female premutation carriers. The aim of this study is to evaluate relationship between the repeats of FMR 1 gene and clinical findings of Fragile X patients.
2 ml of peripheral venous blood samples of patients were collected in EDTA tubes. Genomic DNA was extracted according to the protocol of the kit used [EZ1 Advanced Instruments, Qiagen, Hilden, Germany]. The concentration and purity values of the DNA samples were measured on the NanoDrop device [Nanodrop 2000C, ThermoScientific, USA]. Bisulfite DNA was extracted according to the protocol of the kit [EpiTect Bisulfite convention Kit, Qiagen, Hilden, Germany]. As an alternative method for the diagnosis of Fragile X syndrome, flourescent labelled methyllation spesific PCR was performed. Fragment analysis of flourescent labelled PCR fragments were performed on ABI 3130xl [ABI 3130xl AvantSystem, AppliedBiosystems, USA] and analysed with GeneMapper v5.0 software programme.
The study included 243 patients who were admitted to Trakya University Faculty of Medicine, Medical Genetics Department, Genetic Diseases Diagnosis Center with the diagnosis of Cognitive Disability (123), Premature Ovarian Failure / Primary Amenorrhea (57), Neuromotor Developmental Disorders(90) between March 2014 and August 2018. Twenty-seven patients had both cognitive disability and neuromotor developmental disorders. The age distribution of patients were F: 117 (A: 20.4 ± 12.08), M: 126 (A: 9.9 ± 5.6) by gender. As a result of the analysis, 18 patients were determined to have increased number of repeats in FMR1 gene (CGG).
It is reported in the literature that the FMR1 gene have a genetic anticipation and that tendency to expansion during heredity. Finding of expanded number of CGG repeats in FMR gene in 2 families in this study supports the literature.

Key Words: : FMR1 Gene, Number of CGG Repeats, Cognitive Disabilities, Premature Ovarian Failure, Neuromotor Developmental Disorders

P-074 - Development Retardation: A Case Presentation with Unbalanced Translocation between 5th and 9th Chromosomes

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Development retardation is defined as retardation in the areas of speech and language development, motor development, social development and cognitive development. Development retardation is seen at the rate of 12-16% in childhood group. Genetic factors, as well as environmental factors, should be investigated in etiology of development retardation. Growth development retardation is generally accompanied in chromosomal rearrangements and other single-gene diseases. In this study, it has been aimed to investigate a derivative unbalanced translocation product identified in a chromosome analysis in a case investigated due to growth development retardation.
A 8-year-old female patient applied with the complaint of development retardation also had an intellectual deficiency and ventricular septal defect at echocardiography. Her dysmorphic characteristics were as synophrys, prominent nasolabial sulcus and dermatoglyphic anomalies in her hands. Cytogenetic analysis planned for pre-diagnosis of multiple congenital anomalies.
Short term 72-hour-cell culture has been conducted from a peripheral blood sample taken from the patient for cytogenetic analysis. GTL (giemsa-trypsin-Leishman) banding and karyotype analysis from metaphase plaques performed. An extrachromosomal structure has been identified in the 5th chromosome of the patient and reported 46,XX,der(5)t(5;9)(p15.3;p22). It has been detected that the mother of the patient has reciprocal translocation between 5th and 9th chromosomes in the parental study. DNA sample obtained from peripheral blood and studied by using Affymetrix Cytoscan Optim(315K) microarray system. 5th chromosome partial deletion and 9th chromosome partial deletion detected by molecular karyotyping. So, an abnormal segregation of translocation in the mother and loss of 5.956kbp covering 5p15.33p15.32 area and increase of 15.021kbp covering 9p24.3p22 area have been detected. Molecular karyotyping of the patient has been reported as arr[hg19]5p15.33p15.32(113,576-6,069,867)x1,9p24.3p22.3(203,861-15,225,188)x3.
The etiology of patients with growth development retardation and dysmorphic findings due to chromosomal rearrangement has been clarified as a result of abnormal segregation of balanced translocation of her mother after cytogenetic analysis and molecular karyotyping studies. It has been reported in the databases that the increase in the 9pterm area may cause dysmorphic signs and development retardation. Also, the clinics of our patients have been planned to be re-evaluated in terms of Cri-du-Chat syndrome findings regarding 5p deletion syndrome.

Key Words: Development Retardation, Unbalanced Translocation, Cytogenetics

P-075 - Azospermic Infertile Male with Isochromosome Yp: A Case Report

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Chromosomal anomalies and Y chromosome microdeletions are the leading causes of male infertility. Non-mosaic isochromosome Yp is a rarely seen Y chromosome structural anomaly. In this study, we aimed to present an azospermic infertile case with non-mosaic isochromosome Yp.
A 35-year-old, two years married man was referred from urology policlinic to our department with the diagnosis of infertility and azospermia. His physical examination was normal. Bilateral microlithiasis was detected in her testicles by USG. The patient's hormone profile was; LH: 6 mIU / mL (1.1-7.0), FSH: 13.3 mIU / mL (1.4-18.1), prolactin: 8.4 ng / mL (3.4-24.1), total testosterone: 196 ng / dL (240-950 ng / dL).
Chromosome analysis from peripheral blood in the patient resulted in 46, X, + mar. In the C and NOR banding, the marker chromosome was found to be monocentric and did not contain satellites. In order to determine the origin of the marker chromosome, FISH analysis with centromeric Xp11.1-q11.1 and Yp11.3 (SRY) probes was performed. It is interpreted as non-mosaic isochromosome Yp. The deletions of sY84, sY86 loci of AZF-a region, sY127, sY133, sY134, RBMY loci of AZF-b region, sY157, sY254, sY255 loci of AZF-c region and sY152,sY153 loci of AZF-d region were detected in Y chromosome microdeletion analysis.
Non-mosaic isochromosome Yp is very rare. Seven cases have been described in the literature so far. In this study, we present non-mosaic isochromosome Yp anomaly which is defined by cytogenetic and molecular methods in an azospermic male with normal physical examination.

Key Words: Isochromosome, Azospermıa, Male Infertility

P-076 - A Case with Deletion in Chromosome 3q13.2-q13.31 Region

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We present a patient with interstitial 3q13.2-q13.31 microdeletion and compare her features with the patients previously reported in the literature.
Our patient is a second child of unrelated parents. She was born at term, the birth weight was 3800 gram (75th-90thp). When she was five years old delayed motor function, delayed language development and intellectual disability were determined. She is followed with prediabetes, essential hypertension, high cortisol level by endocrinology department, and consulted to genetic policlinic because of dysmorphic features and intellectual disability.
On physical examination the height was 188 cm, weight was 135 kg (BMI:38.2-obese) and head circumference was 57 cm (+2.4 SD). She had milder intellectual disability at WISC-R test, and macrocephaly, moon face, absent eyebrows, eyelid fullness, epicanthus, short nose, depressed nasal bridge, fullness of cheeks and chin, large ears, buffalo hump, bilateral pes cavus were determined. Chromosome analysis was showed 46,XX normal karyotype. Chromosomal microarray analysis revealed a 3.4 Mb deletion in 3q13.2-q13.31 region [(arr 3q13.2-q13.31 [112,219,752-115,523,299]X1(hg19)]. The region involves 25 USCS genes incluing ZBTB20, DRD3, GAP43, BOC, ZDHHC23 genes, which, according to OMIM database, are defined as possible cause of disease. Chromosome and microarray analysis of patient's parents were normal. Deletions at the proximal part of chromosome 3q is rarely reported in the literature. The patients had deletion at the same region, reported with macrocephaly, mild intellectual disability, delayed motor development, tall stature, delayed language development, generalized hypotonia, epicanthus at DECIPHER. Additionally, such as corpus callosum hypolasia, plagiocephaly, joint laxity, which are not observed in our patient, are reported. In the patients having a deletion at the same chromosomal position with equally length, there may be common features in the findings affected in the phenotype, as well as differences. It may be explained by the influence of other genes in the genome, epigenetic differences and / or environmental modifiers.

Key Words: Microdeletion Syndrome, 3q13.2-q13.31 Deletion, Obesity, Intellectual Disability

P-077 - A Case with Chromosome 4q Deletion (4q21.2- 4q21.23)

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Chromosome 4q21-4q22 deletion syndrome; is a rare disease characterized by growth retardation, learning disability, muscle weakness (hypotonia), inability to stand upright, short stature, cardiac and genitourinary system abnormalities. Typical facial findings are macrocephaly, microcornea, low ears, hypertelorism, flat nose bridge, small and upturned nasal tip. The severity of the disease varies according to the size of the deleted region.
In this report, we present an 11-month-old male patient who was referred to our clinic for developmental delay, hypotonia, motor retardation, ASD and dysmorphic facial findings. Clinical examination revealed short stature, growth retardation, macrocephaly, microcornea, muscle weakness and seizures.
Molecular karyotyping revealed chromosome 4q21.2-q21.23 with 1 copy of 3.702.010 kbp in size. The functions of the genes that have been deleted in the region were compared with the patients' clinic and found compatible.
The disease is presented because of the rarity of molecular karyotyping in patients with multiple congenital anomalies.

Key Words: Chromosome 4q Deletion, Microcornea

P-078 - Maternal Inherited Submicroscopic Duplication in Chromosome Xq22.2 including PLP1, GLRA4 and MORF4L2 Genes Identified by Array-CGH in Male Patient with Neurodevelopmental Disorder

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Array comparative hybridization (Array-CGH) is powerful method to identify genetic causes of neurodevelopmental disorders (NDD) with brain malformations (BM) and Intellectual disability (ID). BM and ID is genetically heterogenous conditions. Although genetic heterogeneity in most neurological diseases is one of the most important limiting factors in the research, genetic association studies for many diseases have been increased along with the development of analysis techniques of the whole genome (Array CGH, SNP array and new generation sequencing).
We performed array-CGH in case with corpus callosum hypoplasia, delayed myelinization, cerebral atrophy and craniofacial anomalies.
We identified maternal inherited Xq22.2 submicroscopic duplication including PLP1, GLRA4 and MORF4L2 genes in male patient gain on chromosome Xq22.2) in male patient was maternal inherited. We filtered CNVs according to the American College of Medical Genetics (ACMG) standards. After first filtering CNV was compared with host CNV morbidity map as region-based. About 449 kbp CNV have been evaluated according to CNV findings in the controls (6459) and cases (16922) for chromosome X, which have been detected by the Eichler group. It has been detected only one case, no any controls. PLP1 (Proteolipid Protein 1) is a protein coding gene. Diseases associated with PLP1 include Spastic Paraplegia 2, X-Linked and Pelizaeus-Merzbacher disease. Mutations in this gene cause Pelizaeus-Merzbacher disease and Spastic Paraplegia Type 2. GLRA4 (Glycine Receptor Alpha 4) is a protein coding gene. Diseases associated with GLRA4 include Pelizaeus-Merzbacher Disease. MORF4L2 (Mortality Factor 4 like 2) is a protein coding gene. Diseases associated with MORF4L2 include Paraneoplastic Cerebellar Degeneration.
Genotype-phenotype correlation supports that duplication may be associated with hypomyelinization. The identification of the genes related to different types of developmental anomalies will increase our knowledge of the neurobiological mechanisms in these anomalies which in turn will help diagnosis, treatment with existing medicine and development of novel and better medicine in the future.

Key Words: Xq22.2, Array-CGH,Brain Malformations, Intellectual Disability

P-079 - Mental Motor Retardation: A Case Presentation with Mosaic Deletion and Duplicatıon on 7th Chromosome

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Mental motor retardation(MMR) is a clinical condition characterized by being under normal limits of developmental stages of intelligence. That condition affects all mental and cognitive abilities and also the stages of motor development. Beside conventional cytogenetic methods, molecular karyotyping is also proposed to detect submicroscopic anomalies recently. The aim of this study is to evaluate the clinical and genetic findings of a 2-year-old patient had mosaic deletions and duplications on 7th chromosome who followed up with MMR indication.
A 2-year-old male patient with growth retardation were examined in our clinic. He walked late, and could pronounce 4-5 words. The dysmorphological features of the patient were hypertelorism, flattened nasal root, microtia, notched ears, 3x3cm hypopigmentation on the upper right breast and micropenis. Decrease in white matter, thinning of the corpus callosum and multiple nodular structures were detected in the patient's brain MRI.
72-hour-cell culture performed from the peripheral blood sample of the patient and GTL,CBG and NOR banding techniques used for chromosome analysis. The presence of a mosaic structure showing both deletions and duplications at 7th chromosome detected. There were deletions at(7)(q33) in 29 of and duplications at(7)(q34q36) in 21 of 50 metapahases. There were no numerical or structural chromosomal anomaly observed at parents and 46,XY,del(7)(q33)dn[29]/46,XY,dup(7)(q34q36)dn[21] karyotype reported. DNA obtained from the patient was studied by using the Affymetrix Cytoscan Optima(315K) microarray system and analyzed in the CHAS3.2.0/GRCh37/hg19 programme.
As a result of cytogenetic study, there was a duplication on the 7th chromosome in a certain ratio of the metaphases of the patient, and a deletion in some of the metaphases. In molecular karyotyping, deletion could be detected due to the fact that total gene copy number was calculated in the same region of the same chromosome and the deletion rate was more than duplication. This case is a special example of the complementarity of both methods and shows their distinctive coverages and limitations. According to databases, the DPP6(OMIM*126141)gene located in the deletion region of the 7th chromosome may cause a phenotype responsible for intellectual disability(OMIM#616311) and suggests that the deletion in our patient may be related to MMR.

Key Words: Mental Motor Retardation, Mosaic Structural Anomaly, Cytogenetics, Dysmorphology

P-080 - Mental Retardation: A Case Presentation with Additive Structure at 14th Chromosome

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Mental retardation (MR)is the condition of general mental functions are significantly lower than the average. MR usually associated with deterioration at behaviours and accomodation to environment. The causes of mental retardation are generally; chromosome anomalies, single gene disorders, developmental brain anomalies, metabolic/neurodegenerative diseases, familial retardation, postnatal/perinatal causes and congenital infections. The incidence is 2-3%in the whole population. In this study, we aimed to investigate a case with MR has an additive chromosome at 14th chromosome.
A 7-year-old girl who was admitted to our outpatient clinic with learning difficulties had growth retardation and significant intellectual disability. She had seizure history and abnormal wave pattern was detected in her EEG. The patient had no similar history in her family. Cytogenetic and molecular karyotyping techniques were planned for investigating the case.
Peripheral blood sample taken for cytogenetic analysis. After 72-hour culture GTL(Giemsa-trypsin-Leishman) banding technique used. An additional structural chromosomal material detected in all 20 metaphases and karyotype was reported as 46,XX,add(14)(q32.3). While there was no anomaly at karyotype of patient mother's(46,XX) there were no results at father's two cultures to analyse. Therefore, it could not be clarified whether the anomaly in the patient was de novo or inherited. Furthermore,Affymetrix Cytoscan Optima(315K) microarray system was used for molecular karyotyping from the DNA and reported as arr[hg19]14q32.33(106,487,026-107,285,437)x1, 20q13.2q13.33(54,475,058-62,915,555)x3. It's thought that patient had the possibility of carrying a derivative 14 due to abnormal segregation of a balanced translocation between the 14th and 20th chromosomes.
Unbalanced translocations, duplications, deletions, extra chromosomes, mosaicism and other structural anomalies in autosomal chromosomes may be the cause of MR. Also, copy number variations(CNV) also have an important role in the research of the etiology of MR. In recently studies it's shown that, unstable reciprocal translocations were responsible for 0.8% of MR cases. In our case, an increase in the distal region of the 14q detected, and with the result of microarray analysis a balanced translocation between 14th and 20th chromosomes investigated. So, it's thought that possibility of carrying derivative 14 arise from abnormal segregation of parents or de novo and also this entity could be related to patient's phenotype.

Key Words: Mental Retardation, Additive Chromosome, Cytogenetics

P-081 - Mental Retardation: Case Report with 18p Duplication

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Mental retardation is a condition that occurs in the developmental periods with low IQ level and appears with deterioration in behavior, restriction in the skill areas and problems in social and daily relationships. While it results from several reasons such as environmental and congenital causes, genetic causes also play an important role. In this study, it is aimed to investigate a metal retardation case on which existence of extra genetic material is identified in the 18th chromosome.
A 6-year-old female patient referred to our clinic due to growth retardation. Prominent forehead, short palpebral fissure, low ears have been observed dysmorphologically as well as findings compatible with hypochondroplasia.The patient also has an intellectual deficiency. There was no consanguinity between her mother and father and no similar history in her family.
The patient's peripheral blood sample were cultured for 72-hours and GTL(Giemsa-trypsin-Leisman) banding performed. Existence of extra genetic material has been identified on p11.3 area of the 18th chromosome in all fields as a result of an investigation of metaphase plaques obtained karyotype reported as 46,XY,add(18)(p11.3). Upon this, an increase of 9.292 kpb covering 18p11.32p11.22 area has been identified as a result of the study conducted by using Affymetrix Cytoscan Optima(315K) microarray system from DNA sample obtained from peripheral blood and it has been reported as arr[hg19]18p11.32p11.22(136,226-9,428,420)x3. And also, there was no mutation at FGFR3 gene's 7,10,13,15and19. exons analysis previously studied.
Mental retardation is observed as a finding in several genetic disorders and chromosomal anomalies are shown as a reason in frequencies varying between 4-34%. Unbalanced translocations, duplications, deletions, extra chromosomes, mosaicisms and other structural anomalies emerge as a reason for mental retardation. At the same time, copy number variation(CNV) has a significant place in the investigations of etiology of mental retardation. That the whole p arm of the 18th chromosome is duplicated is a very rarely seen anomaly and intellectual deficiency, hand and foot anomalies, atypical face and epilepsy can be seen in the cases where trisomy 18p is observed. In our patient, there are 3 copies from p11.32p11.22 area of the 18th chromosome and it's thought that this duplication causes mental retardation.

Key Words:18p Duplication, Mental Retardation, Cytogenetics, Dysmorphology

P-082 - Mental Retardation: A Case Presentation with De Novo Unbalanced Reciprocal Translocation

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Mental Retardation(MR) is defined as general mental functions' being significantly under the average. The major causes of MR include chromosomal abnormalities, single gene disorders, structural central nervous system anomalies, prenatal/perinatal/postnatal factors, environmental/teratogenic causes, metabolic/endocrine causes. In this study,we aimed to present a case with MR due to unbalanced chromosomal regulation.
A one-and-half-year old male patient that no consanguinity between his parents was referred to our clinic because of hydrocephalus and had marked neuromotor developmental disorders.His dysmorphic findings were wide forehead,frontal bossing,hypertelorism, wide and flattened nasal root, laterally floating eyebrows, long eyelashes,long filtrum, anteverted nostrils, microretrognatia, low and posterior rotated ears. The patient's brain MRG revealed a decrease in the frontotemporal lobe volume, dilatation of cortical sulcus and fissures, and bilateral periventricular leukomalacia. Weight was measured as 6kg(<3p) and head circumference was 47cm(75-90p).
For cytogenetic study, 72-hour-cell culture and GTL banding technique made from peripheral blood and then chromosome analysis was performed from twenty metaphase plaque.46,XY,der(17)t(1;17)(q42;q25) karyotype was detected. There were no anomalies at parents' karyotypes and de novo unbalanced reciprocal translocation was detected at patient. Molecular karyotyping was performed by using the Affymetrix Cytoscan Optima(315K) microarray system from DNA and resulted as an increase of 20,942 kbp(marker number:1,206), including 1q42.13q44, an increase of 1,558 kbp in the region 17q25.3(marker number:80) and a loss of 798 kbp 17q25.3(marker number:45).
Chromosomal rearrangements were reported to be 4% to 34% in MR cases according to the degree of MR. Numerical chromosomal anomalies are most common in MR cases and other chromosomal anomalies (deletion,duplication,translocation,etc.)are seen in 25% of cases with severe MR. Copy number variants(CNV)are also have an important role in elucidating the etiology of MR. Unbalanced gametes usually arise from a result of coupling between derivative chromosomes and their normal homologues from balanced reciprocal carriers and also spontaneous abortion or children with anomalies seen at these cases. Rarely, unbalanced translocations are found as de novo similar to our case. In our patient as a result of unbalanced translocation between 17th chromosome 1st chromosome, partial 17q monosomy and partial 1q trisomy occured. It's thought that our patient's neuromotor retardation related with unbalanced translocation and abnormal gen dosage.

Key Words: Mental Retardation, Reciprocal Translocation, Unbalanced Translocation, De Novo Translocation

P-083 - A Rare Finding: Co-Occurrence of 15q11-13 Duplication and Minute Chromosomes

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The characteristic features of 15q11-q13 duplication syndrome are hypotonia, dysmorphisms, growth-development retardation and syndactyly. Prevalence of this syndrome is unknown, to date, less than 100 cases have been reported. Although, small supernumerary marker chromosomes are observed in 0.043% of newborns, the clinical effect of rare marker chromosomes types including minute, ring and inv-dup is unknown. Minute marker chromosomes, which do not contain centromere and telomere, are chromatin structure and are replicable during the cell division. In this case report, we discussed co-occurrence of mosaic marker minute chromosomes 15q11-q13 duplication syndrome and its clinical effects, which was not previously reported in the literature.
A 23-day-old boy was referred for multiple congenital anomalies. Anthropometric measurements; height 48 cm (<3p), weight 2300 g (<3p) and head circumference 32 cm (<3p). In clinical examination, there is no dysmorphic sign, except from postaxial cutaneous polysyndactyly in left foot. ECHO revealed small ASD, bilateral GI hydronephrosis were detected in abdominal USG, and brain MRI showed mild hypoplasia of corpus callosum. The patient had seizures during the intensive care period. In chromosome analysis of the patient, 47,XY,+mar,dn[39]/46,XY[11], and minute chromosomes accompany in many fields. Molecular karyotyping reported as arr (hg19)4q12(52,800,882-54,079,547)x3, 15q11.2q14(22,770,421-34,893,104)x3, 20p11.21q11.21(25,347,220-29,833,609)x3, Yp11.2q11.222(9,511,369-21,694,426)x2. Chromosome analysis of the parents were normal.
Our patient had from some typical features of 15q11-q13 duplication syndrome including growth-development retardation and syndactyly, whereas he didn't have some of them as hypotonia or dysmorphisms. Increment of 4q12, 20p11 and Yp11 regions were investigated in several databases whether they had clinical importance and there is no data related with clinical effects. A study demonstrated, minute chromosomes originated from acrocentric and non-acrocentric chromosomes 5,3% and 18,8% respectively. In our case, we could not differentiate origin of minute chromosomes because both of the acrocentric and non-acrocentric chromosomes increased. According to a theory, in some small and complex form minute chromosomes are degenerated by some cells and it causes mosaism. Our case support this data with 78% mosaism. As a results co-occurence of 15q11-q13 duplication and minute chromosomes has not been reported previously, this case will contribute to the literature.

Key Words: Congenital Anomaly, Minute Chromosome, Chromosome Analysis, Marker Chromosome

P-084 - Chromosomal Array-CGH Analysis in Patients having Neurodevelopmental Delay and Dysmorphic Features

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Array CGH (comparative genomic hybridization) is an important diagnostic method in Medical Genetic Clinics. It is generally used for the patients that have neuromotor development retardation and dysmorphic features with normal karyotype. Our aim in the present study is to discuss the patients having neuromotor and dysmorphic features who were evaluated in Marmara University Medical Genetic Clinic in the last four years for genetic analyses and diagnosed distinct microdeletion syndromes via Array CGH.

Key Words: Dysmorphism, Microarray, Microdeletion

P-085 - Coexistence of Two Disorders with Overlapping Features: Cystic Fibrosis and Xq28 Duplication

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Copy number variants of the X chromosome, including duplications of chromosome Xq28 are common causes of X-linked intellectual disability in males. Xq28 region harbors many low copy repeats that predispose to three clinically distinctive intellectual disability syndromes. Among these; the most distally located int22h1/int22h2 mediated Xq28 duplication syndrome is characterized by cognitive impairment, behavioral problems, recurrent pulmonary infections and obesity. Females with this duplication have either milder phenotypes or are clinically unaffected. Cognitive impairment is caused by increased expression of RAB39B located in Xq28.
The male patient was born to non-consanguineous healthy parents at term with a birth weight of 2750g. He had recurrent pulmonary infections since his neonatal period and was diagnosed with cystic fibrosis. During early childhood, he had recurrent otitis media and pulmonary infections. Sanger sequencing was performed in the patient and compound heterozygous mutation (ΔF508/c.3849G>A) was found in CFTR. At the age of 7 years, he was referred to genetics department due to speech delay, hyperactivity and aggressive behavior, and fragile X analysis was performed which resulted normal. Physical examination at the age of 14 years revealed a height of 155 cm (50p) with a weight of 65 kg (90p) and a head circumference of 52cm(<3p). Psychometric evaluation revealed mild intellectual disability.
The patient was screened for CNVs using the Agilent 8x60K Microarray Kit, analysis revealed a maternally inherited duplication on chromosome Xq28 including RAB39B. His sister was found to carry the same Xq28 duplication.
Cystic fibrosis is seen with a high carrier frequency and the most common mutation is ΔF508, which accounts for %75 in Western populations and %19.4 in Turkish patients. In addition to the diagnosis of cystic fibrosis, it is interesting that he also had Xq28 duplication that is also associated with recurrent pulmonary infections. This study once again shows that when a genetic defect does not fully explain the clinical findings, it is appropriate to consider presence of other accompanying diseases in patients. Follow-up of the patients and genome-wide analyses may reveal more than one genetic disorder that is clinically important for the patient and the family.

Key Words: Recurrent Pulmonary Infections, Cystic Fibrosis, Intellectual Disability, Xq28 Duplication

P-086 - Learning Disability: A Case Presentation of Unbalanced Translocation with 46,XX,der(9)t(7;9)(q34;p24) Karyotype

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Translocations; are one of the most common chromosomal arrangements in humans and is divided into two as balanced and unbalanced depending on whether there is a decrease or increase in genetic material. In this study, it's aimed to discuss unbalanced rearrangements revealed from cytogenetic and microarray analysis of a patient with a complaint of inability to speak.
An 8-year-old girl was admitted to the hospital with the complaint that she could not speak, and she was unable to establish a sentence when she spoke up. Physical examination revealed asymmetrical face, short neck, defective tooth structure, strabismus and left ear hypoplasia.
For cytogenetic analysis, 72 hours of culture was performed by using induced peripheral blood lymphocytes. Metaphase preparations obtained after culture were stained by GTL banding method and chromosomes in 20 metaphase plaques were evaluated in terms of numerical and structural irregularities. 46,XX,der(9)t(7;9)(q34;p24) karyotype was reported. On the other hand, cytogenetic analysis was requested from the parents of the patient but samples could not yet achieved. Molecular karyotyping of the patient was studied by using Affymetrix Cytoscan Optima (315K) microarray system achieved from DNA of peripheral blood samples of the patient. The results of the microarray of the patient were reported as: [hg19] 7q34q36.3 (141,627,148-159,119,707) x3, 9p24.3p24.2 (203,861-4,557,165) x1 and an increase of 17,493 kbp (marker number: 1002) covering 7q34q36.3 region and 4,353kbp loss (number of markers: 312) including 9p24.3p24.2 region were found.
In patients with unbalanced translocation, loss of learning ability and developmental retardation complaints are often seen. Their severity may vary depending on the size and location of the chromosome and the gene regions it contains. Different effects can occur depending on the characteristics of genes in gene fractures and chromosome fractures. In our patient, prominent dysmorphic features were prominent and she could not speak. Lastly, unbalanced translocation of the patient investigated by cytogenetic and microarray studies. It's also thougt that the translocation may arise from a balanced translocation from parents although they haven't yet studied.

Key Words: Unbalanced Translocation, Learning Disability, Cytogenetics, Dysmorpholgy

P-087 - Two Cases with Partial Trısomy of Chromosome 9p and Phenotypic Variability

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Trisomy 9p is the most frequent trisomy following trisomy 21, 18, and 13. It was first time described in 1970 and to date, more than 150 cases have been reported. Characteristic features are intellectual insufficiency, postnatal growth retardation, microcephaly, craniofacial anomalies, congenital heart defects. In addition, Brain anomaly, non-comunican hydrocephalus and hypospadias can be seen in this disease. In this case report, we aimed to present the clinical features of two cases of partial 9p trisomy from two unrelated families.
In first case, a 2-month-old boy was referred for dysmorphic findings. Physical examination revealed a weight of 4.5 kg (<3p), height of 54 cm (<3p), and head circumference of 37 cm (<3 p). Dysmorphic findings; frontal brossing, narrow palpebral fissures, retro-micrognathy, bilateral Simian line, contracture of fingers. The second case, a 1-month-old male patient was consulted for brain malformation and hydrocephalus which was detected in prenatal period. On physical examination, weight was 3.2 kg (<3p) and head circumference was 41 cm (> 97p). Cranial MRI revealed ventricular dilatation and cortical dysplasia.
Chromosome analysis of the first case revealed a partial 9p trisomy as a result of duplication of p arm of chromosome. Karyotype reported as 46,XY,dup(9)(pter→p11::p24→qter). In microarray study, arr [hg19] was found to be 9p24.3p13.1(203,861-38,787,480)x3. The karyotype of the second case was reported as 47, XY,+ del(9)(q11). Microarray result was found as [hg19] 9p24.3q13 (203,861-68,298,352)x3. Chromosome analysis of the parents of both cases were normal. As a result of chromosome analysis and molecular karyotyping, the cases were diagnosed as de novo partial 9p trisomy. Phenotype of patients with 9p trisomy reported in literature can be highly variated including some of prenatal-onset or neonatal-onset. The second case was prenatal-onset with hydrocephaly and brain anomaly. The first case had only microcephaly and dysmorphism. Although the patients were diagnosed same, it is thought that the duplicated region different each other which may cause this variation. Moreover, the fact that the patients are still too young thus it was too difficult to compare their phenotypic degree. Long-term follow-up of such rare syndromes will allow to receive more comprehensive genetic counseling.

Key Words:9p Trisomy, Dysmorphism, Chromosome Analysis, Microarray

P-088 - Partial Monosomy 18 and Partial Trisomy 19 in a Patient

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Derivative chromosomes generally occur due to translocations. Balanced translocation carriers usually do not have any clinical finding as there is no change in the amount of total genetic material.However, during meiotic divisions in the gonads of the carrier, segregation of the translocation could result in an unbalanced genetic content. Here we report on a patient with a der(18) chromosome that is an outcome of a translocation between chromosome 18 and 19 which result in partial monosomy 18q and partial trisomy 19q and discuss the common and different clinical features of the previously reported similar cases in the literature.
The patient was born prematurely to nonconsangineous parents.He was given mechanical ventilation, immediately after birth and was hospitalized in NICU for 8 days.An ecocardiography revealed absence of pulmonary valve ,pulmonary arterial hypertension,Patent ductus arteriosus and atrial septal defect.He was operated because of multiple cardiac anomalies at age of 20 days. Physical examination at the age of 6 months revealed a head circumference of 39cm(<3p), length of 64cm(10p),a weight of 5.5 kg(<3p) . He also had hypotonia, plagiocephaly,brachicephaly, wide nasal bridge, ,sacral dimple, hypospadias,pes cavus.
Conventional karyotype analysis was performed using GTG banding technique(550 band resolution) and demonstrated a der(18). Microarray analysis revealed a deletion of 15,567 kb in 18q22.1q23 and a duplication of 5,819 kb in 19q13.41q13.43.The deleted region contained 30 OMIM genes including MBP and TSHZ1.Parental karyotype analysis indicated presence of paternal balanced translocation between chromosome 18 and 19, which was apparently the source of derivative chromosome in the patient.
18q deletion syndrome which is associated with intellectual disability,short stature,hypotonia,hearing loss, microcephaly, dysmorphic features and cardiac anomalies. Clinical findings of this patient seem to be consistent with 18q deletion syndrome.However, the effects of the increased dosage of genes found in 19q distal region should be further investigated and supported by clinical reports and further molecular studies. Finally, because of paternal balanced translocation, prenatal or preimplantation genetic diagnosis should be recommended to the family in future prengnancies.

Key Words:18q Deletion Syndrome, Partial Trısomy of 19q,Abnormal Segregation, Balanced Translocation,Derivative Chromosome

P-089 - Evaluation of Chromosomal Disorders due to Indication of Pediatric Cases: The Importance of Conventional Cytogenetics!

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In our study, pediatric age group patients who were admitted to Baskent University genetic diseases and diagnosis center for chromosome analysis were examined in the last 10 years with different indications. The purpose of this study is to define the frequency of chromosomal abnormality depends on the reason of coming hospital. 2054 patients whose blood samples were sent for chrosomal analysis to Baskent University Medical Genetics Department Genetic Diseases Diagnostic Center Cytogenetic Laboratory between 2007 and 2017 . Patients were divided into three large groups according to their indications; conjetinal anomaly (multiple-isolated), growth-developmental retardation and epilepsy. The results of chromosomal analysis were determined statistically.
1154 (56.2%) of 2054 patients were female and 900 (43.8%) were male in this study. The average age of patients was 4,7 ± 4,4. Abnormal karyotypes were found in 181 patients (8.8%) . Numerical aneuploidies were detected in 128 patients (70,7%) and structural anomalies were detected in 53 patients (29,3%). When groups were compared each other, the rate of abnormal karyotype in congenital anomaly group, 154 patients (85,1%), was higher than other groups. We observed that the rate of numerical chromosome aneuploidy was higher in congenital anomalies (119 patients, 77,3%), whereas the rate of structural anomalies was higher in developmental retardation (16 patients, 66,6%) and epilepsy (2 patients, 66,6%) groups. The most common abnormal karyotype in all patient groups was down syndrome 4,6% (97 patients). The frequency of normal variation was 1.7% (35 patients) and inv (9) (p12; q13) was the most common variation type (16 patients, 0,8%).
Investigation of genetic disorders in pediatric patients with congenital anomalies and growth-developmental retardation is an important requirement in terms of clinical diagnosis and follow-up. In our study, the prevalence of chromosomal anomaly was 8.8%. In other similar studies the ratio was lower (4,5) than our study. To refer the patients to a Medical Genetics Clinic for cytogenetic investigation can detect some rare chromosomal diseases, but also avoid unnecessary examinations.

Key Words: Cytogenetic Analysis,Chromosomal Anomaly, Karyotypes

P-090 - Phenotypic Variability of Ring Chromosome 15 Syndrome and Recurrent Fetal Loss

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Recurrent pregnancy loss are seen in 0.5-3 % of pregnancies. Coagulation disorders, anatomic factors, immunological causes, hormonal disorders, infections and chromosomal abnormalities are thought to play a role. Chromosomal abnormalities are the one of the most common cause of early pregnancy losses. The underlying cause of many miscarriages is that embryo with abnormal karyotype. However, 4-8 % of those with recurrent pregnancy loss have parental chromosomal abnormalities that may cause chromosomal imbalance in one or both of the couples. Parental chromosomal abnormalities associated with recurrent pregnancy losses are the most common balanced translocations and inversions such as ring chromosomes are observed. In this case report, we aimed to discuss the ring chromosome 15 and its clinical effects.
A 24-year-old female patient with G2P0A2 had early pregnancy losses. The patient had no complaints except from her height was below the target height.
Chromosome analysis of the patient revealed 46,XX,r(15)(p11.2q26). Microarray analysis performed to show break points and loss genetics material during the ring chromosome formation. It was reported as arr [hg19] was 15q26.3 (102,052,633-102,429,111) x1.
Ring chromosome; it is a structural change that results in the breaking of the two ends of the chromosome into a ring shape. Ring chromosomes usually form de novo and ring chromosome 15 is one of the rarest of them. Ring chromosome 15 syndrome was first described by Jacobsen in 1966 and is characterized by pre-postnatal growth retardation, short stature, learning difficulties, hypotonia, craniofacial malformations and extremity anomalies. The fracture points on the chromosome 15 are different and the amount of genetic material lost is the main reason behind the phenotypic variability in the ring chromosome 15 syndrome. In our patient short stature and the absence of any other congenital anomalies support this variability. Although chromosomal abnormalities including translocation or inversion causes usually recurrent pregnancy loss, chromosomal abnormalities such as ring 15 should be taken into account.

Key Words: Recurrent Fetal Loss, Chromosome Analysis, Microarray, Ring Chromosome

P-091 - Trisomy 22: A Case Report

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Trisomy 22 is a common cause of spontaneous abortions, second to trisomy 16. Amniocentesis results have shown an occurrence of 1 in 2833 after the first trimester and the incidence of live births of trisomy 22 is said to be 1 in 30 000–50 000. . More than half of the infants live only 1 week and average life expectancy is 4 days. Dysmorphic features include microcephaly, midface hypoplasia, hypertelorism, epicanthal folds, ear abnormalities, micrognathia, and cleft lip/palate. Additionally, IUGR, urogenital anomalies such as renal agenesis and hypoplasia of the male genitalia, single umbilical artery and digital malformations are frequently observed.
Here we present the clinical manifestations, and cytogenetic findings in a liveborn infant girl with a de novo nonmosaic trisomy 22. She was born to a non-consanguineous family at 40 weeks of gestation with low birth weight. The patient was noted to have cleft lip/palate, microphthalmia, microcornea, low-set and dysmorphic ears with skin tags, short and webbed neck, broad nasal bridge. Genitourinary examination showed anal atresia and recto-vestibular fistula. Transabdominal, transphontanel and thorax ultrasound were normal. Echocardiogram was consistent with a 5 mm VSD, a 6 mm secundum ASD and 1.2 mm PDA. The patient died on the 99. day of life due to respiratory insufficiency.
The cytogenetic analysis of the 30 metaphases resulted in 47,XX,+22 karyotype. FISH analysis showed the presence of three signals relating to the D22S75 probe in all of the 100 cells.
Trisomy 22 syndrome is a rare chromosomal disorder in live-borns. In this study, when we compared the clinical and cytogenetic findings of the patient, there were no findings in previous cases compared with the cases reported in the literature. The aim of this study is to shed light on the findings of the trisomy 22 syndrome in clinical reviews. In the study, we compared the clinical and cytogenetic findings of the patient with the patients in the literature and found that some of the clinical findings correlated with the others but some of them did not. The aim of this study is contribute to the next clinical reviews.

Key Words: Trisomy 22

P-092 - Three Cases with Wolf Hirshhorn Syndrome

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Wolf Hirshhorn Syndrome (WHS), which is a rare syndrome and was first described in 1967, is lead partial deletion in the short arm of chromosome 4. In 85% of cases, deletion is de novo while in 15% of the cases there is a balanced translocation carrier in one of the parents. The cardinal phenotypic features of the disease are severe growth retardation in prenatal and postnatal period, feeding difficulties, seizures, craniofacial anomalies, midline defects, congenital heart defects and skeletal anomalies. We will discuss the partial 4p deletions and their clinical effects in three cases.
The first case, a 6-month-old girl was referred to our clinic with growth failure, seizure. There was no similar history in the family and her parents were not related. The second case, a 4.5-month-old girl was consulted with dysmorphic findings and malnutrition. The patient's weight was 3700g (<3p) length was 58cm (<3p), and head circumference was 37.5cm (3-10p). The enlargement of right ventricle and atrium, and mild hypoplasia of corpus callosum were detected. The last patient was referred to us due to cleft palate-lip, cataract, epilepsy and developmental retardation. The patient's weight was 8500g (<3p), length was 64cm (<3p) and head circumference was 40cm (<3p). There was no similar history in the family and her parents were not related.
In our first case, chromosome analysis revealed 46,XXdel(4)(p16) and microarray was reported as arr[hg19]4p16.3p16.1(68,345-8,417,617)x1. The chromosome analysis of the second case was 46,XY(del4)(p16.1). Chromosome analysis of third case was 46XX,del(4)(p16),t(9;21),(q21; p11.2) and result of the microarray was arr[hg19] 4p16.3p16.1(68,345-8,697,175)x1,22q13.31q13.33 (47,002,679-51,197,838)x3.
In our patients, deletion of the 4p region cause the WHS phenotype. Different from other cases, t (9;21) was considered to be a balanced translocation carrier because of the absence of any genetic material loss in microarray in the third case. All of our cases had dysmorphic findings and growth retardation which is mainly related loss of function of WHSC1, WHSC2 and FGFR3 genes. Variation of break point of chromosomes may cause the phenotypic variability. Thus, genetic counseling is given to patients diagnosed with WHS is provide appropriate follow-up and treatment to improve quality of life.

Key Words: Wolf Hirshhorn Syndrome, Chromosome Analysis, Microarray, Deletion of 4p

P-093 - A Case that Carries Numerical and Structural Disorder of X Chromosome

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Monosomy X is a condition that affects only females, results when complete or partial loss of one X chromosomes. It can be seen different forms like complete or mosaic. This syndrome characterized by short stature, webbed neck and gonadal dysgenesis.
A four-year-old girl was consulted to our genetic disorders diagnosis center with history of epilepsy. Her physical examination long eyelashes, bilateral ptosis, bulbous nose, bilateral large ear, low nape hairline, micrognathy and long philtrum. Sleep EEG normal, length 98 cm (97P). The patient's parents not relative and no history of epilepsy. Chromosome analysis, aneuploidy FISH and arrayCGH studies was planned from peripheral blood.
Chromosome analysis result 47,i(X)(q10)x2[6/50]/45,X[44/50]. FISH result 90% of the X signal was detected one and 10% of the X was detected with three signal. ArrayCGH analysis result was Monosomy X. In the ArrayCGH analysis, we cannot detect the presence of iso Xq mosaicism due to the low number of probes of X and the low mosaic ratio. Aneuploidy FISH and chromosome analysis were performed from parents to determine the inheritance pattern. Father's chromosome analysis result 46,XY. Chromosomal analysis of the mother was 46, XX, and FISH analysis %3 single signal pattern was detected for X. This finding in the mother suggests that the patient may have an inherited basis
In the literature, 47, i(X)(q10) x2 chromosomal anomaly and history of epilepsy has been reported in a small number of cases in whom monosomy X were detected. 47,i(X)(q10)x2 [6/50]/45,X[44/50] chromosomal anomaly with a history of epilepsy in our patient will contribute of the literature.

Key Words: Isochromosome X, Monosomy X, Epilepsy, Karyotyping, Mosaicism

P-094 - A Case Report of a Patient with 47,XX,+idic(15)(q11.2) Presenting Normal Development and Cliteromegaly

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idic(15) syndrome is characterized with a supernumerary inverted duplicated chromosome 15. The incidence is estimated to be 1/30,000 and the actual number is considered to be higher. The patients may show a completely normal phenotype, but may also show a severe phenotype characterized by early central hypotonia, intellectual disability, epilepsy, and autistic behaviors according to the gene composition. This phenotypic difference varies depending on whether the derivative chromosome contains the PWS/AS critical region. Here, we present a case with a familial idic(15) without intellectual disability.
A 7-year-old female patient was admitted with the complaint of clitoromegaly. She was born to a nonconsanguineous parent at 38th gestational week from an IVF gestation. The mother was 36 years old and the father was 38 years old and had ulcerative colitis. The family's son and our patient's twin were healthy. In our patient, bilateral inguinal hernia was detected and operated on day 50. No pathological findings other than clitoromegaly were detected. The hormone analyzes of the patient were normal also. With pelvic USG, left ovary could not be seen.
Karyotype analysis revealed a supernumerary derivative chromosome. In order to find the origin of the of the marker chromosome, FISH analysis with D15S10/D15Z1/PML probes was performed. The marker chromosome had D15Z1 locus (15p11.2) on both arms but did not carry the D15S10 (15q11.2) and PML (15q24) loci. In order to determine the exact breakpoint, an array-CGH analysis was performed. a-CGH revealed an increased copy number of 15pter-15q11.2. So, the patient was diagnosed as 47,XX,+idic (15)(q11.2). The same aberration was also detected as a mosaic form in the father.
Here, we presented a case of a familial idic(15)(q11.2) which didn't contain PWS/AS critical region. The patient's development was normal, but there was only cliteromegaly and ovarian agenesis. When a marker derived from chromosome 15 was detected in the prenatal diagnosis, the evaluation of this chromosome in terms of PWS/AS region is very important for the accurate genetic counseling.

Key Words:IDIC15, Cliteromegaly, Normal Intellectual Status

P-095 - Novel RAB3GAP1 Intronic Mutation Causing Warburg Micro Syndrome in Two Sisters

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Warburg Micro syndrome (WARBM) is a rare autosomal recessive syndrome characterized by brain, eye and endocrine system anomalies. Major findings are microcephaly, microphthalmia, congenital cataracts,optic atrophy,mental retardation and hypogonadism. RAB3GAP1, RAB3GAP2, RAB18 ve TBC1D20 genes are associated with this syndrome. We are reporting two sisters with a novel homozygous intronic c.974-2A>G mutation in RAB3GAP1 gene.

Key Words: Warburg Micro Syndrome, RAB3GAP1, Novel Intronic Mutation, Microphtalmia, Congenital Cataract

P-096 - Identifıcation of Three Novel Variant in CUL 7 Gene in Two Patients with 3M Syndrome

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3M syndrome is autosomal-recessive disorder characterized by severe prenatal and postnatal growth retardation, typical facial features and normal intelligence. In the etiology, bi-allelic loss of function mutations have been reported for CUL7 (77%;MIM # 273750), OBSL1 (16%;MIM # 612921) or CCDC8 (16%;MIM # 614205) with similar phenotypic findings. In this study, molecular diagnosis was aimed in two patients who were clinically diagnosed as 3M syndrome in Istanbul Medical Faculty Medical Genetics Department.
Case1. A 3-month-old boy who was referred to our department because of short stature. He is the first child of a 24-year-old healthy mother and father with no consanguinity (G3A2P1). 3M syndrome was clinically diagnosed with antenatal onset short stature, SGA birth, dysmorphic facial findings and radiological findings.
Case2. A 3-year-old boy who was referred to our department due to radiological findings and dysmorphism. He is the third child 39-year-old healthy mother and 45-year-old healthy father's with consanguinity (G3P3A0 living 2). He was evaluated for growth failure at 1 month of age. 3M syndrome were evaluated with the clinical genetic examination. After DNA isolation from peripheral blood in both cases, 26 exons of the CUL7 (NM_014780, NP_055595) gene and exon-intron regions were sequenced by Sanger methods.
Case1: Heterozygous c.4531C> T (p.Pro1511Ser) in exon 24 and heterozygous c.4582C> T in exon 25 (p.Arg1528Ter, rs762714074) were detected. The study in the mother and father supported the combined heterozygosity in the case. Case2: Heterozygous c.1221G> T (p.Val407 =)in exon 4 and heterozygous c.1233 + 6T> G change in intron 4 were detected. The in silico analysis of these two different changes, which were not previously reported in the literature, suggested that they could cause a splice-site variant. A parent examination was planned to support bi-allelic inheritance.
The variants in case1 was consistent with bi-allelic inheritance. One of them was in the cullin domain and the other leading to early stop codon supported CUL7-associated 3M syndrome.The variants in case 2 have not been defined previously and cause splice-site variant in the prediction programs. Although this condition supports 3M syndrome, bi-allelic inheritance should be demonstrated. Otherwise, evidence of alternative splicing is required by RNA analysis.

Key Words:3M Syndrome, CUL 7 Gene

P-097 - A Case of Two Siblings with VLDLR-Associated Cerebellar Hypoplasia

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VLDLR-associated cerebellar hypoplasia is characterized by non-progressive congenital ataxia and results in delayed ambulation, moderate-to-profound intellectual disability, dysarthria, strabismus, and seizures. Children either learn to walk very late or never achieve independent ambulation. The condition is autosomal reccessive with very low prevalance reported in less than 100 individuals worldwide. We present a case of a couple from low socioeconomic group with first and second kids having the disorder.
Two siblings who are 5 and 3 years old females from consanguineous parents. Family complained about delayed growth and motor development, intellectual disability, ataxia and no development of speech of their children.
Examination revealed severe truncal ataxia, generalized hypotonia, intentional tremor, strabismus, nystagmus, normal deep tendon reflexes and no muscle weakness. Brain and cervicothoracic spine MRI of the 5 years old sister showed cerebellar hypoplasia with absent vermis. Also in the cortex polymicrogyria and pacygyria were found.
WES was ordered for the older female patient. Results came as having VLDLR c.20dupG p.A8Gfs27* homozygous truncating variant. This null variant was not reported in databases. 3 years old sister also had the same genotype and parents were found to be heterozygotes for the variant. Kids were diagnosed with CEREBELLAR ATAXIA, MENTAL RETARDATION, AND DYSEQUILIBRIUM SYNDROME 1.Family was informed about the conditions nature and progress. Prenatal and pregestational options were explained. The large family had 3 more consanguineous marriages in which both parents could be potential carriers. However all of their kids were healthy. Two couples of them were not going to have children anymore, while one couple with two kids had the desire to have more children. They were called for carrier testing and counselling. In our case we want to emphasize the importance of genetic conditions early diagnosis in the first patient of the family if possible. So parents can benefit from prenatal or pregestational options for their next pregnancies.

Key Words:VLDLR, Cerebellar Hypoplasia, Ataxia, Mental Retardation, Dysequilibrium

P-098 - A Feasibiliy Study for the Use of Short Tandem Repeat Markers for Preimplantation Genetic Diagnosis for Beta-Thalassaemia in the Cypriot Population

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Preimplantation Genetic Diagnosis (PGD) for β-hemoglobinopathies was introduced as the most common application among monogenic disorders, for couples at risk of having children affected with β-thalassaemia major, to avoid termination of affected pregnancies. In this study, previously described STRs were selected in order to develop a generic protocol for PGD of β-thalassaemia. In this study the aim is to develop a protocol for haplotype analysis based on STR markers, to complement the currently used protocol. For this purpose, after a review of current bibliography, polymorphic markers (STR's) closely linked to the β-globin locus are selected for this study.

Key Words:PGD, Thalassaemia, IVF

P-099 - Aarskog-Scott Syndrome: Novel Mutation in the FGD1 Gene

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Aarskog-Scott syndrome (AAS, OMIM # 305400), also known as faciogenital dysplasia is an X-linked disorder caused by mutations in the FGD1 gene, characterized by short stature, hypertelorism, shawl scrotum and brachydactyly. Clinical findings are variable; findings such as joint hyperextensibility, inguinal hernia, widow 's peak can also be seen. Although most patients do not have intellectual impairment, but some may have behavior problems. Findings such as widow's peak or subtle short stature can be seen in carrier women.
In this study, a 122/12-year-old boy who was referred to our clinic for short stature was presented. The patient who was not followed-up prenatally was born at term with a birth weight of 2000 g to a healthy nonconsanguineous couple. He had a bilateral orchiopexy operation when he was 6. He did not have developmental delay. In the first examination, except for the head circumference, the other growth parameters were below the 3rd percentile. The patient had hypertelorism, nasal root prominence, incomplete cutaneous syndactyly in bilateral hands and hyperextension in the hand proximal interphalangeal joints and hyperflexion in the distal interphalangeal joints, and shawl scrotum. When the patient was 20 years old; body weight was 53 kg (3p), height 163 cm (3p), and head circumference 54.5 cm (3-10p). In physical examination in addition to the dysmorphic findings at the first examination, groove under the lower lip and widow's peak were noted.
Sequence analysis for the FGD1 gene was performed and a new mutation was detected. Sequence analysis could not be performed in mother because of DNA could not be reached.
Aarskog-Scott syndrome should be considered in male patients with mild short stature, hypertelorism, partial cutaneous syndactyly in the hands and genital anomalies. Although our patient typically exhibited the AAS phenotype, presence of this novel mutation emphasizes the allelic heterogeneity.

Key Words: Aarskog-Scott Syndrome, FGD1, Faciogenital Dysplasia

P-100 - Investigation of Intron 1 Inversion Mutation Frequency in Patients with Severe Hemophilia

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Hemophilia A (HA) is an X-linked coagulation disorder caused by mutations in the F8 gene which encodes the coagulation factor VIII (FVIII). The prevalence is estimated at 1/5,000 male births. Depending on the FVIII activity in the patient's plasma, it is classified as severe (<1%), moderate (1-5%) or mild (5-40%). In severe HA cases, intron 22 inversion is the most prevalent mutation accounting up to 45%. Intron 1 inversion is responsible for approximately 2% of severe HA cases. Both inversion mutations are caused by unequal recombination in homologous sequences in the F8 gene. In this study, we report the frequency of intron 1 inversion mutation in patients with HA referred to the reference molecular laboratory.
Between 2017-2018, 347 male HA cases were referred to our laboratory for molecular analysis. A total of 24 HA patients without any mutation in the F8 gene, including both intron 22 inversion or point mutations, were evaluated for intron 1 inversion. For this purpose, multiplex PCR was performed and amplicon lengths were analyzed by gel electrophoresis.
Among 347 HA patients, 132 (38%) had intron 22 inversion mutation, 191 cases (55%) had missense mutation in F8 gene . An intron 1 inversion mutation analysis was performed for the remaining 24 HA patients and 5 patients (1,4%) were found to be positive for Intron 1 inversion mutation.
The incidence of intron 1 inversion mutation in HA patients referred to our laboratory is around 1,4% which is similar to the incidence reported for the other populations.

Key Words: Hemophilia, Intron 1, Inversion, F8

P-101 - A Coffin-Siris Syndrome Presented with Severe Hypotonia

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Coffin-Siris syndrome should also be considered in a newborn infant in the etiology of hypotonia, if dysmorphic findings are accompanied. Coffin-Siris syndrome is a syndrome that includes many malformations that are characterized by mental retardation, coarse facial features, hypertrichosis, sparse scalp hair, hypoplastic or absent fifth finger or toe nails associated with genetic heterogeneity. Pathogenic variants in the ARID1B gene are associated with Coffin-Siris syndrome type 1 (CSS1), an autosomal dominant disorder.
In this report, we present a case with dysmorphic features referred to because of hypotonia in the newborn period. His medical history revealed that he had two afebrile convulsions and had consanguinity between his parents. Physical examination revealed coarse facial appearance, sparse eyebrows and hair, large lip, pectus excavatum, umbilical hernia, wide toe and hypertrichosis. Cranial MRI showed periventricular hypomyelination. An additional eye examination, hearing test, and abdominal USG were found to be normal. Chromosome analysis and microarray analysis were evaluated as normal. The patient, who had no specific diagnosis with clinical findings, underwent a whole exom-sequencing analysis.Genomic DNA is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted agains t coding regions of ~6700 genes with known clinical significance.
A heterozygous pathogenic variant was identified in the ARID1B variant c.5387_5390del p.(Glu1796Alafs*9). According to HGMD Professional 2017.3, this variant has previously been described as disease causing for Corpus callosum abnormalities in intellectual disability patients by Mignot et al., 2016 (PMID:27474218). This result is consistent with a genetic diagnosis of autosomal dominant Coffin-Siris syndrome type 1.
Coffin-Siris syndrome is a multiple malformation syndrome characterized by mental retardation associated with coarse facial features, hypertrichosis, sparse scalp hair, and hypoplastic or absent fifth fingernails or toenails Other more variable features may include poor overall growth, craniofacial abnormalities, spinal anomalies, and congenital heart defects. Mutations in the ARID1B gene are the most common cause of Coffin- Siris syndrome (OMIM®: 135900). Whole exom sequencing analysis is a very important method in diagnosing phenotypic and genetically heterogeneous diseases such as Coffin Siris syndrome. A multidisciplinary approach involving divisions of neurology, genetic and metabolism are required to clarify the conditions that cause hypotonia.

Key Words: Coffin-Siris Syndrom,Hypotonia,Exome

P-102 - The Results of Familial Mediterrranean Fever in Mediterrranean Region

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent fever and serositis attacks. The MEFV gene responsible for the disease was localized in the 16th chromosome short arm (16p13.3.), Cloned in 1997, when it consisted of 10 exons and coded the Pyrin protein, and there were significant improvements in the diagnosis and treatment of the disease. In this study, our aim was to present the results of the MEFV gene sequence analysis of patients presenting with the initial diagnosis of FMF and to evaluate the current situation in our country.

Key Words: Familial Mediterrranean Fever, Mediterrranean Region

P-103 - A Novel Splice Site Mutation in TRAPPC2 Gene Caused X-Linked Spondyloepiphyseal Dysplasia Tarda in Two Males from a Turkish Family

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Spondyloepiphyseal dysplasia tarda (SEDT) caused by the mutations of TRAPPC2 (SEDL) gene is a X-linked inherited disorder classified in spondylo-epi-(meta)-physeal dysplasia group. Here we report a novel intronic mutation of TRAPPC2 that affect splicing in a male patient with short stature and his affected uncle.
A 18 years-old boy was referred to our medical genetics department because of short stature. He was born at 40 weeks of gestation pregnancy without clinical follow-up. His parents were non-consanguineous but originated from the same small village. There was no information about his birth weight and birth length. Growth percentiles in the first 12 years of life were normal. Then linear growth of the patient began to be retarded. In our physical examination his weight was 44 kg (<3 percantile), height was 137 cm (<3 percantile). Hypertelorism, short neck, bilateral clinodactyly in the 5th fingers of hands, short trunk, increased lumbar lordosis were observed. In the family history; his grandfather (deceased) and his uncle exhibit similar phenotype. In radiological examination of vertebral bones, characteristic superior and inferior "humping" on lateral view and narrow disc spaces were seen.
Karyotyping from peripheral blood sample revealed 46,XY normal chromosomal constitution. Then we performed a molecular genetic analysis for SEDT and found a hemizygous c.324+1 G>T mutation in TRAPPC2 gene. The uncle of our patient who exhibit similar phenotype was also hemizygous for the same mutation..
This novel splice site mutation of TRAPPC2 gene that has not been reported in the literature yet is expected to be "pathogenic" due to a potential alteration of splicing. Discovery of genetic etiology in skeletal disorders has a major proposition in terms of determining the parental carrier status, identifying other family members at risk and providing prenatal genetic counselling.

Key Words: Novel Mutation, Splice Site, Spondyloepiphyseal Dysplasia Tarda, TRAPPC2

P-104 - Results of BTD Gene Molecular Analysis with Clinical Findings in Three Individuals from the Same Family

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Biotinidase deficiency is an autosomal recessive metabolic disorder, which is 5 times more common in Turkey compared to the world. BTD gene consisting of four exons located at long arm (3q25.1) of chromosome 3 region responsible for etiology. Biotinidase deficiency is a neurological and cutaneous manifestation and may be associated with organic acidemia.
DNA was isolated from the peripheral blood sample of the mother and two siblings of the proband and all exons and the exon-intron fusion regions of the BTD gene were amplified by PCR and sequenced by Sanger sequencing. Routine biochemical tests were performed.
A 27-years-old female patient who thought to be biotinidase deficiency with a physical examination and laboratory findings was evaluated. In her pedigree, it was seen that there was consanguinity between his parents, uncle and cousins, who were diagnosed with biotinidase deficiency. She was followed up for neurosarcoidosis and she had mild mental retardation, uveitis history, loss of vision and hearing, loss of fine motor skills in fingers, and involuntary tremors. She had spasticity and loss of muscle strength in both lower extremities and could not walk without the aid of a cane. In the BTD gene sequence analysis, it was determined that proband carried c.1336G>C/pAsp446His and c.511G>C/pAla173Thr mutations as heterozygous in exon 2 of the BTD gene. pD444H(c.1330G>C) and p.A171T(c.511G>A) variants identified as compound heterozygous in the brother of the proband. Proband's mother and sister had symptoms such as alopecia, skin sensitization, nail breakage, but no variant was detected in their BTD gene.
Genetic counseling, early diagnosis and treatment are very important for prevention of complications in patients with BTD deficiency.

Key Words: Biotinidase Deficiency, BTD Gene,Metabolic Disorder

P-105 - SALL4 Deletion in a Patient with Bilateral Radius and Thumb Aplasia

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SALL4 is a gene which has prominent expression in the development of the midbrain, branchial arch, extremity and genital papilla, and heterozygous mutations in this gene have been reported as three distinct phenotypes as SALL4-related diseases: Duane-radial ray syndrome (Okihiro syndrome), acro-renal-ocular syndrome (AROS) and SALL4-related Holt-Oram syndrome (HOS). In addition to point mutations, SALL4 deletions were reported in 10-15% of cases. SALL4 mutations rarely cause clinically typical HOS (radial ray malformations and cardiac malformations without additional findings) phenotype which is caused by TBX5 mutations over 70% of the cases.
A 19/12-year-old girl was referred to our clinic due to radial cleft hand. The patient was born at term with a birth weight of 2750 g to nonconsanguineous healthy couple. The absence of radius and shortening of the upper extremites were detected prenatally. In physical examination; body weight: 10800 g (10-25 p), height: 81 cm (25 p) and head circumference: 48 cm (75 p) and prominent forehead, depressed nasal bridge, bilateral phocomelia in upper extremities, bilateral oligodactyly in the hands, bilateral thumb agenesis and 2-3. cutaneous syndactyly were noted. The audiological and visual examinations were normal and development was compatible with her peers. Abdominal ultrasonography was normal and echocardiography showed small secundum atrial septal defect. The platelet count was found to be normal. Because of the multiple congenital anomalies microarray analysis was performed (Affymetrix CytoScan Optima Array) and a 279 kb deletion was detected in the 20q13.2 region involving the SALL4 gene.
SALL4 deletions have been reported common in Okihiro and AROS syndromes, but rare in HOS phenotype. Many syndromes with upper extremity anomalies have been identified and these syndromes are genetically heterogeneous. Microarray analysis has a wide utility in the diagnostic approach of patients with multiple congenital anomalies.

Key Words: Radial Ray Defect, SALL4 Deletion, Microarray Analysis, Holt-Oram Syndrome

P-106 - A Novel Mutation in COL1A1 Gene in a Family

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Osteogenesis imperfecta (OI) is a group of genetic disorders caused by mutations in collagen genes characterized by deformation in the bone, tendency to break and fractures. At least eight recognized types of osteogenesis imperfecta identified from Type I to Type VIII exhibit a broad spectrum phenotype.Type I is the most common form of disease caused by mutations in the COL1A1 gene.Procollagen biosynthesis is impaired in patients with mutations in this gene.Clinical findings of collagenous tissue such as skin, sclera, tendon, tooth, ligament, middle and inner ear are observed. In this study, we aimed to present a case with a previously unidentified mutation in the COL1A1 gene.
A 7-year-old boy came to our department with a history of recurrent infections and repetitive bone fractures.In physical examination; the patient had blue sclera and short stature.A family history was obtained from pedigree analysis.His mother and sister also had a blue sclera.The mother had bone deformities in fingers and toes.She had a history of multiple fractures.The bone age of patient, assessed to be consistent with 4 years of age by analysis of hand-wrist radiograph.His hearing test showed no abnormality.Karyotype analysis and next generation DNA sequence analysis of COL1A1, COL3A1, COL4A4 and COL5A1 genes were performed.
Chromosome analysis of the patient was 46,XY.The COL1A1, COL3A1, COL4A4, and COL5A1 genes were analyzed by the next generation sequencing method in the illuminal miniseq platform of the NEXTflex Alport-Ehlers Danlos amplicon panel containing all exons and neighboring intronic regions.A heterogeneous ENST0000225964.5 c.661G>A (p.Gly221Ser) pathogenic missense variant was detected in 9th exon of the COL1A1 gene.This variant was also present in other family members.There were no pathogenic or pathogenic variations in other genes analyzed.The NGS results were analyzed through the Mutation tester, Ensemble, Clinvar, Sift, Polyphen and NCBI databases.
We presented a case of OI associated with a new single point mutation detected by NGS in the COL1A1 gene.Since the clinical findings of the case were consistent with the OI clinic, the mutation was evaluated as pathogenic variant and genetic counseling was given to the family. This presentation emphasizes that genetic testing is necessary in the presence of clinical findings in OI patients.

Key Words: Osteogenesis Imperfecta, COL1A1 Gene

P-107 - A Novel Nonsense Mutation in the EYA1 Gene Found in a Patient with BOR Syndrome

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Branchio-oto-renal syndrome (BOR), is an autosomal dominant disorder characterized by the coexistence anomalies of the external,middle or inner ear malformations with pre-auricular pits or tags, conductive, sensorineural or mixed hearing loss, branchial cleft anomalies, and renal anomalies ranging from mild, asymptomatic hypoplasia to complete renal agenesis.We present this case of BOR syndrome with a novel mutation at EYA1 gene in order to contribute to the literatüre.
A 38 years old male patient was referred us because of chronic renal insufficiency and hearing impairment
Clinical examination showed auricular deformity, pre/post-auricular pits, operated bilateral branchial fistulae and unilateral peripheral facial nerve palsy. Abdominal ultrasound revealed unilateral kidney hypoplasia. An audiogram showed right sided moderate mix hearing loss and left sided sensorineural hearing loss. Laboratory tests resulted in high blood urea nitrogen (BUN) 23 mg/dL and serum creatinine 1.81 mg/dL; low glomerular filtration rate (GFR) 46 mL/min. We performed sequence analysis for the EYA1 gene which is responsible for 40% of the etiology.
We found a premature stop codon mutation on p.Tyr182* (c.546C>G) of the EYA1 gene. It is a novel mutation and based on ACMG 2015 criteria, it was considered as a pathogenic variant that clearly causes severe damage on protein function.

Key Words:BOR Syndrome, EYA1, Facial Nerve Palsy, Hearing Impairment

P-108 - A Case with Charcot-Marie-Tooth (CMT) Syndrome

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Charcot-Marie-Tooth (CMT) disease (prevalence is 1/2500) is a hereditary neuropathy with clinically slow progressive, symmetrical muscle weakness and atrophy of the distal extremities, problems with sensation, decreased deep tendon reflexes, and deformities in the feet. In the majority of patients with CMT, duplication of the PMP22 region on chromosome 17 is observed. The most common type is CMT1A, which constitutes 55% of all CMT cases and 66% of CMT1 cases. Other CMT forms (CMT2, CMTX, HNPP) are more rare
Clinical and electrophysiological studies were performed in the family members of the pedigree. DNA from peripheral blood leukocytes was obtained from the fresh blood sample taken from the proband and other family members. In order to distinguish the deletions / duplications associated with CMT, the MLPA and STR fragment analysis were performed to analyze the PMP22, COX10, TEKT3 genes.
A 17-year-old male patient with complaints of ataxia and weakness in his feet since the last 4 years had pes cavus especially in right foot and hammer fingers on both thumbs. The patient's EMG revealed changes consistent with common axonal polyneuropathy with a predominant sensory effect. In the lower extremities, bilateral sense of touch was decreased, positive deep sensory and deep tendon reflexes were decreased. No abnormalities were detected in the upper extremities. The patient had consanguinity between her parents and had two healthy brothers.
Duplication was detected in PMP22, COX10, TEKT3 genes of the patient. It is konown that duplications in the PMP22 gene cause CMT1A disease. These mutations can develop as familial or de nova. Analyzes including family members are ongoing.

Key Words:CMT, PMP22, Neuropathy

P-109 - A Case with Charge Syndrome

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CHARGE syndrome (OMIM #214800) is a rare autosomal dominantly inherited disorder with an estimated incidence of 1 /10,000 live births. CHARGE syndrome consist of C-coloboma of the eyes, H-heart defects, A-atresia of the choanae, R-retarded growth and development, G-genital abnormalities, and E-ear anomalies. Major anomalies may not be seen together in every case. CHARGE syndrome is caused by heterozygous mutation in the CHD7 gene on chromosome 8q12. Infants with CHARGE syndrome frequently have multiple serious medical conditions. Feeding difficulties are a major cause of morbidity in all ages.
A 6-month-old male child was referred to genetic clinic with multiple congenital anomaly. In the neonatal period, he had undergone repair for tetralogy of fallot. At 3-months of age the patient had undergone percutaneous endoscopic gastrostomy due to feeding difficulties. Examination in the genetic clinic indicated a weight of 4 kg (less than third centile), occipital–frontal circumference of 37.3 cm (less than third centile), facial hypertrichosis, bilateral asymetric dysplastic ears, long eyelashes, downslanting palpebral fissures, facial asymmetry, long philtrum, high arched palate. He had no orofacial clefts, and his eye examination was normal. In ear-nose-throat examination, congenital aural atresia on the right side, choanal atresia and unilateral facial palsy were observed. He had normal karyotype.
Patient has choanal atresia, facial palsy, abnormal outer ears, developmental delay, cardiovascular malformations and growth deficiency thus satisfying the criteria for CHARGE syndrome. Heterozygous for a non-sense mutation at the second exon of CHD7 gene, c.1645C>T (p. Q549X) (NM_017780.3), was detected in the patient.
CHARGE syndrome is a rare genetic disease that can be easily recognized even in the neonatal period. Molecular genetic testing is important to confirm clinical diagnosis, to provide appropriate genetic counseling and to provide prenatal diagnosis possibilities for subsequent pregnancies.

Key Words: Charge Syndrome, CHD7 Gene

P-110 - The Affects of SRY Genes over Sexual Development and Phenotypical Changes

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There are many factors playing an essential role for sexual differentiation on the Y chromosome but the most well known of these is SRY. Active functioning of SRY gene initiates testis development and provides male phenotype. Presence of SRY locus determines the male and female phenotype. Here, we aimed to demonstrate the role of different phenotypic properties of SRY gene in two different cases.
The first patient , A 29 years-old woman was referred to our clinic because of primer amenorrhea. In the physical examination her external genitalia was normal. MRI relatively small uterus and noduler parenchymal tissue in the left adnexal region , compatible with streak gonad. The second patient, A 51 years-old man was referred because of infertility. In the clinical examination gynecomastia and micropenis were present.Azoospermia was detected in the spermiogram and Doppler USG revealed decreased testicular blood flow. Both patients had hormone levels compatible with hypergonadotropic hypogonadism. Karyotyping from peripheral blood sample resulted in 46, XY chromosomal constitution in the first patient and 46, XX in the second patient. .FISH analysis showed the presence of SRY locus in both patients. Molecular analysis for AZF regions were normal of the the first patient, while AZFa , AZFb, AZFc were deleted in the second patient .
While patient 1 was SRY + , male phenotypical findings were not seen , probably due to the mutations or microdeletions existing on SRY locus. Also the factors and genes other than SRY which are responsible for sexual devolopment may have an influence on the phenotypes of the patients. In addition, gonadectomy should be recommended in SRY (+) females due to the risk of gonadoblastoma. In the second case, the SRY locus on the Y chromosome crossed over to the X chromosome during meiosis in the paternal sperm cell and its activation resulted in the current clinical situation.

Key Words:SRY, Sexual Development, Y Chromosome

P-111 - Cohen Syndrome; A Novel Mutatıon in VPS13B Gene

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Cohen syndrome (CS) is a rare autosomal recessive disease which shows genetic heterogeneity and which is characterized with microcephalia, mental-motor retardation, short stature, obesity, joint hypermobility, progressive retinal dystrophy and myopia. Characteristic dysmorphic features are thick eyebrows, long eyelashes, prominent nasal bridge. moderate neutropenia and recurrent infections are seen in affected individuals. VPS13B gene is localized at 8q22.2, it has 62 exons and it encodes vacuolar sorting 13 homolog B protein consisting of 4022 amino acids. Although exact function of VPS13B gene is not known, studies have shown that protein is a part of Golgi apparatus and thus fulfils its functions. VPS13B protein is a transmembrane protein that can function in vesicle-associated transport and decomposition of intracellular proteins and it participates in protein glycosylation. In our study, we examined a case with a new mutation found in VPS13B gene.
4-year-old male case whose parents were first cousins referred with complaints of motor retardation, speech retardation and stereotypic movement. Anthropometric measurements of height, weight and head circumference were in <3 percentile. Physical examination showed prominent nasal bridge, long eyelashes, short philtrum. The patient's karyotype analysis showed 46,XY and FMR1 fragment analysis showed 36 CGG repetition. The patient's VPS13B whole gene sequencing analysis showed that he carried p.Tyr524Serfs*4 (c.1571 delA) change homozygously at 12th exon. In silico algorithms which assess unidentified variant predict that the change is "a probable pathogenesis". The parents' tests are still continuing. The patient was diagnosed as CS according to clinical results and genetic test result.
Although most of the more than 200 CS cases reported in literature have Amish or Finnish origins, the disease can be seen in many ethnic groups. It is thought that CS is one of the undiagnosed genetic diseases. Bardet-Biedl syndrome, Alstrom and Williams syndromes are among differential diagnoses. Characteristic clinical findings of p.Tyr524Serfs*4 new mutation defined in VPS13B gene are necessary for definitive CS diagnosis. Genetic counselling should report that there is no decrease in life expectancy; however, quality of life will decrease due to visual impairment. Since CS is an autosomal recessively inherited disease, genetic counselling is recommended for individuals under risk.

Key Words: Cohen, VPS13B, Retinal Dystropy

P-112 - Evaluation 10 Patients with Metaphyseal Dysplasia Caused by COL10A1 and RMRP Gene Mutations

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Metaphyseal Dysplasia is a skeletal dysplasia characterized by short stature with short limbs, genu varum and irregular metaphyses. Schmid type Metaphyseal Chondrodysplasia(SCMD), the mild and common form, is caused by heterozygous mutations in the COL10A1 gene. Patients with SCMD in early childhood are often misdiagnosed with Rickets and Blount's disease. Type X Collagen, synthesized by hypertrophic chondrocytes during endochondral ossification, provides appropriate environment for hematopoiesis and mineralization by leading the accumulation of other molecules into this area. McKusick type Cartilage-hair hypoplasia(CHH), the least and severe form, is caused by homozygote mutation in the RMRP gene. RMRP, functional subunit of Mitochondrial RNA processing ribonuclease (RNaseMRP), is crucial for cell growth, division and osteoblast reproduction.
The aim of this research is to analyze the genotype and phenotype of the patients with SCMD and CHH metaphyseal dysplasia.
NGS analyzes of COL10A1 and RPRM were carried out with Illumina MiSeq for 8 SCMD cases and 2 CHH cases, respectively. Initial symptom of SCMD patients was genu varum starting between 1-3 years old, whereas first symptom of CHH patients was short stature distinguished prenatally. Compatible with autosomal dominant inheritance patterns, one family had 4, second family had 3 and third family had 2 more patients diagnosed with SCMD. All patients had severe genu varum, waddling gait, increased lumbar lordosis, moderate short limbs, widening and irregular metaphyses, coxa vara and large epiphyses of femoral head. Height standard deviation scores (SDS) vary between -1.4 and -1.6. However SDS of two cases of CHH had -3.1 and -3.9 at neonatal period and -5.1 and -5.4 at 5 and 13 years, respectively. Furthermore, they had genu varum, increased lumber lordosis, fine and sparse hair, eyebrow and eyelash, metaphyseal irregularity, short tibia, radioulnar synostosis and cone-shaped epiphyses.
In SCMD patients whose clinical findings were very similar, all heterozygous mutations detected in the COL10A1 were located in the NC1 region, the most common position of mutation. Two new mutations (c.1948_1959del GTGTGGCTCCAG and c.1870_1871delAC(p.T624LfsX2) were identified. Two patients with CHH had nucleotide substitutions within transcribed region of RMRP. While, prominent feature of CHH patients was short stature, SCMD patients had severe genu varum requiring surgical operation.

Key Words: Schmid Type Chondrometaphyseal Dysplasia, COL10A1, Mckusick Type Cartilage Hair Hypoplasia, RMRP

P-113 - A Novel Mutation in COL2A1 Leading to Osteogenesis Imperfecta: Substitution by Glycine, not of Glycine in Collagen Tripeptide Repeat Sequence

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Osteogenesis imperfecta is a connective tissue disorder that leads to bone fragility due to decreased bone resistance. The principal component providing shear stress resistance is type I collagen in bone matrix. Type I collagen is formed by tropocollagen building blocks that are formed by folding of 3 protocollagen peptides into the triple collagen helix. Mutations in 2 protocollagen genes (COL1A1 and COL1A2) that contribute to type I collagen make up at least 50% of genetic variations that cause osteogenesis imperfecta. In this study, we discuss the clinical findings of a girl that applied to Zeynep Kamil Women and Children's Hospital Medical Genetics and Pediatric Endocrinology clinics and characteristics of a novel mutation found in COL1A2.
The 15-year-old girl has been operated twice for fractures in left head of femur and hip —one occured after trauma and the other is spontaneous. She had congenital unilateral deformity of foot which was treated traditionally. Physical examination showed downslanted palpebral fissures, pointed chin and white sclerae. She was ambulatory without aid. Her height was 150cm (<5p) and the lumbal DEXA scan showed a Z-score of -2.1. With these findings, she can classified as Osteogenezis imperfecta type IV.
All protein-coding exons of COL1A1 and COL1A2 were Sanger sequenced in proband, which revealed c.2750T>G (p.Val917Gly) heterozygous variant in COL1A2. This variant was de novo as was observed in neither parents. To best of our knowledge, this variant has not been reported previously, not found in ExAC database and affects an evolutionarily conserved region.
Almost 3/4s of mutations in peptides encoded by COL1A1 and COL1A2 affect glycine residues in collagen tripeptide repeat sequence (X-Y-Glycine). These mutations disturb protein folding and post-translational modifications, preventing formation of collagen triple helix. It is suggested that the small side chains of glycine residues provide flexibility required for the collagen helix formation. The p.Val917Gly mutation leads to two adjacent glyicine residues in tripeptide repeat sequence which may lead to an increased flexibility in collagen helix and disturb proper folding. In conclusion, this case shows that substitution of other amino acid residues by glycine in tripeptide repeat sequences of type I collagen genes may lead to Osteogenesis imperfecta.

Key Words: Osteogenesis imperfecta, Collagen, COL2A1, Triple Helix

P-114 - Two Brothers with Homozygous IN2G Mutation in the CYP21A2 Gene

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Congenital adrenal hyperplasia (CAD) is a common group of diseases caused by a genetic defect in one of the enzymes involved steroidogenesis in the adrenal cortex. CAD is an autosomal recessive transition and the most common form is 21-hydroxylase deficiency. The classic clinical manifestation occurs depending on inadequate cortisol, aldesterone biosynthesis and/or hyperandrogenism. Two brothers (14 and 4 years old) with classical congenital adrenal hyperplasia were evaluated. Chromosome analysis was performed and CYP21A2 gene sequence analysis and MLPA analysis were performed in the isolated DNAs. Routine biochemical tests were performed.
Our patient was first examined at 2 age with the complaint of seizure accompanied by loss of consciousness. His systemic examination revealed ambiguous genitalia and early pubic hair. He was defined as congenital adrenal hyperplasia.
Genital correction surgery was performed and oral hydrocortisone treatment was started. The patient, incompatible with follow-up and treatment, was brought back to our hospital at the age of 14 to be operated due to penile distal hypospadias and penile cordi. In the clinic, the testicles could not be palpated, skin hyperpigmentation and short stature (<3p) were observed. The younger brother first presented at the age of 2 with a complaint of enlargement of the penis. In the clinic, penile growth early pubic hair, bone age progression (compatible with age 5), normal testis size and scrotal hyperpigmentation were observed. Both cases had elevated ACTH, 17-hydroxyprogesterone, 1,4-delta androstenedione, 11-deoxycortisole, and plasma renin activity. Cortisol, Na and K levels were normal however, DHEA-SO4 levels were high in proband, and aldesterone levels were high in his brother. The proband was 46,XX, his brother was 46,XY and SRY gene analysis was planned for the proband. CYP21 gene sequence analysis revealed In2G (G/G) homozygote in proband and In2G (A/C-G) homozygous in his brother. POR gene sequence analysis of the proband and 11 beta hydroxylase gene analysis of his brother were normal.
Genetic counseling, early diagnosis and treatment are very important for prevention of complications in patients with CAD.

Key Words: Congenital Adrenal Hyperplasia, 21-Hydroxylase Deficiency, CYP21A2 Gene

P-115 - Coexistence of Down Syndrome and Achondroplasia

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Down syndrome (OMIM # 190685) is the most common cytogenetic abnormality seen in infants with hipotonia, intellectual disability and characteristics facial features. Its frequency is 1 in 800 live births. It is the most common genetic cause of intellectual disability. The relationship with advanced maternal age is known. Achondroplasia (OMIM # 100800) is the most common genetic disorder of the skeleton characterized by disproportionately short stature with short extremity. Findings such as macrocephaly, frontal bossing, flat nose and brachydactyly are also observed. The frequency ranges from 1: 10000-1.30000. It is associated with advanced paternal age. The coexistence of these two conditions has been reported very rarely in the literature.
A one year old girl was evaluated for rhizomelic short stature and Down syndrome phenotype in our clinic. She was born to a 38-year-old mother and 48-year-old father, at 40th gestational week with C/S due to fetal distress, with a birth weight of 2920 g. Prenatal screening tests were normal. Fetal ultrasonography detected rhizomelic shortness and birth length was 45 cm. On physical examination, prominent forehead, depressed nasal root , brachydactyly, and macrocephaly were noted. In addition, the patient's phenotype was compatible with achondroplasia and the radiographs of the lumbar spine showed no increase in the interpedincular distance, the vertebral peduncles were short, the rhizomelic shortness and the radiolucent area in the proximal femur were observed.
The patient's karyotype analysis was 47,XY,+21 and FGFR3 gene analysis revealed a de novo heterozygote mutation causing achondroplasia.
Despite Down syndrome and achondroplasia are common genetic disorders, their coexistence has rarely been reported. Findings such as short stature, motor developmental delay, depressed nasal root and brachydactyly are common in both. However, prominent rhizomelic shortness and macrocephaly in Down syndrome and intellectual disability in achondroplasia are not among the expected findings. In the literature, seven patients with Down syndrome and achondroplasia have been reported previously. In cases within parental advanced ages, this coexistence should be kept in mind and the patient should be evaluated with clinical and radiological findings. Genetic analyzes should be planned accordingly.

Key Words: Down Syndrome, Achondroplasia, Advanced Maternal Age, Advanced Paternal Age, Disease Association

P-116 - A Case Consistent With Type 2b of Limb-Girdle Muscular Dystrophy Determined as Homozygous c.3166C>T Mutation in The DYSF Gene

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A 28-year-old male patient had weakness and atrophy of the muscles, especially with proximal muscle groups. It was noted that the patient, who had complaints of progressive progression starting at around 15 years of age in foot, was now able to walk with support.There is a consanguinity story between patient's parents and his 2 male and 3 female siblings had no similar clinical problems. Families did not have a history of similar disease. There were higher CK levels and EMG result showe markedly severe myopathic involvement in proximal muscles
Routine biochemical tests, electrophysiological studies and required radiological examinations were performed in the case. DNA was isolated from the peripheral blood sample and necessary examinations were made and NGS (next generation sequencing) method was used for the whole EXS Sequencing (WES) Miseq platform.
The whole exom sequencing method includes approximately 2% of the genome, and 85% of the mutations causing the disease can be detected by this method. As a result of the analysis, the variant of c.3166C> T, (p.Arg1056 *) was found to be homozygous in the DYSF gene exon 29. Together with obtained the bioinformatics and in-silico analysis data, it is possible that this result may lead to the muscular dystrophy clinic inhereted as OR, and the clinical and laboratory findings of the patient are consistent with the detected molecular genetic result. Segregation analyzes involving family members are ongoing.
Dysferlinopathy includes a spectrum of muscle disease mainly characterized by two phenotypes, caused by pathogenic variants in the DYSF gene: Miyoshi myopathy with the major distal weakness and Limb-girdle muscular dystrophy type 2B (LGMD2B) leading to primarily proximal weakness. Our patient's clinic was compatible with LGMD2B. In order to prevent contractures, genetic counseling was given to the family along with the clinical follow-up plan such as stretching exercises, muscle strength, annual monitoring of the range of motion and respiratory function, cardiology controls for cardiac involvement, weight control to prevent obesity, and avoidance of steroid treatment.

Key Words: DYSF Gene, Dysferlinopathy, Limb-Girdle Type 2b

P-117 - A Case Report with Epstein Syndrome

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MYH9-related disorders are characterized by macrotrombocytopenia, (>40 % of platelets >3.9 µm in diameter and platelet count <150 x 109/L), hearing loss, renal dysfunction and the incidence is not yet known. The MYH9 gene encodes the nonmuscle myosin heavy chain IIA (NMMHC-IIA)is expresed in many tissues such as platelets, kidney, leukocytes and cochlea. In this disorder, progressive sensorineural hearing loss, glaucoma or cataract, elevated liver enzymes and glomerular nephropathy advancing to renal failure, polymorphonuclear inclusions called Döhle-like bodies in addition to macrotrombocytopenia are other associated symptoms. Diagnosis of MYH9-related disorders including Epstein syndrome, Fechtner syndrome, May-Hegglin anomaly, Sebastian syndrome is based on the combination of symptoms.
We did DNA sequencing analyse of the MYH9 gene of a 23-year-old male patient with thrombocytopenia, bilateral renal insufficiency and hearing loss. Variations were evaluated with clinical findings and literature.
We detected heterozygous mutation c287C> T (p.Ser96Leu) in his MYH9 gene. The patient had bilateral renal insufficiency for approximately 13 years and 5% hearing loss in his left ear. Thrombocyte count was 20000, hemoglobin 7.7 and hypochromic microcyter erythrocytes, large platelets ,anisocytosis,no leukocyte-inclusions were observed in his peripheral blood spread. No glaucoma or cataracts were found on his eye examination. In his family story, there was only hypertension in his uncle and aunt and no consanguineous marriage.
The differences of MYH9-related syndromes are as follows: Macrotrombocytopenia and leukocyte inclusion bodies are associated with May-Hegglin anomaly and Sebastian Syndrome, while all symptoms are associated with Fetchner Syndrome. Differences in the structure of the Döhle-like bodies distinguish Sebastian syndrome and May-Hegglin anomaly. In Epstein Syndrome, macrotrombocytopenia, hearing loss and renal findings are observed but no leukocyte inclusion bodies and eye findings are expected. As a result, his detected mutation and symptoms are compatible with Epstein's syndrome, which is a very rare disease that this case is presented as a contribution to the literature.

Key Words: Macrothrombocytopenia, Deafness, Kidney, Failure

P-118 - A Novel Mutation in FANCC Gene in a Fanconi Anemia Patient

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Fanconi anemia is a rare autosomal recessive or X linked disease, characterized by chromosome breakage, progressive bone marrow failure, pancytopenia, developmental delay, dysmorphic features and susceptibility to cancer. Molecular background of Fanconi Anemia is heterogenous and at least 16 different genes contribute the pathogenesis. FANCA, FANCC and FACG mutations have been reported in 85- 90 % of the patients. In the current study, A Fanconi Anemia patient with a novel FANCC mutation is presented.
An 8 years old girl who have been admitted to medical genetics clinic due to pancytopenia, was born to 46 years old father and 44 years old mother who were first degree cousins. In addition to pancytopenia, microcephaly, upslanting palpebral fissur and hypo/hyperpigmented lesions were detected in physical examination.
The mutation was detected by next generation sequencing and confirmed by sanger sequencing. A c.456+2T>C mutation was detected in FANCC gene which effects splice site and was determined as pathogenic (Class I) variant according to ACMG.
Our results suggest that FANCC gene that is mutated in 15 % of the cases, should be included in next generation sequencing panels for the diagnosis of Fanconi Anemia.

Key Words: Fanconi Anemia ,FANCC, Mutation

P-119 - From Fenotype to Genotype : Cornelia De Lange Syndrome Case Report

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Cornelia de Lange Syndrome is a disease which has attributions of genetic heterogenity, characterized by marked facial features,growth retardation,hirsutism and upper extremity anomalies.It shows autosomal dominant (NIPBL, SMC3, RAD21) and X-linked dominant (SMC1A, HDAC8) inheritance.Common craniofacial features include synophrysis,bow-shaped eyebrows, long eyelashes, short nose and microcephaly.Mutations in NIPBL gene are the most common causes of Cornelia de Lange syndrome, and constitute more than half of all cases.Localized at 5p13,the 47 exons NIPBL gene encodes the delangin protein for controlling the activity of chromosomes during cellular division.Prevalence is between 1/10000 and 1/50000.99% of the cases are sporadic.In this report,we investigated the case with heterozygous NIPBL gene mutation causing Type 1 Cornelia de Lange Syndrome
A 6-year-old girl who was referred to our outpatient clinic because of short stature was the offspring of parents with secondary degree consanguineous marriage.Head circumference,height and body weight were measured as <3p at baseline. Physical examination revealed low anterior hairline,bow-shaped eyebrows,synophrysis,long eyelashes,short nose,flattened nasal root,antevert nostrils,pointed jaw,thin lips,long filtrum,low-set ear,short neck,discrete and small nipples,single transverse line on left hand,clinodactyly on 5th finger in both hands and bilateral syndactylia on 2nd-3rd toe.While hearing test and brain MRI were normal,echocardiography revealed aortic coarctation and aortic insufficiency.
Chromosome analysis was reported as 46,XX.Selected exon sequence analysis of NIPBL gene detected c.64 + 1 G> A heterozygote mutation.The alteration of patient was defined pathogenic in ClinVar.According to clinical findings and genetic analysis,she was diagnosed with type 1 Cornelia de Lange.
For many individuals affected by Cornelia de Lange syndrome,there is a developmental condition that affects behavioral problems,communication and social interaction similar to autism.Due to the risk of recurrence (1.5%) in the next pregnancies and the possibility of prenatal diagnosis,it is very important to provide genetic counseling for the family.More than 300 mutations in the NIPBL gene have been identified in people with Cornelia de Lange syndrome,which is a developmental disorder affecting many parts of the body.Patients can be diagnosed with type 1 Cornelia de lange syndrome according to the definitive diagnosis,clinical findings and results of genetic analysis

Key Words: Cornelia De Lange, NIPBL

P-120 - A Novel Mutation in GATA-1 Related a Novel Mutation in GATA Related X Linked Cytopenia

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GATA-1 gene, located on the x chromosome encodes a transcription factor that plays an important role in the development of several hematopoietic cell lines, including the erythroid, megakaryocyte (MK), eosinophil, and mast cell lineages. Also, the transcription factor GATA-1 is involved in both the biosynthesis of the globin and heme in erythrocytes. GATA-1 mutations have been associated with GATA-1-associated X-linked cytopenia reported in 22 families in the literature. This disease is characterized by thrombocytopenia and / or anemia. beta-thalassemia, neutropenia and congenital erythropoietic porphyria may be added to the clinic, depending on the mutation. In this study, a Turkish family with GATA-1-associated X-related thrombocytopenia and a previously unidentified mutation on the GATA-1 gene was examined.
The proband applied to our clinic with anemia and epistaxis.
In the laboratory findings; hemoglobin: 7,4 g/dL, WBC: 6.5/103 µL, MCV: 53.5 fL, Platelet: 258/103 µL, ferritin: 2 ng/ml, iron binding capacity: 440 µg/dL were detected. In the hemoglobin electrophoresis: HbA0: 80.2%, HbA2: 5.3%, hbF: 0.6% were detected. Alpha and beta thalassemia mutation analyzes were performed. No mutation was detected. The patient was treated with oral iron. After the treatment, the laboratory findings revealed hypochromatic, microcytic anemia and macrothrombocytopenia. GATA-1 gene sequence analysis showed a heterozygous novel mutation on the GATA-1 gene; c.715A /T (p.R239W), which was not previously reported in the literature. After the mutation analysis of the parents , the same heterozygote mutation was detected in the mother. Hemogram analysis of the mother revealed a hypochromic microcytic anemia and accompanying mild thrombocytopenia. We detected the same mutation in the patient's aunt and she had mild thrombocytopenia in the hemogram analysis. The thalassemia mutation analysis studies of the other patients are going on.
In the current study, the clinical and laboratory findings of a Turkish family carrying a novel GATA-1 mutation with GATA-1 associated X-linked cytopenia clinic was discussed. The mutation detected was defined as a pathogenic mutation type, according to the analysis programs (DANN, Mutation taster, SIFT) which predicts the effect of mutations

Key Words: GATA-1, X Linked Cytopenia

P-121 - Two Sisters with Cystic Fibrosis Admitted to Out-Patient Clinic as Pseudobartter Syndrome

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Cystic Fibrosis is a disease that can occur in the clinic with symptoms and clinical findings in a wide spectrum. Intestinal obstruction and pulmonary infections are the most common symptoms.
Two sisters between the ages of 4.5 and 2.5 years old, were admitted to our Medical Genetics Outpatient Clinic. In the history of one sister; she was hospitalized with bronchiolitic attack, sepsis, hypochloremic metabolic alkalosis findings at the age of 2 months. She was discharged following the preliminary diagnosis of Bartter syndrome.

Key Words: Pseudobartter Syndrome, Cystic Fibrosis, Hypochloremic Metabolic Alkalosis

P-122 - A Case Report of Glass Syndrome

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Glass syndrome (SATB2-associated syndrome-SAS; OMIM 612313) is a rare genetic disease characterized by intellectual disability, severe speech problems, dental and craniofacial anomalies. De novo heterozygote mutation, deletion/duplication or translocation of the SATB2 gene are observed in SAS patients. All of patients were described similar features regardless of alteration of SATB2 gene. Almost all patients demonstrated developmental retardation, intellectual disability in addition to absent or limited speech.
A 2,5 years old male patient who was born to a 35 years old mother by cesarean section with a birth weight of 2600 g at 39 weeks of gestation was referred to pediatric genetics department because of macrocephaly, developmental retardation, absence of speech and intellectual disability. Prenatal/natal history was unremarkable. Birth length and head circumference were unknown. When the stages of development were questioned, it was learned that head control and sitting without support was on time but onset of walking was at around 17 months of age and he had communicated only using hand gestures. When he was 1 year old, he had had one episode of febrile seizure which did not recur. He had broken his arm twice, due to falling out of bed when he was around 6-7 years old. He is the second child to a nonconsanguineous healthy parents. His 12 and 5 years old brothers are healthy. None of the family members or the relatives showed such symptoms. At our initial physical exam, he patient's body weight was 10-25percentile, height was 75-90percentile and head circumference was 75-90percentile. The dysmorphic features include; long and triangular facies, high forehead, deeply set eyes, malar hypoplasia, broad nasal tip, low columella, smooth philtrum, thin vermilion of the upper lip, large and long upper anterior incisors, diastema, distorted tooth alignment, discoloration of teeth, high palate and protruding chin. Musculoskeletal examination revealed bilaterally limited extension of the proximal interphalangeal joint of fifth finger.
In patients with intellectual disability, developmental retardation and dysmorphic face aCGH made it easier to make the diagnosis of the syndrome. Especially in the presence of teeth anomalies with accompanying intellectual disability and absent or limited speech SAS should be considered.

Key Words: Glass Syndrome, SATB2

P-123 - A Case with Glycogen Storage Disease Type 1

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Glycogen storage disease type 1 (GSDI) is a metabolic and OR-inherited disease group, which occurs as a result of dysfunction in the glucose-6-phosphatase system that plays a key role in the regulation of blood glucose. It is characterized by accumulation of glycogen and fat accumulation in the liver and kidneys and results in hepatomegaly and renomegaly.A 2.5-year-old girl was referred to us with suspicion of glycogen storage disease because of having episodes of hypoglycemia since birth, hepatomegaly in the abdomen USG (128 mm longitudinal dimension) and presence of consanguinity story between the parents.
Peripheral blood samples were taken from the patient and the DNA was isolated. All exons and exon-intron junction sites of the G6PC gene were amplified by PCR and sequenced by Sanger sequencing. Routine biochemical analysis and radiological examinations were performed.
When laboratory parameters of the patient were evaluated, there were ALT, AST elevation, hypertriglyceridemia, lactic acidosis and hyperuricemia accompanying hypoglycemia.She had a stone infant face and neuromotor development was behind.The patient was considered to have glycogen storage type 1, and the molecular analysis revealed a homozygous variant in exon 2 of the G6PC gene (c.247C> T (p.R83C).This result is likely to lead to a Type 1 clinic of Glycogen storage disease inherited as OR. The clinical and laboratory findings of the patient were consistent with the molecular genetic results.
When bioinformatics and in-silico analysis data, allele frequency of the variant and the patient's clinical and laboratory findings were evaluated together, the variant was thought to be pathogenic.Segregation studies are continuing in family members.Although glycogen storage disease type 1 is a rare condition, it is one of the inherited diseases which should be considered first in the presence of hepatomegaly and hypoglycemia due to its life threatening complications.Along with the early diagnosis, the patient is provided with adequate metabolic control by regulating the diet; In this way, the development of complications can be prevented and the quality of life of the patients can be increased.

Key Words: G6PC, Hypoglycemia, Glycogen Storage Disease

P-124 - GPC3 Deletion in Simpson Golabi Behmel Syndrome

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Simpson Golabi Behmel syndrome (OMIM # 312870) is a rare syndrome characterized by overgrowth. Prenatal and postnatal macrosomia are accompanied by macrocephaly, organomegaly, dysmorphic facial features (coarse face, macrostomia, macroglossia, palatal abnormalities) and intellectual disability. In addition, accessory nipple, skeletal abnormalities, congenital heart defects, genitourinary anomalies may be seen in patients. The disease is caused by mutations in the GPC3 (glypican-3) gene localized on Xq26. Although the disease primarily affects males, heterozygous female carriers may have mild to moderate clinical findings due to the skewing in X inactivation.
A five - month - old boy presented to our clinic with macrosomia (head circumference and body lenght and weight above 97th percentile). This was the third pregnancy of 26-year-old mother , and at 35 4/7 weeks of gestation with C/S (recurrent) he was born with a birth weight of 2940 g (75-90 p). There was history of polyhydramnios during prenatal follow-up. The patient who was operated for bilateral inguinal hernia on the 50th day of life, was also followed by pediatric surgery due to diastasis recti and hydrocele. He was followed up in the pediatric cardiology due to small secundum ASD. On physical examination, he had coarse facial appearance and accessory nipple. His body weight, height and head circumference were above the 97th percentile. There were 6 lumbar vertebrae on his X-ray.
Microarray analysis revealed, a 53 kb deletion in the Xq26.2 region including the GPC3 gene and this deletion was confirmed by MLPA . The patient's mother had no deletion and therefore the case was de novo.
In the literature, the rate of point mutations in the GPC3 gene was reported to be between 37% and 70%, and it is recommended to perform sequencing first, then to investigate the deletion and duplication of GPC3 and GPC4 genes as a second step if no mutation was detected. This syndrome should be kept in mind in the presence of macrosomia, multiple congenital abnormalities, intellectual disability, organomegaly and male gender, and genetic analysis should be planned accordingly. Genetic counseling should be given to carrier women.

Key Words: Simpson-Golabi-Behmel Syndrome, Macrosomia, GPC3, X-Linked Transmission, Multiple Congenital Anomalies

P-125 - HPLC and DNA Sequencing Analysis in Hemoglobinopathy Screening

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Hemoglobinopathy is an important public health problem in our country. Within the framework of the Hemoglobinopathy Prevention Program initiated by the Ministry of Health in 2003, 37 primary care hemoglobinopathy diagnosis centers were established in 33 provinces and 90% new births were prevented. In hemoglobinopathy screening, hemoglobin electrophoresis and capillary electrophoresis and high performance liquid chromatography (HPLC) methods have been used in recent years. The Hemoglobinopathy Diagnosis Center of the Mediterranean Blood Diseases Foundation was licensed in 2004 by the Ministry of Health. In our center, both capillary electrophoresis and all HPLC devices in our country have been used in different years. In this study, we aimed to compare the results of the molecular analysis with the HPLC results and to emphasize the importance of molecular genetic analysis by molecular analysis of the HPLC results we have used for the last five years.

Key Words: Hemoglobinopathy ,HPLC, DNA Sequencing

P-126 - Clinical Findings and Molecular Genetic Analysis Results in Patients with Hemochromatosis

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Hereditary hemochromatosis is an autosomal recessive disease characterized by excessive iron absorption in the gastrointestinal tract, resulting from mutations in the HFE gene located on the short arm of chromosome 6 (6p21.3). Although the exact prevalence of the disease is not known, the most common (85-90%) mutation is known as C282Y. Compound heterozygotes (C282Y/H63D) comprise less than 1% of patients. Disorders in genes encoding TFR2, Hepcidin, ferroportin, and DMT1 proteins are grouped as non-HFE-related forms, which are more rare than hemochromatosis. As a result of progressive iron accumulation in many tissues such as heart, joint, liver, skin, pancreas, pituitary gland, clinical findings occur.
Peripheral blood samples were collected from 7 male patients aged between 23 and 61 years pre-diagnosed with hemochromatosis and genomic DNA was isolated. All exons of the HFE gene and the TFR2 gene exon 4-6-16 were examined by sequence analysis method.
Three of five patients with heterozygous change in exon 2 of HFE gene had c.187C>G/p.His63Asp and other two patients had p.H63D/c.187C>G variation. One of the heterozygote carriers had cardiomyopathy and melanoderma, one had diabetes mellitus and arthritis, one had liver cirrhosis and hypothyroidism and two had hepatomegaly. Transferrin saturation was 57% in the patient with homozygous c.845G>A/p.C282Y variation in exon 4 in the HFE gene. The patient with homozygous c.124delG/p.Glu42ArgfsTer15 and c.266C>T/p.Ala89Val variant in exon 2 of the TFR2 gene had diabetes mellitus, coronary artery disease, history of CABG and abdominal ultrasonography showed increased liver and bilateral renal parenchymal echogenicity. Serum iron and ferritin levels were found to be high in all affected individuals.
Complications have been observed to be comman in patients and it was aimed to draw attention to the importance of early diagnosis and treatment. Genetic counselling was given to cases

Key Words: Hereditary Hemochromatosis, HFE Gene, C282Y Mutation

P-127 - A Case with Hunter Syndrome

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Hunter syndrome (MPS type II, MIM 309900) is a progressive, multisystemic disease that develops due to faulty disintegration of heparan and dermatan sulfate from glycosaminoglycans and intracellular progressive GAG accumulation. The disease occurs as a result of the mutation in the iduronate 2-sulfatase (IDS) gene and there are more than 300 known mutations in the gene. Symptoms occur between 4 and 8 years with variable rate of progression, and findings such as short stature, coarse facial features, joint contractures, and hepatosplenomegaly are typically seen.In this study, we wanted to raise awareness about this rare disease with enzyme replacement therapy and to draw attention to the importance of early diagnosis of the disease.
A 7-year-old male patient with short stature and bilateral contracture in his hands, mild coarse facial appearance and a normal mental status. The height of the patient was 113 cm (<3p), weight: 25 kg (50-75p). There was no hepatosplenomegaly. The child underwent surgery because of hydrocele and had no family history of consanguinity.Skeletal films, urinary glycosaminoglycan levels were requested from the patient on suspicion of storage disease
Glycosaminoglycan (dermatan and heperan sulfate) was positive in urine. In the enzymatic analysis, the presence of iduronate sulfatase enzyme activity [0 nmol/ml/4 hours (n: 494-1113)] was diagnosed as Hunter's syndrome.In the IDS gene at intron 6, (c.879 + 2T>C) mutation was detected as hemizigote and the diagnosis was confirmed. The patient had two sisters and one of them was heterozygous for (c.879+2T>C) change and the other was normal. The family was given genetic counseling about the resultsThe patient was referred to the Pediatric Metabolism Clinic and the enzyme replacement therapy was started.
In MPS II patients, bone marrow transplantation (BMT) was the only treatment option in the past, Nowadays, enzyme replacement therapy is performed with idursulfase. If not treated, patients typically die between 20 and 60 years of age. Clinical studies showed improvement in walking and respiratory functions after this treatment, reduction in growing liver and spleen size to normal and improvement in cardiac deterioration. However, no improvement in neurological findings was reported. Life expectancy was significantly reduced in patients with severe disease.

Key Words: Hunter Syndrome, MPS Type 2, IDS Gene

P-128 - Investigation of Variable Expressivities and CAG Repeats of 5 Patients with Huntington Disease

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Huntington's disease (HH) is a progressive neurodegenerative disease characterized by autosomal dominant genetic transmission, motor, psychiatric and cognitive clinical findings. The gene, localized to the short arm of the fourth chromosome, is referred to as IT15 and encodes the huntingtin protein. In HH, this protein has more CAG repeat sequence increase than normal. The aim of our study is to determine the number of CAG repeat and variable expressivity and founder effect.
CAG triple repeat region in the HTT (IT15) gene encoding the Huntington protein was evaluated in capillary electrophoresis by fluorescence PCR. Allele TP-PCR (Triple Primers Polymerase Chain Reaction) method was analyzed. Afterwards, the CAG repeat numbers of these 5 patients were compared with the age at onset of the disease, clinical severity of the disease, radiological and laboratory findings. In addition, detailed pedigree analysis of the patients was performed and the Founder effect in the Afyonkarahisar region was detected with the premature and variable expressivity of the disease.
CAG repeat numbers of IT15 gene were determined as 37,37,40,40,45 in 5 different patients in different regions of Afyonkarahisar. The age of onset of the disease was determined as 48,54,62,67,41, respectively. Some of the patients were found to be disease specific in their brain MRI, while others did not have any pathology. Pedigree analyzes were performed in all patients and some patients had variable expressivity due to premutation.
Although there is an inverse relationship between the CAG increase and the age of onset in Huntington's disease, there is no relationship between clinical findings and CAG repeat count. Korean movements, cognitive disorders leading up to dementia and psychiatric findings are the main features of the clinical picture. It is a disease with premutation and clinical variability. In our study, some patients had premutation and in some patients variable expression (variable expression) was observed. As premutation and variable expression are common, patients should be evaluated in general, in detail, genetically, clinically, radiologically and laboratoryly. Genetic counseling should be done by establishing the definitive diagnosis with genetic examination.

Key Words: Huntington Disease, CAG Repeat, Premutation, Variable Expressivity, Founder Effect

P-129 - A Severe Combined Immune Deficiency (SCID) Case with a Homozygous Mutation in the IKBKB Gene

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Primary immunodeficiency disorder (PID) refersto a large heterogeneous group of disorders that result from defects in immune system development and/or function. The most severe form of primary immunodeficiencies. Severe Combined Immunodeficiency (SCID). Patients present T cell deficiency or dysfunction in the first months of life. SCID is a genetically heterogeneous disease. Mutations in the T cellreceptor (TCR) gene, genes involved in DNA rearrangement /repair(RAG1, RAG2, LIG4, DCLRE1C, NHEJ, PRKCD), DNA synthesis/metabolism (ADA, AK2, PNP) or TCR signaling pathway (PTPRC, IL2RG, JAK3, IL7RA, CDE, CDZ, CORO1A) are associated with SCID. Recently, mutations in the IKBKB gene have been discovered in immuno deficient patients and this mutation has been described in some SCID patients too. In this report, we present a SCID patient with a homozygous G102X mutation in the IKBKB gene.
An 8-month-old boy was admitted with recurrent fever, vomiting and infection. His parents were 3rd degree relatives. Physical examination revealed hepatosplenomegaly, edema in the legs, maculopapular rash on the skin and lymphadenopathy. He had neutropenia, lymphopenia, hypogammaglobulinemia, elevated CRP and ferritin levels. Lymphocyte subtyping revealed absence of CD45RO and active T cells. One month later, the patient developed hemophagocytic syndrome and died. Primary immunodeficiency gene panel was studied in our patient and homozygous G102X mutation was detected in the IKBKB gene.
In this study, a SCID patient with homozygous nonsense mutation in IKBKB gene wasreported. hypogammaglobulinemia, lymphopenia, andabsence of active T cellweredetectedin our patients and these findings were consistent with literature. The mutation detected was in the exon 4, cause a stop codon and was evaluated as pathogenic in prediction programs. Our patient had hemaphagocytic syndrome and this combination have not been reported in the literature. This may be related to the IKBKB gene or may be caused by multigenic mutations. The importance of all exome or whole genom estudies is revealed for the further evolution of such patients.

Key Words: SCID, IKBKB Gene, Hemophagocytic Syndrome

P-130 - Two Laminopathy Cases: Phenotypes Related to LMNA Gene Mutations

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Lamins are structural protein components of the nuclear lamina. The LMNA gene encodes lamin A/C. LMNA gene mutations are associated with laminopathies such as skeletal/cardiac muscle dystrophies, lipodystrophies, Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia. Our aim is to discuss genotype-phenotype relationships of partial lipodystrophy type2 and mandibuloacral dysplasia type A cases with LMNA gene mutations.

Key Words: : LMNA Gene, Laminopathies, Partial Lipodystrophy, Mandibuloacral Dysplasia

P-131 - A CASE WITH GENERALIZED INVOLVEMENT CUTIS MARMORATA TELANGIECTATICA CONGENITA

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Cutis marmorata telangiectatica congenita (CMTC) is a very rare, cutaneous vascular congenital anomaly. Lesions with telangiectasia and phlebectasia may be localized or generalized. These lesions may be accompanied by ulcers and atrophies. CMTC is a sporadic condition which affects both sexes equally. The disease has a generally good prognosis. Approximately 50% of the cases have additional congenital anomalies. We aimed to present a case with CMTC accompanied by minor anomalies and to emphasize the points that should be considered in the follow-up of these patients.
Our patient is a newborn girl of non-consanguineous parents whose prenatal medical and family history were unremarkable. Physical examination revealed diffuse telangiectasia and phlebectasia, with ulcers in the reticular pattern on the skin that covering whole of the body. Our patient had high palate and micrognathia. Liver and kidney function tests and routine hematological laboratory tests of our patient were normal. Abdomen and transfontanel ultrasound, echocardiogram findings were unremarkable. Histopathologic examination of skin biopsy showed vascular proliferation and congestion.
CMTC is a congenital vascular anomaly of unknown etiology. The diagnosis of CMTC is usually established by clinical findings. In the literature, additional abnormalities have been reported in some of the cases, such as body asymmetry, ocular defects, cardiac and renal anomalies, central nervous system anomalies, psychomotor and mental retardation, hypothyroidism. In the literature febril convulsion, idiopathic hypertension, motor-mental retardation were observed during the follow-up of patients with CMTC. In conclusion, it is important to diagnose this disease which is characterized by dramatic skin manifestations in the neonatal period. Although, the lesions usually regress within two years, the prognosis depends on the presence of associated malformations. Therefore, all patients should be evaluated in terms of accompanying abnormalities. Even if no additional malformation is detected, long-term follow-up of the patients is important to detect pathologies that may develop in the future.

Key Words: Cutıs Marmorata Telangiectatica Congenita , Generalized Involvement, High Palate, Micrognathia

P-132 - Mutation Spectrum of the KMT2D Gene for the Kabuki Syndrome

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Kabuki syndrome (KS) is a rare syndrome, characterized by dysmorphic facial features, congenital anomalies including congenital cardiac and urogenital anomalies, developmental delay, hypotonia, short stature and immune dysfunction. KMT2D and KDM6A are only causative genes which are known to cause KS and found 43-76% and 1-6% of KS patients, respectively. 24-57% of KS patients had no mutations in both genes. While KMT2D-related KS is inherited in an autosomal dominant manner, KDM6A-related KS has an X-linked inheritance pattern. About 659 different mutations in the KMT2D gene have been reported in patients with KS (http://www.hgmd.org). Of these, 190 are nonsense mutations, 183 are small deletion mutations, 137 are missense mutations, 76 duplication and 10 small insertion mutations. Rather smaller ratio of the mutations consists of nine splice, three small indels, one gross deletion and one complex rearrangement. In the KDM6A gene, only 65 different mutations have been reported to date. Here, we report a mutation screening of the KMT2D gene in unpublished case series of 11 KS with a clinical suspicion of KS.
We screened 11 patients with clinically defined KS for mutations in KMT2D.
Mutation analysis revealed 11 distinct pathogenic/likely pathogenic mutations including 4 missense, 3 nonsense, 2 small deletion, 2 small insertion, 1 splice mutation. All of them are de novo mutations. Of the known pathogenic variants (4/11); 3 were nonsense and 1 was a frameshift duplication mutation. Previously unreported mutations (7/11) were 3 missense, 1 splice, 2 deletion, and 1 insertion mutation. This study revealed that novel mutations are common in the KMT2D gene. All of the patients had typical facial dysmorphism, short stature, developmental delay and prominent finger pads. Some of the patients also had renal anomalies (5/11), bifid uvula (3/11), cleft palate (2/11), cryptorchidism (3/11), bicuspid aorta (3/11), congenital hip dislocations (3/11), congenital hypothyroidism (1/11), and premature thelarche (1/11).
KMT2D mutations have been identified as the main cause for KS. The novel mutations identified in this study expanded the mutation spectrum of the disorder. Because the clinical phenotype of KS is highly variable, the very typical facial phenotype is particularly important for the initial clinical diagnosis.

Key Words: KMT2D Gene, KDM6A Gene, Kabuki Syndrome

P-133 - A Patient with Familial Candidiasis due to Hereditary IL-17F Deficiency

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Familial candidiasis-related gene mutations cause chronic mucocutaneous candidiasis (CMC). There are autosomal recessive(CARD9, IL17A) and autosomal dominant(STAT1, IL17F) transitional CMC subtypes. Affected individuals tend to be infected by candida and a lesser extent Staphylococcus aureus species of the skin, nails and mucous membranes. Phenotype may also include nail and tooth enamel anomalies, hematuria, hemoptysis, recurrent respiratory and urinary tract infections, hepatitis and meningitis. Candida-related immunodeficiency may be associated with endocrine and autoimmune disorders. In most of the cases, CMC begins in infancy. We report a case of late onset isolated CMC with autosomal dominant IL-17F deficiency.
A 40-year-old, male patient referred persistent itchy skin lesions with onset in age of 36. Initially his itchy rashes emerged in his both legs and transformed into inflamed wounds. Our case was previously followed up as porokeratosis mibelli.The patient did not benefit from the treatments for 4 years. His history revealed that patient's healed hepatitis infection, patient's father had psoriasis, patient's aunt had inflammatory joint disease and one of the patient's sister had Behcet disease. It was learned that his child had oral candidiasis and cheilitis a few times.
At the physical examination, he presented scattered atrophic patch lesions and crusts on the lower extremity and genital area. He had no lesions on oral mucosa, scalp and nails. Our patient did not have a history of urinary tract infection but microscopic hematuria was detected in the previous urine analysises. Biopsy of the lesions were performed. The histopathological study evidenced parakeratosis in stratum corneum, spongiosis in epidermis and mild inflammation (perivascular lymphocyte infiltration) in upper dermis. According to PAS staining, fungal hyphae was detected in stratum corneum. HIV and hepatitis B serology, dosages of immunoglobulins, endocrine tests, complete blood count showed normal parameters. Whole exome sequence was performed. The heterozygote mutation of p.E126G (c.3777A>G) was detected in IL17F gene.
Mutations in IL17F may explain increased susceptibility to fungal infection in our case, leading to defective Th17 responses and decreased IL-17 production. We think that this change, defined as a variant that cannot be classified in the CentroMD database, is pathogenic.

Key Words: Familial Candidiasis,Chronic Mucocutaneous Candidiasis,IL-17F Deficiency

P-134 - A Novel Pathogenic Variant of the CFTR Gene in a Patient with CF Phenotype: c.4096A>G

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Difficulties in assessing genotype – phenotype relationship make it important to report new changes in clinically compatible patients and their accessibility to genetic counselors. In this study, we present a patient whose clinical findings were consistent with cystic fibrosis and showed a homozygous missense change that is not previously reported in the CFTR gene, as pathogenic.
The patient was admitted to an external center with complaints of inability to feed, difficulty to breath during eating, and rapid breathing at 3.5 months. She was cachectic and was referred to our institution because she had multiple dyspnea attacks during her hospitalization and was complicated by recurrent respiratory infections. She was 3500gr (<3p), 60 cm (<3p) and head circumference was 36 cm [<3p] at 4 months of age. Patient then got referred to our Genetic Center with a preliminary diagnosis of Cystic Fibrosis, due to her respiratory findings (such as difficulty in breathing, fast paced respiration, and chronic cough) and accompanying malabsorption. There were no features in her prenatal history, and no relative was detected in her pedigree with symptoms and findings alike. A Next- Generation Sequence Analysis of her CFTR gene was performed.
In the next generation sequencing analysis, homozygous c.4096A> T single nucleotide exchange (I1366F (p.Ile1366Phe), missense) was shown in both alleles of the patient's CFTR gene
This variant has not yet been previously reported (VarSome, ClinVar, MutationTaster, Ensembl, dbSNP, Pubmed). The DANN score was calculated as 0.9882 through in silico data analysis from VarSome database. Pathogenic protein product of the patient, UniProt protein CFTR_HUMAN domain 'ABC transporter 2' has 76 classified variants and 68 of them are pathogenic= 88.2% (greater than 66.7%), that strengthens the possibility that the variant is pathogenic. Computational analysis from DANN, GERP, dbNSFP, FATHMM, LRT, MetaLR, MetaSVM, MutationAssessor, MutationTaster and PROVEAN databases showed 0 estimated benign results vs. 9 estimated pathogenic results. There is no validated genotype – phenotype association on the dbSNP database, and reference sequence (rs770345073) seems to be validated only by frequency. We do consider the change as pathogenic, since the patient's findings were compatible with cystic fibrosis and the data analysis was in favor of pathogenicity.

Key Words: CFTR, Novel, Ngs, Cystic Fıbrosis, Variant

P-135 - Koolen-De Vries Syndrome: A New Case

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The prevalence of Koolen-De Vries syndrome (KdVS) (OMIM # 610443), also known as 17q21.31 microdeletion syndrome, is estimated at around 1:16.000 in the general population. KdVS can be caused either by a recurrent 500-650 kb heterozygous deletion of several genes, including CRHR1 (OMIM*122561), STH (OMIM *607067), MAPT (OMIM *157140), SPPL2C (OMIM*608284) and KANSL1 (OMIM *612452) or by heterozygous mutation in the KANSL1 gene (612452) on chromosome 17q21.31. KdVS is characterized by moderate to severe intellectual disability, hypotonia, friendly demeanor, and characteristic facial dysmorphism.
The case presented to our policlinic with complaints of speech disorder and epilepsy. We carried out detailed analysis of the clinical phenotype of this patient and investigated the genetic basis by using standard karyotyping and chromosomal microarray analysis. The case is a 4-year-old girl, the fourth of four siblings. Her parents were one degree cousins and there is not a significant family history. The case was born at 36 weeks' gestation by cesarean section with a birth weight of 2100 g. She began to control her head at around 18 months, sit without any support at 20 months and began walking at 30 months.
The patient has an extensive medical history including epilepsy, hypotonia, developmental delay, intellectuel disability, aortic regurgitation, patent foramen ovale, hyperactivity, and stereotypic behaviour. Dysmorphic features including broad forehead, upslanting palpebral fissures, hypertelorism, nystagmus, a bulbous nose, widely spaced teeth, high palate, low-set ears, long-slender fingers, and a patch with homogeneous depigmentation. The phenotype found in our case showed similar features of KDVS. Standard karyotyping displayed no visible numerical or structural alterations in the chromosomes. The patient showed female karyotype (46,XX). Using chromosomal microarray analysis, we identified a microdeletion of 523 kb on chromosome 17q21.31, resulting in the heterozygous loss of CRHR1, STH, MAPT, SPPL2C and KANSL1 genes.
Since quite little is known about most rare diseases, we believe that studies on rare syndromic disorders, such as this one, will contribute to the literature on how the rare diseases develop and progress.

Key Words: Koolen-De Vries Syndrome, 17q21.31 Microdeletion Syndrome, Rare Disease

P-136 - Clinical and Molecular Findings in Five Turkish Patients with Krabbe Disease: Report of Two Novel Mutation of the GALC Gene

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Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive metabolic neurodegenerative disease that affects the nervous system. It is caused by mutations in the GALC gene coding for the lysosomal enzyme galactocerebrosidase. To date, 247 mutations have been reported in the HGMD Human Genome Mutation Database) database.
We studied five Turkish patients whose clinical, biochemical and radiological findings were compatible with Krabbe Disease.
DNA sequencing revealed 4 distinct pathogenic mutations including 2 previously unreported in the GALC gene. We identified the homozygous novel missense mutation c.1394C>T (p. Thr465Ile) at a highly conserved amino acid in the GALC gene and the homozygous novel nonsense mutation c.1623G>A (p.Trp541Ter) in two families of our study.
We report clinical, neuroradiological and molecular findings in five Turkish patients with Krabbe disease. Investigating the genotype of patients with Krabbe disease is important to contribute to the creation of a Turkish mutation database and to further study possible genotype-phenotype correlations of the disease.

Key Words: Krabbe Disease, GALC Gene

P-137 - Limb-Girdle Muscular Dystrophy: A Family with Three Cases

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Limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of muscular dystrophies. It is most common characterized by weakness and wasting of the proximal muscles in the arms and legs. The clinical course is typically progressive. It has a prevalence of 1/15.000. Due to wide clinical and genetic variability, an precise diagnosis can be difficult. Serum creatine kinase (CK) concentration is usually elevated. The diagnosis is based on muscle biopsy followed by genetic confirmation. Pathogenic variants at more than 25 gene have been shown to cause LGMD. SGCD gene is one of responsible genes, and localized on the chromosome 5q33. We report here a male child whom two siblings had the characteristics of this syndrome. We report this case because the presence of a family with three patients with LGMD2F is rare, and to emphasize the importance of anamnesis.
We report a 14 months old male child. The propositus was directed to the medical genetic outpatient clinic for his mother's observation with associated himself. According to the mother; the propositus had hard leg muscles like his two older siblings, when they were young. But their leg muscles gradually softened. Their muscle weakness began in the legs, over time it increased both severity and spread. Ambulation was achieved but was lost after 10-years old. They could neither lift their arms nor reach into objects. In family history; his parents were relative. On examination; height was 75 cm (10-25 p), and OFC 45,5 cm (10-25 p). He could walk. He had calf hypertrophy, and showed positive Gowers sign.
Serum CK concentration was increased. His karyotype was normal. Whole gene sequence analysis showed c.493C>T homozygous mutation in SGCD gene.

Key Words: Limb-Girdle Muscular Dystrophy, Govers Sign, Calf Hypertrophy, Creatine Kinase

P-138 - Germline P53 Mutation in a Case of Li-Fraumeni Syndrome

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Li-Fraumeni syndrome (LFS, OMIM #151623) is an autosomal dominant cancer predisposition disorder that is caused by germline mutations of the p53 tumor suppressor gene. LFS is characterized by early onset of tumors, multiple tumors within an individual and multiple affected family members. LFS related tumors have a wide spectrum including osteosarcomas, adrenocortical carcinoma (ACC), central nervous system (CNS) tumors, and soft tissue sarcoma (STS) in childhood. In adults, the tumor spectrum is more limited and is characterized by mostly premenopausal breast cancer and STS.
We report on a 16-year-old male diagnosed with chondroblastic osteosarcoma and a renal cyst. He had a family history of multiple LFS related tumors. His father died at the age of 36 due to CNS cancer and his mother was healthy, aged 46. The patient had five siblings; the eldest was a healthy 27-year-old male with two healthy children. The second was a 26-year-old female, operated for adrenal and breast tumor. The third and fourth siblings, one male and one female, both died at the age of seven from ACC. The female sibling was also reported to have Wilms tumor. The youngest sibling was a 11-year-old healthy male. The paternal grandmother and two of his aunts died due to breast cancer. Two of his paternal uncles died because of brain cancer.
Classic LFS diagnostic criteria was met and a family screening for TP53 mutations has been done for the patient. Sanger analysis revealed missense mutation p.Arg337Cys in our patient and his sister. Further evaluation for tumors in the affected individuals are being done.
Pathogenic missense mutations in TP53 is associated with earlier onset of cancer. In a recent study, the average age of tumor onset in heterozygotes for a TP53 missense variant was eight years earlier (20.9 years) than for those with nonsense or other types of pathogenic variants (28.9 years). The presented family further supports this conclusion and highlights the need for careful examination, inspection and notification of the risks of family members diagnosed with LFS.

Key Words: Li-Fraumeni Syndrome, Osteosarcoma, TP53, Missense Mutation

P-139 - A Case Presentation with 10p15.3 Microdeletion Derived from a Maternal Reciprocal Translocation t(4;10)(q28;p15)

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Balanced reciprocal translocation carriers may have unbalanced gamets as a result of abnormal segregation of homolog chromosomes. In consequence of the unbalanced translocations; abortus, perinatal missings or patients with abnormal phenotypes could be observed. Aim of this study is to examine a case with unbalanced translocation arise from her mother's balanced reciprocal translocation.
A one-and-half year old child who her parents had no consanguinity was referred for genetic consultation because of dismorfic signs. The patient was born at the 37th pregnancy week with like low birth weight (1780gr), and she was intensive care unit for 25 days because of respiratory distress and developmental delay. In history of the patient; secundum type atrial septal defect and increased flow in pulmonary arteries, abnormal EEG pattern, some pathological symptoms like cerebral atrophy and epidermoidal cyst on the left occipital in brain-MRI and mental retardation was detected. Also her dysmorphic features were broad face, frontal hirsutism, hypertelorism, wide and flat nasal root, posteriorly rotated low-set ears, thick antihelix, simian crease on hands, distinct papillas and hypertrichosis.
72-hour-cell-culture performed from her peripheric blood sample and conventional cytogenetic analysis studied after GTL(Giemsa-tripsin-Leishman) bandig.Her karyotype was detected as 46,XX,der(10)t(4;10)(q28;p15)at all 20metaphase plaques. While her father's karyotype was46,XY, her mother was a carrier of a balanced reciprocal translocation as46,XX,t(4;10)(q28;p15). Results were explained with der(10) in our case was derived from maternal reciprocal translocation. Then, microarray analysis were performed from her DNA by Affymetrix Cytoscan Optima(315K) system and analysed in CHAS3.2.0/GRCh37/hg19 programme and reported as arr[hg19]4q28.3q35.2(134,093-190,557,473)x3,10p15.3(100.026-2,144,362)x1 and partial trisomy of 4q and partial monosomy of 10p were detected. Databases show us the mutations at ZMYND11(608668) gene located in 10p15.3 may cause this phenotype.
Unbalanced chromosomal rearrengements arised from a balanced reciprocal translocation carrier mother and their effects on patient's phenotype were explained by using the cytogenetic and molecular karyotyping methods at our case. According to databases,it's noticed that 10p15.3 microdeletion syndrome and mutations(OMIM#616083)at ZMYND11 (OMIM*608668) causes mental retardation, neural system defects, behavioural differences, hypotonia, low birth weight, developmental delay, dysmorphic signs, congenital heart defects. All the studies and clinical signs suggest that our case is 10p15.3 microdeletion syndrome.

Key Words: 10p15.3 Microdeletion, ZMYND11, Reciprocal Translocation, Unbalanced Translocation, Cytogenetics

P-140 - The Results of Molecular Genetic Analysis in Patients with Hemoglobinopathy in Our Center

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Hemoglobinopathies are usually classified in two groups; alpha, beta, gammaemia consisting of gamma and delta genes, or hemoglobin variants due to structural abnormalities in these chains. Sequence analysis for Globin-Strip, Gap-PCR, MLPA, point mutations for deletions after tests such as history, physical examination, complete blood count and peripheral smear, isoelectric focus, high performance liquid chromatography, stability test and oxygen affinity in diagnosis of hemoglobinopathies it is made. Sequence analysis for the alpha, beta, gamma and delta mutations starting from the promoter region to the poly A region is examined. In the world 220 alpha, 344 beta, 34 delta, 42 delta / beta, 28 εδβeta thalassemia, as well as 460 alpha, 601 beta, 99 gamma, 74 delta chain variant and 38 HPFH 1940 hemoglobinopathy was published.In this study, the aim of this study is to present the results of the series analysis of patients who presented with alpha, beta thalassemia and abnormal hemoglobin diagnosis and compare them with the current situation in our country.

Key Words: Molecular Genetic Analysis, Hemoglobinopathy

P-141 - A Novel Variation in the Promoter Region of HNF1A Gene in a Patient With MODY3 Phenotype

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MODY (Maturity-Onset Diabetes of the Young) is constituting 1-2% of all diabetes patients and MODY3 is the most commonly seen among all MODY patients. The genetic etiology of MODY3 comes from heterozygote pathogenic variations of hepatocyte nuclear factor-1 alpha (HNF1A) gene which has 10 exons, resides on 12q24.31 and encodes a protein composed of 631 amino acids. Here we present a MODY3 case with a novel variation in HNF1A gene which has not been reported in the literature before.
Thirteen years old male patient referred to us with the diagnosis of diabetic ketoacidosis. During his admittance, his blood glucose levels had been lowered to normal levels, he had been screened for possible complications of diabetes and he was discharged with diabetes education and strict insulin regime. There was no medical history considering the patient's non-consanguineous Turkish parents and 18 years old sister but his grandparents and uncle from mother's side have diabetes mellitus diagnosed after 25 years of age.
We performed next-generation sequence analysis using NEXTflex MODY-1 amplicon panel kit for HNF1A and GCK genes within İllumina MiniSeq platform. The analysis showed heterozygote c.-182C>T substitution in HNF1A gene (RefSeq: NM_000545; Transcript ID: ENST00000257555). As a result of literature research including PubMed, CLINVAR, Ensemble databases, we did not find any previous report of this substitution and considered it to be novel. The in silico analysis using VarSome database calculated DANN score as 0,8224 and Mutation Taster in silico analysis reported this substitution as a "disease causing" variant.
Considering multiple reports of pathogenic variations in highly conserved regions of the promoter of HNF1A gene and the clinical features of the patient; the possibility of the substitution of c.-182C>T being pathogenic seems to be likely. We do believe reporting this novel variant is a contribution to literature and naturally, an additional step toward more efficient ways of treatment by understanding mechanisms that lead to the development of Maturity-Onset Diabetes of the Young.

Key Words: HNF1A, MODY3, MODY, Promoter

P-142 - Mutation Analysis of the PMP22, GJB1 and MPZ Genes in Patients with Demyelinating Charcot Marie Tooth Disease

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The aim of this study was to determine causative mutations and thereby genotypes of Turkish Cypriot demyelinating CMT patients. Also this study is the first molecular diagnostic investigation of CMT patients from the Turkish Cypriot population. It is a known truth that there are CMT patients also in the Turkish Cypriot population. However, a prevalence study of responsible mutations for the disease has not been performed before in the Turkish Cypriot population. To begin with, it is required to perform a molecular diagnosis of CMT for 3 common mutations; PMP22, MPZ and GJB1.
Patient`s Clinical Examination DNA Extraction and Quantification Polymerase Chain Reaction (PCR) and Agarose Gel Electrophoresis Copy Number Quantification – Multiplex Ligation-dependent Probe Amplification
Gene copy number of all patients is determined from the peaks of electropherogram and the analysis of electropherogram results via peak ratios. All six studied patients (140167, 140171, 140172, 140189, 170197 and 140237) were investigated for PMP22 duplication with the MLPA technique. It is found that only patient, 140197, has a PMP22 duplication. The rest of the patients were excluded from PMP22 duplication. Sequencing analysis was performed for the genes PMP22, MPZ and GJB1 genes to the rest of the samples except 140197, which was diagnosed with PMP22 duplication. In two of patients point mutation were detected. Patients 140167, 140172 and 140237 were excluded from point mutation in the PMP22, MPZ and GJB1 genes.
Analysis of common causative genes concluded that; PMP22 duplication (CMT1A), GJB1 mutation (CMT1X) and MPZ mutation which cause DSS is present in the Turkish Cypriot population. Considering previous de novo mutations associated with CMT in the Greek Cypriot population, a diagnostic algorithm has to be constituted with patient`s ethnic background, phenotypic-genotypic correlation of disease subtypes and mode of inheritance. Identifying disease causing genes becomes very useful for clinicians for correct diagnosis of the CMT subtypes. Also it is important for the patients in the perspective of counseling and therapy developments.

Key Words: Charcot Marie Tooth Disease, Mutation Detection, Molecular Diagnosis, Copy Number Quantification

P-143 - A Case Report of Rarely Genetic Condition; Cleidocranial Dysplasia

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We aimed to discuss our case with the others of the literature and contribute to the literature.
Cleidocranial dysplasia is a rare autosomal dominant skeletal syndrome (1: 1,000,000) and caused by heterozygous mutation in the RUNX2 gene, encoding transcription factor CBFA1, on chromosome 6p21. The main clinical features of cleidocranial dysplasia include persistently open skull sutures with bulging calvaria, hypoplasia or aplasia of the clavicles permitting abnormal facility in apposing the shoulders, wide pubic symphysis, short middle phalanx of the fifth fingers, dental anomalies, and often vertebral malformation.
A 12−year−old girl was referred to our clinic because of short stature. Her parents pointed out that her anterior fontanel closed at 5 years old. Physical examination revealed a height of 133 cm(< 3p), parietal bossing, midface hypoplasia, hypertelorism, low nasal bridge, delayed eruption of permanent teeth, sloping shoulders, broad thumbs, brachydactyly, pes planus of foot. Radiological findings are: persistently open skull sutures, calvarial thickening, hypoplastic paranasal sinuses and maxilla, hypoplastic clavicles, narrow pelvis, wide pubic symphysis, broad femoral head with short femoral neck, hypoplastic iliac wing , short middle phalanges of second and fifth fingers, nonunion fractures of left hand distal phalanges
We diagnosed the patient with clinical and radiological findings and confirmed with RUNX2 mutation analysis. Because of no family history, we thought de novo mutation. Cleidocranial dysplasia should be kept in mind as a cause of delayed closure of the anterior fontanelle, dental anomalies and short stature.

Key Words: Cleidocranial Dysplasia, Cleidocranial Dysostosis, Aplasia of Clavicle

P-144 - A Rare Disease: Raine Syndrome

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Raine Syndrome is a rare genetic disease with autosomal recessive inheritance characterized by exophtalmus, coanal atresia, osteosclerosis and cerebral calcification. Most of the patients die after birth but recently there have been some cases which are diagnosed in childhood and adulthood. Hearing loss, developmental retardation, epilepsy and amelogenesis imperfecta can be seen in nonlethal forms. Here, we report a case of a clinically diagnosed Raine Syndrome.
Patient is a male who was born to a 24 years old G1P1L1 mother by spontaneous vaginal delivery with a birth weight of 3805 g at 40 weeks of gestation. In the prenatal follow-up, cordocentesis was performed due to hypoplastic nasal bone and abnormal shaped calvarium which were detected on detailed fetal USG. 46,-- was reported on caryotype analysis. At birth; height was 54cm(>97p) and head circumference was 34cm(10-50p). There is no consanguinity between his parents, and neither of the family members has similar findings. On the physical examination of the patient who was consulted to us when he was 5.5 months old, his weight was 25-50percentile, his height was -3-4sd and head circumceference was 25.percentile. The dysmorphic features include cloverloaf skull, midfacies hypoplasia, flat face profile, prominent and broad forehead, exophthalmos, corneal clouding, hypoplastic nose, anteverted nares, fishlike mouth, hypertrophic palatine ridges, micrognathia, short neck, brachydactyly of hands with rizomelic shortness. Lab. study showed ALP 899U/L(116-450), phosphorus 2,6mg/dl(4-6,5). On echocardiogram mild MY and TY was seen. Deformation of calvarium, bilateral periventricular calcifications at whitematter and agenesis of corpus callosum were noted on kranial CT. Generalised osteosclerosis, thick and irregular clavicula, cleft vertebrae, dumbellshaped humerus and hypoplasia of sacrum were seen on infantogram. Based on all these findings, FAM20C gene analysis was sent considering Raine Syndrome.
Raine Syndrome which is also known as osteosclerotic bone dysplasia; its prevalence is estimated to be less than 1 / 1,000,000. FAM20C gene in chromosome band 7p22.3 is critical in bone development and its expressed in osteoblast/ osteocytes, ameloblast ve odontoblast cells. Although it's rare, it should not be forgotten that it can be easily recognized by its typical dysmorphism and radiological findings.

Key Words: Raine Syndrome, FAM20C, Osteosclerosis

P-145 - Clinical Evalution of Patients with NF1 Deletion

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Neurofibromatosis type 1 (NF1, OMIM # 162200) is an autosomal dominant disorder characterized by cafe au lait spots, fibromatous tumors of the skin and Lisch nodules. It is caused by heterozygous mutations and deletions in the neurofibromin gene (NF1) on chromosome 17q11.2. NF1 is a tumor suppressor gene important in the control of cell growth and development. Only 5% of cases have deletions in the NF1 gene, and cognitive functions may be significantly affected in these cases.
Eleven patients with clinical diagnosis of NF1, age range between 1.5 to 32 years (mean age 11 years) were included. They had deletions detected by FISH (ten patients –two were mosaic deletions) and microarray (one patient) analysis. In one patient a deletion in the 17q11.2 region, including the NF1 gene was detected by microarray analysis (Affymetrix CytoScan Optima Array).
The most common finding was cafe au lait spots in ten patients. Neurofibromas, Lisch nodules and optic glioma were detected in three patients. There were four patients with lesions consistent with NF1 in the brain MRI, and one of these patients had a history of seizures. Three patients had hypothyroidism and one of them had also delayed puberty. Cognitive defects were found in three patients. The clinical findings of patients with mosaic deletion were found to be milder than the other patients. The association of NF1 with arterial aneurysm is known despite being uncommon. In our case series, one patient had a giant aneurysm in the right cervical internal carotid artery.
Although neurofibromatosis type 1 is mostly caused by NF1 mutations, deletions are responsible in a small number of patients. Especially in patients with cognitive impairment testing for deletions is recommended. In addition, due to the hypothyroidism detected in three patients in our case series, it would be beneficial to evaluate these patients from the endocrinological point of view. Although it is rare, since the complications can be serious and fatal, it is important for the clinicians to be aware of arterial aneurysms and to evaluate patients in this respect.

Key Words: NF1, Deletion, Microarray, Aneurysm, Cafe Au Lait

P-146 - Craniosynostosis in Patients with Noonan Syndrome 7

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Craniosynostosis is defined as the premature fusion of one or more sutures. Craniosynostosis can be isolated nonsyndromic or it may be part of a larger syndrome with digital malformations, skeletal defects, cardiac defect, or other organ anomalies. More than 180 syndromes exist that contain craniosynostosis. Craniosynostosis is very heterogeneous in terms of its causes, presentation, and management.
Two sisters of non-consanguineous parents were admitted for diagnostic evaluation of craniosynostosis They present with microcephaly, craniofacial dysmorphisms (down slanting palpebral fissures, a pointed nose, smooth philtrum, wide dysplastic ears). They showed an mild developmental and speech delay.
Genomic DNA is enzymatically fragmented and regions of interest are selectively enriched using capture probes targeted agains t coding regions of ~6700 genes w ith know n clinical significance. Libraries are generated w ith Illumina compatible adaptors and sequenced on an Illumina platform. Raw sequence data analysis, including base calling, demultiplexing, alignment to the hg19 human reference genome and variant calling is performed using validated Ingenuity Pathway Analysis software.
A heterozygous pathogenic variant was identified in the BRAF gene. The genetic diagnosis of autosomal dominant RASopathie is confirmed. The BRAF variant c.1952C>T:p.T651I causes an amino acid change from Tre to Iso at position 651. ClinVar lists this variant as pathogenic. This variant has been confirmed by Sanger sequencing. Pathogenic variants in the BRAF gene have been associated with several allelic autosomal dominant phenotypes, including cardiofaciocutaneous (CFC) syndrome type 1 (OMIM® 115150), LEOPARD syndrome 3 (OMIM® 613707) and Noonan syndrome 7 (OMIM® 613706). For example, Noonan syndrome-7 is characterized byfeatures included poor neonatal growth, variable feeding difficulties, short stature, mild to moderate cognitive defects, skeletal anomalies, and hypotonia. Dysmorphic facial features included dolichocephaly, prominent forehead, hypertelorism, and low-set ears with thickened helices. We present two patients with severe craniosynostosis and Noonan syndrome-7 due to de novo mutations in BRAF. However, the detailed pathogenic mechanism by which RAS/MAPK signaling pathway-mediated craniosynostosis occurs remains unknown, though previous reports of craniosynostosis and Noonan syndrome speculated about an possible interaction between the FGFR and RAS/MAPK signaling pathways.

Key Words: Craniosynostosis, BRAF

P-147 - A New Varıant in a Patient with Neurofibromatosis Type 1(NF1): Case Report

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NF1 is an autosomal dominant inherited neurocutaneous disease with characteristic clinical features such as café au lait spots, Lisch nodules, neurofibromas, freckling in axiller or inguinal areas and skeletal dysplasia with an estimated incidence of 1/3500-4000. In about half of the cases, it is an familial, and in there maining cases, it results from de novo mutations. It is aimed to present an NF1 patient with a new mutation.
A 20-month-old male patient was referred to us because of increasing number of café au lait spots, growth retardation and autism spectrum disorder. Prenatal, natal history and pedigree information could not be obtained because the patient was brought by the foster-family. The motor and language development of the case was retarded. The examination revealed more than 10 café au lait spots of different sizes. Craniofacial examination revealed macrocephaly, frontal bossing, upslanting palpebral fissures and bilateral epicanthic folds. Conducted brain MR imaging in T2-weighted sequences; bilateral optic nerves were thick and folded, increased CSF sheath volumes around them, thickening of the optic tract, and increased intensity of subcortical areas in the frontal regions of the white matter. Karyotype, FISH and NF1 gene analysis were planned.
Chromosome analysis was 46, XY. There was no disease specific deletion in FISH analysis. NF1 and NF2 genes were analyzed by NEXTflex neurofibromatosis amplicon panel which contains all exons and neighboring intronic regions in illumina miniseq platform. The frameshift mutation of c.3524_3525insA (NM_001042492) was detected in the NF1 gene.
The determined c.3524_3525insA mutation was classified as probable pathogenic in the varsome and mutation taster in silico analyzes. This mutation was not reported in the Ensemble, NCBI, LOVD NF1 database, CentoMD databases. After 19 amino acids from the existing c.3524_3525insA mutation, an early stop codon is formed and protein synthesis is terminated. In this case, the protein synthesized from the gene remains short. Since the clinical findings of the case were consistent with the NF1 clinic, the mutation was evaluated as pathogenic variant and genetic counseling was given to the family. The case was presented in order to contribute to the literature.

Key Words: Neurofibromatosis Type 1, NF1 Gene, Novel Mutation, Next Generation Sequencing

P-148 - Genotype-Phenotype Evaluation of NF1 Gene Variatıons in Neurofibromatosis Type 1 Suspect Cases

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Neurofibromatosis Type I disease (OMIM # 162200) called "cafe au lait spots" that is a autosomal dominant gene and characterized by light brown macular, axillary-inguinal freckling, cutaneous neurofibromas and iris nodules. The aim of this study was to investigate the genotype-phenotype correlation of the genetic analysis data in patients who were referred to our center with suspicion of neurofibromatosis. 7 men and 7 women, aged between 1 and 40 years, a total of 14 cases were referred for suspicion of neurofibromatosis between September 2017 and September 2018 in the Yeni Yuzyil University Faculty of Medicine Genetic Diseases Diagnosis Center. PCR-Amplification with specific intronic primers of fragments corresponding to coding and flanking intronic regions of full exons of NF1 gene (NM_000267). Preparation of the targeted sequences library using Nextera XT (Illumina). Paired-end Sequencing 2X151bp using MiSeq sequencer (Illumina) with a mean coverage in the analyzed regions of 245.67X, and 28.42% of bases are > 20X covered. The variants were generated by alignment against reference genome (UCSC hg19) using BWA aligner and GATK variant caller. Annotation of the variants according to reference sequence mentioned in Human Gene Mutation Database (HGMD).
As a result of the study, heterozygote pathogenic variants were identified in the NF1 gene of 5 cases with only “pat cafe au lait spots” (at least 6 on the skin): p.Cys379*;(c.1137C>A), c.2850+2T>G, c.1261-1G>A, p.Ile322Val;(c.964A>G), p.Trp2369*;(c.7106G>A). These variants have not been previously described in the literature and in the “Mutation Taster” and “PolyPhen” bioinformatics programs predict “disease causing” and “likely pathogenic”. Pathogenicly identified variants in HGMD were detected as heterozygous in 3 patients that has axillary-inguinal freckling, cutaneous neurofibromas and iris nodules: (p.His553Arg;(c.1658A>G), p.Glu196*;(c.586G>T), p.Val341Hisfs*11;(c.1021_1022delGT). No pathogenic variation was found in NF1 gene of other 6 cases.
Neurofibromatosis can predispose to cancers such as glioblastoma, optic gliom, breast cancer, ovarian cancer and melanoma, so genetic test are recommended to develop effective strategies. Genetic counseling is recommended to the family for risk management if there is a pathogenic variation on this gene.

Key Words: NF1,Neurofibromatosis Type

P-149 - Evaluation of Serum miRNA (miR-26a, miR-29a, miR-133a) Expression Levels in Patients Diagnosed with Osteogenesis Imperfecta

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Osteogenesis Imperfecta(OI) is associated with long bone deformities and fractures, accompanied by a genetic connective tissue disorder with visible blue sclera, tooth disturbances, hearing loss and ligamentous laceration. According to their clinical, inherited, and radiological characteristics, OI classically divides into four classes by Sillence et al. Today,OI has reported 17different types in OMIM database. There are autosomal dominant(OD) and autosomal recessive(OR) transitions, although they differ according to inheritance patterns. MicroRNAs(miRNAs),a class of small non-coding RNAs, play an important role in processes such as development, homeostasis, immune system and ossification. In this study we aimed to identify the role of microRNAs in OI in clinical heterogenity, contribute to the understanding of its utility as a biomarker, and to identify expression differences between patient and healthy control groups of miR-26a,miR-29a,miR-133a from bone-associated miRNAs for the possibility of a new therapeutic target.
Control group was made up healthy children between the ages of 0 and 18 who applied to the General Child clinic of Akdeniz University, had no disease. Patient group was 0-18age children, followed by OI diagnosis in Akdeniz University, Child Genetics and Endocrinology clinic. There was a noticeable difference between the miRNA levels of the patient and control groups and the miRNA levels of the patient group were higher. Serum calcium and vitamin D levels of patients with higher miR-133a levels were lower than those of the other groups. There was no statistically significant difference between the incidence of dentinogenesis imperfecta and miRNA levels. However,expression of miR-26a was increased in dentinogenesis imperfectant patients(p=0.09).
OI is characterized by diffuse osteoporosis, recurrent bone fractures and resulting deformities, and there is no definitive treatment. Identification of biomarkers that can be used for OI diagnosis and follow-up, detection of the disease at an early stage, and may be important in monitoring the response to treatment, miRNAs that are likely to be a new therapeutic target. microRNAs are shedding light on early detection and possible treatments by shedding light on the dark areas of the disease. Osteogenesis Imperfecta is also one of these diseases. Currently with sufficient and extensive clinical trials being needed microRNAs can be used as biomarkers.

Key Words: Osteogenesis Imperfecta, miRNA

P-150 - A Further Case of Autosomal Recessive Brachyolmia having a Novel Mutation in PAPSS2 Gene

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Brachyolmia is a rare bone disorder primarily affects the spine. It is characterized by short trunk, short stature, scoliosis and generalized platyspondyly. There are distinct forms of brachiolmia inherited in autosomal recessive and autosomal dominant manner. One of the autosomal recessive form of barchiolmia is associated with PAPSS2 gene mutations, Brachyolmia Type 4 with Mild Epiphyseal and Metaphyseal Changes (BCYM4 MIM ID: #612847). The aim of this study is to report a further case of BCYM4 having a novel homozygous truncating mutation in PAPSS2 gene with clinical findings.
A 7 year-old girl referred to Marmara University Pediatric Endocrinology Clinic because of short stature and premature pubarche. She was complaining of back pain and uses colchicine with a diagnosis of familial mediterrian fever. She was born to consangiounus parents following an uneventful pregnancy. There was no similar case in the family. In physical examination, her height was -2.1 SDS, she had short tubular bones, pubic hair was at Tanner stage 2, axillary hair was present. Her DHEA (Dehydroepiandrosterone) DHEA-S (Dehydroepiandrosterone sulphate) levels were low. Vertebrate X-ray showed platyspondyly, irregular end plates, reduced interpedicular distance. Mild metaphyseal changes and short tubular bones were detected in long bone X-rays. She was diagnosed as BCYM4 with these clinical findings. PAPSS2 gene all exons and exon intron boundaries were sequenced via Sanger sequencing. We found a homozygous 13bp deletion in PAPSS2 gene. The mutation was not reported previously, however it causes a shift in reading frame of gene resulting a premature stop codon, it was interpreted as a pathogenic mutation.
Brachyolmia is a rare clinically and genetically heterogenous group of skeletal disorders. Fewer than a hundred cases have been reported to date which of most autosomal recessive cases were from Turkey. However it is thought to be underrecognized. Here we present this case to remind the clinical characteristic of BCYM4 and report a novel mutation in PAPSS2 gene.

Key Words: Brachyolmia, PAPSS2, Hyperandrogenism

P-151 - Three Patients with Persistent Microhematuria and a New Variant p.Gln936ter (c.2806C> T) in COL4A3 Gene

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Alport syndrome is an inherited, progressive disease with approximately 1/50.000 incidence of type IV collagen deficiency, resulting from mutations in COL4A3, COL4A4 and COL4A5 genes. The COL4A5 mutation observed in 80% of the cases shows the X-linked dominant inheritance. Mutations in the COL4A3 or COL4A4 gene are rare and 15% have an autosomal recessive and 5% have an autosomal dominant transition. Various ocular pathologies, bilateral sensorineural hearing loss and nephritis are expected in affected individuals. We present three female patients with 6(case1), 7(case2) and 4(case3) years of age who had a new mutation to contribute to genotype-phenotype correlation studies.
DNA was isolated from the peripheral blood sample of the patients and all exons of the COL4A3, 4A4, 4A5 gene and the exon-intron boundaries regions were amplified by PCR and sequenced with Sanger sequencing. Biochemical tests and radiological examination were performed.
There was no consanguinity between the parents of all three cases. Urinary examinations revealed erythrocyte positivity and case 3 had additionally proteinuria. There were no pathological findings in visual examination and renal ultrasonography. Kidney function test values were normal. Case 1 had a history of renal stone in mother, father, grandfather and uncle. Case 2 had bilateral sensorineural hearing loss of 20 db at frequencies higher than 2000 Hz in audiometric examination. Case1 was found to carry heterozygous c221G>A/p.Arg74Gln variant (X-linked dominant) in the exon 3 of the COL4A5 gene. The same mutation was determined in the mother, too. Case2 was found to carry heterozygous c.665C>T/p.Pro222Leu and c.4421C>T/p.Thr1474Met variants in the exons 11 and 46 of the COL4A4 gene. Case 3 was heterozygous carrier of a new c.2806C>T/p.Gln936Ter mutation in the exon 34 of the COL4A3 gene. To the best of our knowledge, this variant was not previously identified in the literature and might be pathogenic because it leads to early termination according to the ACMG guidelines. Genetic counseling was given to the families.
Genetic counseling, early diagnosis and treatment are very important for prevention of common complications in patients with Alport syndrome.

Key Words: Alport Syndrome, COL4A3 Gene, COL4A4 Gene, COL4A5 Gene, Persistent Microhematuria

P-152 - Terminal Osseous Dysplasia with Pigmentary Defects (TODPD) in a Turkish Girl with New Skin Findings

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Terminal osseous dysplasia with pigmentary defects (TODPD; MIM#300244) is an extremely rare, X-linked dominant, in utero male-lethal disease, characterized by skeletal dysplasia of the limbs, pigmentary defects of the skin, and recurrent digital fibromatosis of childhood. Delayed/abnormal ossification of bones of the hands and feet, joint contractures and dysmorphic facial features may accompany. A single recurrent mutation (c.5217 G>A) of the FLNA gene was identified as the cause of the disease. We here present the first TODPD case along with molecular data from Turkey with full blown phenotype who further exhibits unique additional findings, hypopigmented patch on the lower extremity following Blaschko's lines and smooth muscle hamartoma of the scalp.
3 months old baby girl was referred to medical genetic clinics due to skin findings, short stature, iris coloboma and limb deformities. At 3 months of age, she had short stature(-3.62SD), mild facial dysmorphism, partial alopecia, aberrant eyelashes, hypertelorism, right iris coloboma, depressed nasal bridge and two accessory frenulae was noted. She had brachycamptodactyly, overlapping toes and short/broad trunk with prominent arcus costalis. At the age of 8 months, bilateral skin colored nodules on the dorsolateral of the fingers were clinically diagnosed as digital fibromas. Malar atrophic papules were more prominent and hypopigmented patch on left leg was less noticeable. The biopsy of the alopecic area was consistent with congenital smooth muscle hamartoma. At the age of 15 months, radiograms showed bilateral abnormal ossification of metacarpals, scoliosis and S-shaped tibia. Also digital fibromas regressed and hypopigmented patch disappeared.
The patient was followed up from 3 months to 15 months of age. At first examination the most striking finding was the skin changes which were reminiscent of forceps marks, pigmentary spots on cheeks, alopecia and hypopigmented patch on the left leg. Skeletal findings were not prominent and there were no digital fibromas. Second visit at 8 months, digital fibromas, the hallmark of TODPD, were present. This observation underlies the importance of follow up of undiagnosed cases and dictates the clinical handle which led to the definite diagnosis at second visit would have been missed if the case was not followed up regularly.

Key Words: TODPD, Digital Fibroma, Filamin A, Smooth Muscle Hamartoma, Hypopigmented Patch

P-153 - A Case with Muscle-Eye-Brain Disease Considered to be a Rare Disease in Which Frameshift Mutation was Detected in POMGNT1 Gene Exon 16 Contribution to Diversity of Clinical Features

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Muscle-eye-brain disease (MEB), is a congenital muscular dystrophy-dystroglycanopathy (MDDG) syndrome characterized by decreased glycosylation of A-dystroglycan associated with the mutation of the gene encoding protein O-mannose-b-1,2-N-acetylglucosaminyltransferase (POMGNT1). The aim of this case report is to draw attention to the diversity of clinical findings of muscle-eye-brain disease (MEB) resulting from homozygous frameshift mutation in exon 16 of the POMGnT1 gene, accompanied by non-classical dysmorphologic and ocular clinical findings.
A 7-year-10 month-old male presented with severe motor and cognitive delay with intellectual disability. Our patient was the second child of a kindred couple. He had an 18-year old unaffected brother who was being treated for lack of 21-hydroxylase deficiency. In this family, two previous pregnancies were terminated due to severe fetal hydrocephalus.
In clinical examination microcephaly, micrognathia, enlarged nares, short forehead, prominent ears, hypertelorism, thin upper lip short neck, dental crowding, unilaterally talipes equinovarus right were found. His testicle on the right side was not palpable. The ultrasonographic evaluation revealed undescended testis. In the neuroradiological evaluation, there were classical features of MEB with cerebellar cysts, polymicrogyria and white matter changes. Ocular examination demonstrated right eye exotropia, severe dry eye, right corneal opacity and punctate epitheliopathy in both eyes. Although the fundus could not be observed on the right, there was a pale and small optic disc on the left. POMGNT1 gene analysis was performed with sanger sequence and frameshift mutation was detected in exon16. In the evaluation of in silico genetic prediction analysis with Mutationtaster and Clinvar, the present change was interpreted as pathological.
Only two cases of the same mutation with different clinical and ophthalmologic findings have been reported in the literature. Interestingly, these two cases have been reported from Turkey. This case is the third case reported from Turkey with the same mutation and describes the previously unreported dysmorphologic features, clinical and ophthalmologic findings in patients with MEB disease and supports the idea that there may be severe phenotypic-genotypic expression differences between individuals with the same mutation. It is important to adopt a multidisciplinary approach in coordination with pediatric neurologists, ophthalmologists and clinical geneticists due to various clinical problems in MEB patients.

Key Words: Muscle-Eye-Brain Disease, POMGNT1, Phenotype, Turkey

P-154 - Molecular Genetic Analysis of Hot-Spot Exons of DNAH5 Gene in Cases with Primary Ciliary Dyskinesia

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Primary ciliary dyskinesia is an autosomal recessive disorder characterized by the dysfunction of the axonal structure of motile cilia. The estimated prevalence of the PCD is 1/10.000-1/20.000 and affect both genders equally. The pathophysiological basis of PCD is the result of the deficient or dysfunctional structures of the cilia localized especially in the inner and/or outer dynein arms. Lack of ciliary movement or the immobilization of the cilia leads to absence of mucociliary transport that is associated with chronic upper and lower respiratory tract infections, male infertility and situs inversus. Till date, genetic mutations were mostly detected at DNAH5 gene in PCD cases. DNAH5 gene is located on 5p15.2, has 86 exons and encodes a protein for heavy chain of the outer dynein arm. Mutations in DNAH5 were detected in approximately 15-24% of all PCD cases. Therefore, we aimed to clarify the diagnostic rate of hot-spot exons in Turkish population.
We planned to sequence five hot-spot exons (#34, 50, 63, 76, 77) of DNAH5 gene by using Sanger sequencing in a cohort of unrelated 16 PCD cases who had wild CFTR gene. As a result of DNA sequencing analysis, the genotype-phenotype evaluation of the cases was done by using genotypic date in combination with phenotypic data. As a result of sequencing analysis of the 16 PCD cases, p.Ile4450Val variation was detected as homozygous state in seven of the cases (cases05, 07, 09, 11, 13, 14, 16) and heterozygous state in four of the cases (cases01, 02, 03, 12). Following the in silico SIFT analysis, it has been determined that this variant is tolerated with a score of 0.254. Moreover, the allele frequency of p.Ile4450Val variation in ExAC has been observed as~0,5. No pathogenic variations were detected in any of the PCD cases. In Turkish population, as the consanguineous marriage rate is high (18.5-40.7%), genetic diagnosis of recessive diseases like PCD is of great importance. Based on this, we believe that screening the other related genes as well as other exons of DNAH5 will reveal more information for the genetic background of PCD disorder. Acknowledgement: This project was supported by TUBITAK-2209-A [Project # 1919B01100081].

Key Words: Prımary Ciliary Dyskinesia, DNAH5, Molecular Genetics, Sanger Sequencing

P-155 - A Case of Schmid Type Metaphyial Dysplasia

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Schmid type metaphyseal chondrodysplasia is a disorder characterized by irregularity and widening of metaphyses inherited as OD, which results in moderate short stature and the final height varies between 130 and 160 cm. Depending on the mutations in the COL10A1 gene, the three-stranded strands of type X collagen are disrupted and the extracellular transport of type X collagen are impaired and the endochondral ossification is adversely affected.We present this rare disease to contribute to the literature.
A 2-year-old male patient was referred to us because of the short stature, genu varum and tibial bowing.Neuromotor development was found to be compatible with the peers. Physical examination revealed a height of 77.7 cm (<3 p), weight of 13.5 kg (50-75 p), and a head circumference of 47 cm (10 p).In the skeletal X-ray films of the patient, irregularity was observed in the metaphyseal contours .
Peripheral blood samples were taken from the patient and the DNA was isolated and all of the exons and the exon-intron junctions were amplified by PCR and sequenced by Sanger sequencing. Routine biochemical tests and necessary radiological examinations were performed.A novel heterozygotes (c.1768A>C (p.Thr590Pro)) variant in exon3 was The pathogenicity data of the variant is shared in the table. Similar phenotype was present in the father and his two aunts.
As far as we know, this variant has not been previously reported in the literature, bioinformatics and in-silico analysis data, allele frequency of the variant, clinical and laboratory findings of the patient were considered together, the variant was thought to be pathogenic.Segregation studies are continuing in family members. More information can be obtained as the number of individuals carrying the variant increases.

Key Words: Schmid Type, Metaphyial Dysplasia, COL10A1 Gene

P-156 - ADNP Gene in the Etiology of Syndromic Autism: A Case Report

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Autism spectrum disorder (ASD) is a neuropsychiatric disease with an estimated prevalence of 1-2%. ASD can be arisen by a single gene mutation in addition to multifactorial etiology. ADNP is one of the most frequently reported genes in genome-wide studies where genetic causes of ASD were investigated. The patients with ADNP mutations have intellectual disability, dysmorphic facial features and multiple organ system abnormalities in addition to ASD. Herein, we present a patient diagnosed with ADNP syndrome /Helsmoortel-van der Aa syndrome (HVDAS) via whole exome (WES) analysis.
A 3-year and 9-month-old boy with non-consanguineous parents had intellectual disability, motor delay, speech delay, autistic features including stereotypic movements and behavioural abnormalities, short stature, microcephaly, dysmorphic facial features, fifth finger clinodactyly, gastroesophageal reflux, chronic constipation and microgenitalia. Metabolic screening, cardiologic evaluation, hearing and visual tests were normal.
The heterozygous c.190dupA (p.T64Nfs*35) (rs886041741) mutation was detected in exon 4 of ADNP gene (NM¬_015339.4) via WES analysis and the variant was interpreted as pathogenic. The variant was found de novo by Sanger sequencing analysis from the parents.
HVDAS, which mainly presents with neuropsychiatric system findings, can cause problems such as cardiovascular, endocrine, immune, genitourinary, musculoskeletal and gastrointestinal systems, as well as vision, hearing, growth, nutrition and sleep problems. In addition to neuropsychiatric findings, our patient had dysmorphic features, gastrointestinal and genitourinary system anomalies and feeding and growth problems. This case is presented to raise awareness about that HVDAS is a condition mainly diagnosed with WES analysis instead of clinical diagnosis and therefore less frequently reported than it should be.

Key Words: ADNP, Helsmoortel-Van Der AA Syndrome, Syndromic Autism

P-157 - Deletion of the SOX3 Gene Causes Panhypopituitarism: A Case Report

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Microduplications containing the SOX3 gene and intragenic SOX3 duplications cause pan hypopituitarism which can be accompanied by intellectual disability (OMIM: 300123, 312000). Here we present the first panhypopituitarism case with the deletion at q27.1q27.3 region of X chromosome including SOX3 gene.
A 15,5-year-old boyhad growth retardation, delayed puberty, panhypopituitarism, behavioral problems and a mild history of language development. It was learned from the anamnesis that school success was low and social relations were poor.
Array CGH (Agilent ISCA 8x60K) analysis showed a 3,961 kb deletion of X chromosome on the region of q27.1q27.3 including SOX3 gene.
Duplications on the q27 region of chromosome X including SOX3 gene cause panhypopituitarism, learning disabilities, and intellectual disability. Intragenic duplications that lead to loss of function also cause panhypopituitarism. That is, both the high dosage and loss of function of the SOX3 gene are responsible for panhypopituitarism. It was implied that the deletion caused by the null variant in the SOX3 gene in our patient was responsible for panhypopituitarism, behavioral problems and speech delay. Other genes in the deletion region have not yet been directly associated with any disease. In the DECIPHER database, a male patient with a deletion of 5.33Mb, which included the SOX3 gene and largely overlapping with our patient, was described and the patient was reported to have facial dysmorphic features, cryptorchidism, speech retardation, mild global growth retardation, and stereotype. Our case was presented because of the first case of panhypopituitarism defined due to SOX3 deletion.

Key Words: Sox3 Deletion, Xq27.1q27.3 Deletion, Panhypopituitarism

P-158 - A Case of Thiamine Response Megaloblastic Anemia (TRMA) Syndrome

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Thiamine-dependent megaloblastic anemia syndrome is a rare autosomal recessive childhood-onset disorder. To date it has been reported in 50 families in the literature. Mutations in the SCL19A2 gene located at 1q24.22 disrupt the synthesis of thiamine carrier plasma proteins and cause disease. Thiamine response megaloblastic anemia (TRMA) syndrome is an Main clinical findings of the syndrome are megaloblastic anemia, diabetes mellitus and sensorineural deafness. Diagnosis is difficult because clinical findings can be observed in a number of other syndromes and early diagnosis is important in preventing some findings of the disease. In this study, we present a case that was diagnosed with TRMA as a result of re-evaluation in our clinic and confirmed by molecular analysis.
A couple who had a child with a clinical diagnosis of Wolfram was admitted to our outpatient clinic because of a healthy child request. They were first degree cousins. Their 8 year-old children had bilateral sensorineural hearing loss, Type 1 DM, and thiamine - responsive megaloblastic anemia without transfusion requirement and she has been followed-up with the diagnosis of Wolfram syndrome for years by another departments. However, WFS1 gene analysis and DEB test for megaloblastic anemia in the case were found to be normal.
On admission, her physical examination showed normal growth and mental development for the age. Her school success was good. After re-evaluating the clinical features it was considered that she could be TRMA syndrome because she had cardinal findings of this syndrome such as sensorineural hearing loss, Type 1 DM and megaloblastic anemia. She was checked for other systems abnormalities particularly ophthalmologic and cardiac anomalies, and myelodysplastic anemia which are reported to be accompanying findings. Molecular analysis of SCL19A2 gene which is responsible for TRMA syndrome was performed and Hom. c.242dup (p.Y18X) mutation was detected in the gene. Mother and father were found to be the carrier for this mutation.
Differential diagnosis of TRMA syndrome is important for its involvement with MDS and mitochondrial diseases. With early diagnosis and high-dose thiamine treatment, megaloblastic anemia and DM can be prevented, but hearing loss and other anomalies are permanent.

Key Words: THİAMİNE-İNDUCED MEGALOBLASTİC ANEMİA SYNDROME, WOLFRAM SYNDROME, DİABETES MELLİTUS, SENSORİNEURAL DEAFNESS, MEGALOBLASTİC ANEMİA

P-159 - A NOVEL MUTATION IDENTIFIED IN A CASE DIAGNOSED WITH TRICHORHINOPHALANGEAL SYNDROME

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An adult girl is consulted and so she is examined to diagnose who has short stature and anomalies in her hands. Here we present to report a novel mutation of a patient with a rare disease.
24 years old girl with short stature and brachydactyly is consulted to our polyclinic to be diagnosed.
Clinical genetics examination : Prominent and long eyelashes, short stature, bilateral brachydactyly, long face, bilateral pes planus, bilateral short hallux, short palpebral fissures, narrow thorax, small ears. She described that she has pain in her knees while walking. Medical history : It is understood that she has been followed up with diagnosis of anxiety, trigeminal neuralgia, migraine and anhedonia. Laboratory findings : High levels of ALP, LDH, IGF-1 and Pi. Radiology :Bilateral nephrolitiasis, hydronephrosis on the right side, flattening on cervical vertebra, rheumatismal valve disease Pedigree : Individuals diagnosed with migraine and asthma are frequent. No any other evident data detected. Clinical Genetics Preliminary Diagnoses : Sugarman Brachydactyly , Trichorhinophalangeal Syndrome, Aarskog-Scott Syndrome, Nicolaides-Baraitser Syndrome, Coffin-Siris Syndrome. Her karyotype was 46,XX and we performed entire gene sequence analysis of TRPS1 gene to diagnose Trichorhinophalangeal Syndrome. Molecular analysis revealed a heterozygous c.2732A>G (p.N911S) change. No data has been found in databases about this change. An opinion occurred that, this change is responsible for the clinical manifestation. Since, Trichorhinophalangeal Syndrome has autosomal dominant inheritance and there are some individuals with short stature in the pedigree, we determined that this change is a novel mutation and clinical findings comply with Trichorhinophalangeal Syndrome features. A novel mutation is described in a rare disease.

Key Words: Trichorhinophalangeal Syndrome, Novel Mutation

P-160 - Importance of Rare Compound Heterozygous c.12580t> C Variant in the USH2A Gene

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With the development of technology in recent years, significant advances have been made in the identification of pathogenic variants concerning retina, such as retinitis pigmentosa (RP), Leber congenital amarosis (LKA). In this study, the importance of the variant c.12580T> C, p.Cys4194Arg in the USH2A gene was investigated.
RP is a common retinal degeneration disease characterized by deterioration of rod and cone photoreceptors, leading to progressive loss of vision or adult blindness. Heredity may be autosomal dominant, recessive, X-linked and mitochondrial.A 38-year-old man diagnosed with RP reported that he had difficulty in driving in night and rainy weather, and difficulty in adapting to dark areas. In the pedigree analysis, there were no other individuals in the family and no RP complaints. LKA is a family of congenital retinal dystrophy resulting in severe visual loss at an early age.LKA is usually inherited in autosomal recessive retinal diseases. In the pedigree of a male patient who was diagnosed with LKA at the age of 6 years and also LKA in his 18 year old sister, the other 1 and 2 generation parents also have LKA history.
In this study, a multigen panel containing 87 genes related to RP was studied in two Turkish patients diagnosed with RP and LKA. The patient with RP was observed to be heterozygous with NM_206933(USH2A):c.9165_9168delCTAT and c.12580T>C .In the other patient with the diagnosis of LKA, c.12580T> C variant was observed.
c.12580T> C change has not been previously reported in the Turkish population.When ACMG criteria are taken into consideration, it is thought that this change may be probable pathogenic variant.The change in c.12580T> C has been previously reported in a single patient in the literature and is predicted to be one of the 'retinal-specific alleles'. All retinal-specific variants on the Usherin protein were localized in the Laminin Type EGF-Like Domain and Fibronectin Type 3 Domain.c.12580T> C variant is also located in this region.The findings of this study were thought to contribute to the interpretation of autosomal recessive conditions in the Turkish population.Large-scale studies are needed to understand the importance of such variants in the pathogenesis of RP and other retinal related diseases.

Key Words: Retinal Disease,USH2A,c.12580t>C,Next Generation Sequencing

P-161 - The Investigation of the Genotype and Phenotype Findings of Two Siblings with Wolfram Syndrome

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Wolfram syndrome is the association of juvenile-onset diabetes mellitus and optic atrophy, and is sometimes called DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). There are two types of Wolfram syndrome (type 1 and type 2) which are differentiated with different gene mutations. Type 1 is caused by mutations in the WFS1 gene, while type 2 is caused by mutations in the CISD2 gene. Both forms are inherited in an autosomal recessive inheritance. In our study, we aimed to compare the development, biochemical parameters and phenotype of two siblings these are 10-year-old a girl who consulted with diabetes mellitus and visual loss, and a 5- year-old boy who consult with diabetes mellitus.
Genotypes and phenotypes of two siblings were compared. The reflection of the same mutation to the clinic was discussed.
At drawn pedigree we found that parents of these sibling have 3th degree cousin consanguineous marriage.WFS1 gene analysis was performed because of pre-diagnosis of Wolfram Syndrome for these two siblings who were consulted different times to our clinic. The homozygous same mutation was detected in both of the WFS1 genes [NM_006005.3 (WFS1) : c.1541_1543delTCT (p.515delF) (p.515delPhe) (Homozygous)]. When we examine the developmental stages of these two children, mild retardation was detected, to be especially evident on girl . (Boy has started to walking at 14 months old and start to speaking one word at 12 month old and girl was started to walking at 15 months old and start to speaking one word at 18 month old). At the physical examination, microcephaly was detected at the girl but the head circumference of the brother was normal according to his age. At the same time sister have visual losing, but brother have not started such this complaint yet.
As seen in our study, phenotypic differences can be possible even among individuals of the same family with the same mutation. That's why; detailed approach is required when evaluating syndromic individuals. One important thing to be considered is that even though the individuals with the same mutation are siblings, the differences in clinical presentation should be taken into consideration. Each individual should be treated as a separate case. In addition, multidisciplinary and holistic approach is important for diagnosis.

Key Words: : Wolfram Syndrome, Diabetes Mellitus, Optic Atrophy, Didmoad

P-162 - Pelizaeus-Merzbacher-Like Disease (PMLD) Case with a Novel Mutation

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Pelizaeus-Merzbacher-like disease (PMLD) is a slowly progressive leukodystrophy that typically presents during the neonatal or early-infantile period with nystagmus, hypotonia, delayed development of motor milestones, speech delay, and dysarthria. Over time the hypotonia develop to spasticity that caused inability to walk. Cerebellar symptomes such as gait ataxia, dysmetria, tremor, head titubation, and dysdiadochokinesia are frequently seen at childhood. Most individuals have normal cognitive skills or mild intellectual disability but the two diseases have different genetic causes. PMLD is caused by homozygous or compound heterozygous mutations in the GJC2 gene and this is an autosomal recessive inheritance disease. The aim of this study is to present a patient with PMLD who has a novel mutation that has not been previously reported in the literature, stages of from symptom to diagnose.
A 13-year-old male patient was admitted to our genetic department with presenting problems of inability to walk, introversion and cerebral palsy. When he was 6 months old he presented with complaints of strabismus and head tremor and it was told that he was hypotonic by pediatrician. It was detected delayed development of motor milestones of patient (head neck control time at 6 months, unsupported sitting at 1 year), and delayed at the start of the speech was detected. (Started at 3 years old). The parents of the patient have consanguineous marriages and they are first degree cousins. At physical examination determined bilateral nystagmus, difficulty in speech and inability to walk. At MRI of the patient was seen hypomyelination and considered as metabolic neurodegenerative disease .
Pelizaeus-Merzbacher's disease and X-linked adrenoleukodystrophy disease were evaluated in the differential diagnosis. In the PLP1 gene analysis, which is the gene responsible for Pelizaeus-Merzbacher disease, no mutation was detected. Afterwards, a homozygous novel mutation was then detected in the GJC2 gene responsible for PMLD.
As seen in our patient, if we are sure about the clinically pre-diagnose , we must to analyze all the genes that can cause pre-diagnosed disease. This shows the importance of clinical examination before starting the test.

Key Words: Pelizaeus-Merzbacher-Like Disease (PMLD), Leukodystrophy, Neurodegenerative Disease