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Meeting Reports: Notes and commentaries on Turkish Medical Genetics Association and Cyprus Turkish Genetic Union Meeting

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Background

A momentous first step was undertaken by the members of the Faculty of Medicine and DESAM Institute from Near East University and Executive Board Members of Turkish Medical Genetics Association (Tıbbi Genetik Derneği) on February, 22th 2020 at the V. Internationally Participated Erciyes Medicine Genetics Days Congress in Cappadocia, Turkey. The purpose of this article is to essentially pinpoint the common difficulties and problems that the medical geneticists have been facing in North Cyprus and to emphasize some possible solutions which were discussed during the meeting between the two communities.

The first human genome sequence was established at the beginning of the third millennium. Since then advanced life sciences has been shaping economies, societies, bodies and minds. For many diagnostic and research laboratories in the developing world, a lack of funding and insufficient scientific knowledge of the governments, technical and logistical difficulties are just some of the major hurdles to establish molecular medicine laboratories and producing DNA sequence data.

Here, we introduce our case for North Cyprus and illustrate the problems of adjusting to the 'new molecular genetics era', since it is an example of a developing country that is striving to progress from an agrarian to an industrial and research technology development society. Cyprus, which is 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 minority groups including the Maronites, the Armenians, and the Latins. Given an account of 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. Turkish Cypriots are located at the Northern Cyprus which is *de facto* state that comprises the northeastern portion of the island of Cyprus. North Cyprus is recognized only by Turkey and considered by the international community to be part of the Republic of Cyprus. Due to its lack of recognition, ~350.000 population of Northern Cyprus is heavily dependent on Turkey for economic, political and military support. Past two decades, health tourism has been contributing to country's economy. Despite hosting well equipped hospitals and IVF centers, lack of legal regulations in medical genetics and genetic counseling fields have urged the aforementioned meeting.

Overall, two parties in the meeting have agreed that the establishment of Cyprus Turkish Genetic Association is necessary for rising awareness of the genetics field in the population, providing a common and strong voice to government for drawing attention to following developments in medical genetic diagnosis and enhancing the health-

care system in North Cyprus. We hope to achieve our mission through a number of community building activities including organizing seminars, symposiums and meetings with the support of the Medical Genetics Association in the future.

The Topics that were discussed at the V. Internationally Participated National Erciyes Medicine Genetics Days Congress

The technological advancement in genomic analysis and sophisticated sequencing tools have revolutionized the diagnosis and interpretation of genetic diseases within the past ten years (Cho et al., 2017). One of the key features of analysis in genetics is the association of sequence variation with heritable phenotypes. Genetic variations in the human genome can be observed in different forms such as single nucleotide changes or substitutions, tandem repeats, insertion and deletions (indels). Single nucleotide polymorphisms (SNPs), the most common genetic variations, are structural variants and often categorized as 'specific' and 'shared' based on their distribution in a single population or a range of populations. An SNP might be specific to an individual or a family or to a population or to an ancestral group. Therefore, population-specific SNPs might be critical while analyzing characteristic phenotypes and disease susceptibility/protection to a population (Choudhury et al., 2014). In light of the evidence from previous studies, a number of polymorphisms on several genes and rare genetic disorders have been previously studied in the Turkish Cypriot population. Also, some of these studies shed light on learning more about the association of different polymorphisms and the susceptibility of the Turkish Cypriot population to diseases such as cardiovascular conditions, dyslipidemia and hypercholesterolemia and obesity as well as understanding the molecular mechanisms of rare genetic disorders. As a result, a substantial amount of genetic data has been generated which requires storage in a population specific database that strengthens the curation, clinical interpretation and sharing of genomic data, therefore, lowering destructive errors or delayed diagnosis (Thorogood, Touré, Ordish, Hall, & Knoppers, 2018).

Turkish National Genetic Variants Database Consortium has been found under the presidency of Prof. Munis Dundar (Professor of Medical Genetics, Erciyes University, Kayseri, Turkey). The consortium is one of the commissions of the Medical Genetic Association, therefore, public and private medical genetic diagnosis laboratories have been providing genetic variation data to the consortium. As, the consortium have also been accepting the genetic variation data from Turkish Cypriot and Turkish populations living North Cyprus, Near East University has been an important part in this consortium.

Noticeably, high-throughput DNA Sequencing technologies such as next generation sequencing (NGS) have been very quickly adopted in majority of clinical laboratories globally (Petersen, Fredrich, Hoeppner, Ellinghaus, & Franke, 2017). Moreover, NGS platforms helps to examine gene panels, exome genome sequencing for disease-causing variations for many diseases such as cancer and rare disorders. During the meeting, the participants have been agreed that NGS technology should be also established since it is a breakthrough technology which analyzes genetic information easier, faster, and less expensive compare to conventional methods. Particularly, lack of genetic laboratory regulations, some private medical biochemistry diagnostic laboratories offer many genetic tests genetic tests which are not performed in North Cyprus. Firstly, the genetic tests should be requested from genetic laboratories or clinical geneticists and even then, the interpretation of these test results still remain a big problem for patients and their families. Therefore, further strategies should be developed between the two associations to find solutions for these important health-care problems.

Another relevant topic which was discussed at the meeting was the importance of a resident Clinical Geneticist in North Cyprus. Clinical geneticists work in hospitals and centers in cooperation with genetic counsellors and medical scientists to provide genetic services to the community (Kosztolányi & Cassiman, 2010; Paneque et al., 2017).
Unfortunately, currently there is no clinical geneticist working in North Cyprus. Consequently, with the implicit approval of Republic of Turkish Ministry of Health, Medical Genetic Association Executive Board Members have been agreed to appoint a clinical geneticist to refer patients for diagnosis and management of genetic testing in North Cyprus if it will have requested by TRNC Ministry of Health.

Discussion

The main purpose of this meeting was to bring together the executive members of Turkish Medical Genetics Association and Near East University Faculty of Medicine and DESAM Institute Members to point out the challenges and difficulties in genetic field in North Cyprus. During the meeting, The Congress President Prof. Munis Dundar emphasized the importance of the Cyprus Turkish Genetic Association establishment in order to find a solution and achieve the aims

that were mentioned above. Additionally, heterogeneity of members of the Cyprus Turkish Genetic Association is curial, therefore, all scientist or clinicians in the genetic field should be engaged in the process. Thus, it will become easier to convey the problems and challenges to the TRNC Ministry of Health as well as other institutions.

Undoubtedly, the executive members of Medical Genetics Association stated that they are always ready to convey their experiences with Turkish Cypriot Genetic Community. In order to do this, due to financial problems, education programs which will be held in North Cyprus can be arranged as a first step by Medical Genetics Association. Notably, sponsorships can be a powerful way of preparing educational programs such as symposiums and conferences with a huge number of participants. Therefore, Turkish Medical Genetic Association Members were advised to expand the potential research areas in TRNC. Clearly, if the right judicial mechanisms are followed, it will not take long time to establish the Cyprus Turkish Genetic Association. However, until then, there is still the option of being an associate member of Medical Genetics Society of Turkey, which was also debated at the meeting. Moreover, Molecular Medicine Philosophy Doctorate (PhD) program can be more modified according the Medical Genetics curriculum. In addition, clinical genetic diagnosis laboratory regulation standards and guidelines should be prepared under considering European Union Medical Laboratory Regulations. Finally, it was pinpointed that the communication and the distribution of work between the members of the Cyprus Turkish Genetic Community is very crucial.

Conclusion

In order to achieve the aims written above, all of the attendees agreed that the necessary establishment the Cyprus Turkish Genetic Association. Furthermore, a direct communication between the executive board of Turkish Medical Genetic Association and Turkish Cypriot Genetic Community has been emphasized. Subsequently, one of the board members or society member from Turkish Medical Genetics Association ought to be responsible from the progression during the establishment of the Cyprus Turkish Genetic Community in North Cyprus. Overall, important topics related to human health have been discussed and negotiated during the meeting. The meeting that gathered together two parties was successfully concluded with mutually agreed upon decisions.

V. International Participated Erciyes Medical Genetics Days Congress, Medical Genetic Association and Cyprus Turkish Genetic Community meeting participants:

The Congress President and the session moderator
Prof. Munis Dündar

The President of Medical Genetics Association and the chairperson of the session
Prof. Mehmet Ali Ergün

Medical Genetic Association Executive Board Members
Prof. Haluk Akın
Assoc. Prof. Gözde Yeşil
Assoc. Prof. Beyhan Durak Anas
Assist. Prof. Evren Gümüş
Specialist Dr. Taha Bahsi
Specialist Dr. Abdülkadir Bakır

Cyprus Turkish Genetic Community
Prof. Gamze Mocan
Assoc. Prof. Mahmut Çerkez Ergören
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Invited Speaker Abstracts

Do we use epigenetic marks as a biomarker in physiological and pathological conditions?

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Epigenetics refers to the inherited gene regulation that leads to phenotypic changes without altering the primary DNA sequence. Epigenetics mechanisms includes, DNA methylation, histone modifications and RNA modifications. DNA methylation is an epigenetic modification with an important role in gene expression, X chromosome inactivation, development and cancer. DNA methylation is a reversible modification on 5th carbon on cytosine. Diet, physical exercise, environmental factors, hormonal status affects and modulates epigenetic alterations. Differences in DNA methylation have considerable potential as a biomarker for a number of diseases imprinting disorders and cancer. The reversible nature of epigenetic modifications makes them important targets for a possible therapy targets in different conditions. In cancer, epigenetic alterations used as a guide for therapy. The present talk will focus on the role of the DNA methylation alterations on RANK/RANKL pathway in unexplained pregnancy losses, obesity and menopause. Potential epigenetic biomarkers and their association with these conditions will be discussed and their role will be highlighted with up to date literature and guidelines. Findings of these studies hold promise for the future development of new therapeutic and preventive approaches of these conditions.

Keywords: Epigenetics, Methylation, Biomarker

Biomolecular modeling in medical genetics: A case-based approach to the analysis of non-silent mutations in disease-associated genes

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One of the major challenges in modern genetics is understanding the consequences of the enormous quantity of variants being disclosed through sequencing projects. Non-silent, or non-synonymous, single nucleotide polymorphisms in human genes can result in phenotypes where the underlying pathological mechanisms may not be obvious due to the lack of mutant protein structures. A unifying theme in protein evolution is that function correlates more highly with structure than with sequence. Protein structures can therefore be considered as "molecular phenotypes" potentially linking genetic variants to human disease. Experimental investigation of the functional effects of disease-associated missense mutations on three-dimensional protein structures is a time-consuming and cost-intensive task. Such an investigation may well be facilitated by the implementation of a plethora of *in silico* tools which (i) allow for the modelling of amino acid substitutions in wild-type proteins and (ii) help analyze the interactions of the mutant proteins with their binding partners such as metal ions, small-molecule ligands, and other proteins. We present here, from our own cases, several novel variants associated with etiologies ranging from inborn errors of metabolism to connective tissue diseases. We start with a brief account on the previously established roles of the wild-type proteins of interest in human health. Then, we describe the steps, tools and techniques required to build the three-dimensional models that correspond to their mutant counterparts. Last, we discuss the use of the predicted models to better understand the relevant molecular and cellular mechanisms underlying human disease. We believe that our studies provide powerful and useful insights into the structural consequences of pathogenic non-silent variants and also allow for prioritizing further *in vitro* and/or *in vivo* research to functionally annotate these variants.

Keywords: Biomolecular Modeling, Computational Biology, Medical Genetics, Molecular Phenotype, Non-Silent Variant, Non-Synonymous Variant

Peptide nucleotide analogs and uses

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Peptide nucleic acid (PNA) is a DNA analogue consisting of various purine and pyrimidine bases that are artificially synthesized, bound by methyl carbonyl bonds to the repeat (2-aminoethyl) glycin peptide backbone. It was discovered in 1991 by Peter E. Nielsen et al. PNAs bind to complementary DNA or RNA in accordance with both Watson-Crick and Hoogsteen matching rules. These attachment patterns are duplex and triplex homopurine and homo primidine invasion. Because these analogs do not contain charged phosphate groups and neutral, they are bound very strongly to the target DNA and RNA even at low salt concentrations. PNAs stabilizing at acidic pH and having high thermal melting temperature are among the factors that give them affinity. PNAs provide capacity to block the activity of annatural polyamide backbone, polymerase, telomerase, reverse transcriptase, endonuclease and transcription factors. Therefore, both in-vitro in-vivo resistance to nuclesae and protease induced enzymatic degradation and high affinity characteristics make PNA an advantage as a diagnostic and therapeutic agent. In addition,the most important disadvantage in the use of PNA is its difficulty in the intake of cells. Many different entry mechanisms have been developed to increase the uptake of PNA into cells. The most effective of these is the CPP (Cell-penetrating peptide) method. With this, method, PNAs are delivered cobjugated to peptides (eg Polio-Arginine) that penetrate the target cell. PNAs have many uses. Some of these are those. 1) PNA as a therapeutic agent as antigen and antisense 2) PNA as FISH probe for diagnosis and detection 3) PNA used in the detection and treatment of multidrug resistant bacteria.4) PNA as biosensor. PNA studies targeting oncogenes and tumor suppressors that cause many cancers as antigens and antises have been conducted. PNAs inhibit the transcription factor by the binding to the promoter regions of the target genes by invasing triplex in antigen applications. PNAs that form triplex of homopyrimidine can interfere with transcription extension and lead to cut products. In antisense applications, PNA oligomers neither activate ribonucleas H (RNaz H) nor block RNA-induced silencing complexes (RISC), so there are diferent mechanisms rather than mRNA degredation. PNAs inhibit translation by RNA transport to the cytoplasm, initiation of translation, such as elongation process and ribosome set up. These inhibitory effects depend on the hybridization power and the well accessible sequence on the mRNA molecule (These sequence are transcription start codon AUG and 5' UTR). One of the application areas of PNAs is to act on alternative splicing mechanisms by blocking specific intron-exon junctions in the pre mRNA molecule, making exon skipping or insertion modifications leading to intron retention. Fluorescently labeled PNA probes are also used in the detection and diagnosis of various bacteria and yeasts by the anti-PNA FISH method, targeting species-species rRNA sequences. This method is a fast method compared to other bacteria and microorganism diagnostic methods. The therapeutic application of PNAs as anti-miR agents has proven to be effective in inducing anti-tumor effects, both in-vitro and in-vivo, aganist tumor associated miRNAs.In addition, PNA biosensor technology is promising for the fast and cost-effective detection of specific DNA sequences with point mutations. Peptide nucleic acids are a compound that is very similar to DNA but has many features in biotechnology and medical science. Considering the results of the studies with this hybrid structure, many obstacles still need to be overcome. Considering the development of PNA due to new technologies, it is thought that it will have the potential and importance that will open up different horizons in terms of new applications.

Keywords: Peptide Nucleic Acid, Cancer, Gene Therapy,

Prenatal markers in infants with Down syndrome; evaluation in terms of genetic counseling

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Down syndrome (DS) is the most common of chromosomal disorders with the birth incidence 1:700-1000. The risk of giving birth to a baby with Down syndrome is investigated during pregnancy by prenatal screening programs. Maternal age, first ± second trimester biochemical screening test, non-invasive prenatal testing (NIPT) and ultrasound examination provide the risk assessment for having pregnancies with DS. Thus, approximately 60% of DS cases are detected prenatally. In this study, prenatal findings of 50 infants with DS diagnosed after birth were summarized retrospectively. All cases had typical DS phenotypic findings. Conventional karyotypes from peripheral blood samplings were performed to confirm DS diagnosis. Standard form of trisomy 21 was found in 46 cases (92%). Robertsonian translocation (RT) was detected in three patients (6%). All of them were de novo. Mosaicism was shown in only one case. The prenatal karyotype indications of the families are shown in Table 1. Among the 50 families, 44 (88%) were evaluated in the high-risk group, 6 (12%) were in the low-risk group. However, only nine families have had fetal karyotypes by chorionic villus sampling (CVS) or amniocentesis. Major congenital malformations were detected postnatally in 34 DS infants (68%). Prenatal and postnatal genetic counseling is extremely important in Down syndrome and hence detection of severe malformations is one of the most important factor affecting family decisions about whether or not to maintain the pregnancy.

Keywords: Amniocentesis, Chorionic Villus Sampling (CVS), Down Syndrome, Genetic Counseling, Prenatal Diagnosis, Prenatal Screening

Role of telomere length and Telomeric Repeat Containing RNA (TERRA) in etiology of Psoriasis

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Psoriasis is a chronic and recurrent inflammatory skin disease characterized by abnormal keratinocyte proliferation, vascular hyperplasia and infiltration of inflammatory cells into the dermis and epidermis. Although there are many studies showing the genetic transmission of the disease, it is not known exactly how this transition occurs. Genetic and immunological factors are thought to play a key role in the emergence of psoriasis. Tissue reaction in psoriasis involves complex immunological reactions resulting in epidermal hyperproliferation. Keratinocytes normally differentiate in about 40 days, whereas in patients with psoriasis, this process is 4-8 days. This suggests that the telomeres regions involved in cell division and the ends of chromosomes may play a role in keratinocyte differentiation in psoriasis. Telomerase activity and telomere length play a role in cellular aging, human aging, and pathobiology of certain human diseases. It has also recently been discovered that RNAs which are not encoded long from the telomere regions (TERRA), are transcribed and that the TERRAs protect chromosome ends from degradation, provide genome stabilization, and play a role in cellular aging. In this study, telomere length and expression levels of TERRA molecules were determined comparatively from tissue samples taken from lesional and non-lesional from 20 patients with psoriasis and 15 healthy controls and the role of telomere function in the formation mechanism of psoriasis was shown.

Telomere length was determined by qPCR method after DNA isolation from tissue samples taken from patients and controls. TERRA expression level was determined by qPCR method from total RNA and DNA: RNA hybrid. As a result of the study, it was found that psoriasis patients had significantly shorter telomere lengths in tissues with lesion than tissues without lesion ($p < 0.05$). The length of the telomere in the non-lesion tissue was the same as in the healthy control, whereas the length of the telomere in the lesioned tissue was shorter. In addition, TERRA expression was found to be increased in psoriatic patients with and without lesion skin tissues compared to the control group. As a result of this study, the role of epigenetic inheritance in psoriasis was clearly demonstrated by showing the expression difference of TERRA, which is a long non-encoded RNA, for the first time in the literature that telomere lengths were controlled locally in psoriasis disease and had an important role in genome stabilization. Psoriasis, which has no clear treatment yet, we believe that it will contribute to the diagnosis and treatment of the disease.

Keywords: Psoriasis, Telomere Lenght, TERRA

Genetics of aging

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Aging is characterized by the progressive loss of normal cellular function leading to an increased risk of mortality. Aging is a key risk factor for these chronic diseases and individuals who reach advanced age are likely to suffer from multiple chronic diseases concurrently. Loss of physical well-being leads to an increased risk of mortality and susceptibility to multiple age-related pathologies, including neurodegenerative disorders, cardiovascular disease, osteoporosis, sarcopenia, and cancer.

Recent studies have also shown that miRNAs regulate age-associated processes and pathologies in a diverse array of mammalian tissues, including brain, heart, bone, and muscle. MicroRNAs (miRNAs) have been increasingly recognized as important regulators of the aging process and modulators of longevity.

Research into the mechanisms of aging and longevity has focused on deterioration of DNA and protein quality control. RNA processing, especially pre-mRNA splicing is recognized as both an important contributor to the aging process and a real mediator of longevity interventions. The interplay between protein damage and its repair or removal from the cell may influence longevity and aging. Induction of heat shock proteins (HSPs), a conserved reaction to damaged intracellular proteins. HSPs protect the proteome by folding denatured polypeptides and promoting the degradation of severely damaged proteins. Activation of HSF1 is coupled functionally to fundamental pathways of longevity and orchestrates the evasion of aging through HSP induction and antagonism of protein aggregation.

A wide range of cellular functions are now known to be regulated by mitochondria, including multiple age-related processes, such as metabolism, unfolded protein response, autophagy, and inflammation.

One important and conserved aging mechanism is the nutrient-sensing pathway, of which the most important players are the insulin/insulin-like growth factor (IGF) and TOR (Target of Rapamycin). Insulin and IGF both signal the presence of nutrient such as glucose, and through a cascade of events, activates TOR kinase. TOR is the most important node of nutrient-sensing pathway. TOR is a pro-aging factor that is highly conserved throughout evolution, and has homologs with similar molecular functions in yeast, worms, fies and humans. Dietary restriction, or caloric restriction, which is known to efectively extend lifespan in virtually every model tested, functions partially by inhibition of TOR signaling.

Keywords: Aging, Protein Quality, Pre-mRNA, microRNA, Calorie Restriction

The relationship between the human genome and microbiome

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It is known that there are about 100 trillion microorganisms in the human body, consisting of bacteria, viruses, fungi and many micro-eukaryotes. The microorganism, where microorganisms formed by certain single-celled eukaryotes, such as bacteria, viruses and yeast, live in a specific place in the specific body of the human body, is called "Microbiome" and the entire microorganism population, genetic features and metabolites in the body are called "Microbiome". Factors effective in the formation of human microbiota are human genotype, birth type (vaginal / cesarean), hygiene status, diet (macronutrients, fibrous foods, phytochemicals, alcohol, etc.), some drugs (antibiotics, proton pump inhibitors, NSAIDs) and stress (social, emotional).

These microbial cells form a symbiotic "superoganism" with human and 90% of the human organism is composed of microbial cells. Microbiome elements with more than 3,000,000 different genes have the potential to encode proteome and produce metabolome much more than the human genome with about 22,000 genes.

The development of high-throughput sequencing technologies broke new ground in our possibilities to explore the compositions and dynamics of microbial communities that exist in different environments. The microbiota is unique to the individual. Each person has a microbial "fingerprint".

The functions of the intestinal microbiome are digestion and metabolism, energy and nutrient production, vitamin and metabolite production, protection from infections, maintenance of the intestinal barrier and immune modulation. In addition, low molecular weight compounds produced by microbiota by digesting nutrients change the substrate pool and change the activation of enzymes.

While the human genome is effective in deciding which microorganisms will form our microbiome, the microbiome is also effective on the functioning and evolution of the human genome. It shows the effect of microbiota on the human genome with epigenetic mechanisms-it changes the gene expression of the host.

It affects epigenetic mechanisms in two ways by changing the substrate pool used in epigenetic mechanisms to the microbiota or by changing the activation of enzymes and enzymes with the various metabolites they produce. The term "dysbiosis" is used for unhealthy microbiota that can develop as a result of many internal and external factors. While the studies examining the state of the human microbiome in the state of disease / health are quite new, these studies focus only on the relationship between the microbiome and the disease phenotype (human metabolism or disease dysbiosis regardless of its genome). For example, in atherosclerosis, obesity, type I and type II diabetes, Crohn's disease, inflammatory bowel disease, and colon cancer, the intestinal microbiome has been shown to be dysbiosis and take on a different metabolic character. In addition, it has been suggested that the intestinal flora has a complex communication effect through the autonomic neural, enteric neural, neuroendocrine and immune channels in interaction in the axis of the central nervous system and gastrointestinal tract. In case of dysbiosis, changes in these pathways; can contribute to the development of neurodegeneration, many neurological diseases such as Alzheimer's disease (AH), Parkinson's disease (PH).

Today, dysbiosis treatment options include prebiotics, probiotics and dietary interventions, and treatment strategies such as fecal transplantation.

In conclusion there is a constant and close relationship between microbiota and our various organ cells. It is one of the main actors of epigenomic regulation in the microbiota in the host (human). The human genome is also effective in the formation of the microbiota. Integrative studies targeting microbiome and genome will be the most important step of precision medicine.

Keywords: Microbiome, Genome, Dysbiosis, Epigenetic

Genetics of endothelium - vascular smooth muscle interaction: Lessons from ELMO2-related intraosseous vascular malformation

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Blood vessels are essential parts of almost every tissue providing oxygen and nutrients and removing waste products. Different calibers and types of vessels all include 2 primary cell populations: the endothelium which lines inside of a vessel and forms the blood-tissue barrier; the perivascular cells which vessel integrity and vascular tone. The formation of a blood vessel begins with endothelial proliferation which is followed by maturation that involves perivascular cell recruitment. The interaction between these perivascular cells, which are usually in the form of vascular smooth muscle cells (vSMC) in veins and arteries, are initiated and maintained by a plethora of signaling molecules. These molecules include paracrine factors such as Platelet-Derived Growth Factor, Transforming Growth Factor β, Angiopoietin, Sphingosines Phosphates, Hepatocyte Growth Factor and by cell-cell contact forming molecules such as Notch, Eph/ephrins and connexins. The disruption of the healthy relation between endothelium-vSMC is indicated in a variety of human disorders. Among them complex acquired diseases form the majority of the disorders, including diabetes mellitus, atherosclerosis, cancer and many more.

A rare group of inherited, or rarely acquired genetic disorders, usually in the form of vascular malformations, arise due to dysregulation between vascular cells. One such disorder, primary intraosseous vascular malformation (VMOS), is a rare autosomal recessively inherited disorder that arises as a result of biallelic loss-of-function mutations in *ELMO2*. VMOS is characterized by severe progressive life-threatening craniofacial vascular malformations and supraumbilical raphe. Until today, 8 individuals from 5 unrelated families with VMOS have been described. Pathological examination of the VMOS lesions reveals bones with abnormally expanded and malformed blood vessels lacking mature vascular smooth muscle layer. ELMO2 conveys extracellular signals to cytoskeleton and ELMO2-deficient cells have a significant downregulation of the associated partner DOCK1 leading to reduced activation of RAC1 - a key factor in controlling cell migration. Primary fibroblasts from an affected individual with VMOS show impaired cell migration, which is an essential process during angiogenesis, and this is rescued by external ELMO2 protein. ELMO2 is strongly expressed in vSMCs and in connection with its role in cell migration, it may have a critical role in the recruitment of perivascular cells. VMOS exclusively affects craniofacial bones which are formed through intramembranous ossification, sparing bones that appear through enchondral ossification. Interestingly, the comparative phylogenetic analysis points out that Elmo2 first appeared with the divergence of jawed vertebrates from other vertebrates and might have acquired novel functions in jawed vertebrates. Recent studies on detailed characterization of blood vessels indicate that morphologically similar vessel structures may be formed by vascular cells of different molecular make-ups in different tissue backgrounds. Thus, ELMO2 may be a specific factor for which loss-of-function cannot be rescued in the craniofacial bone environment.

Disruption of the complex structure of blood vessels including the tight relationship between endothelium and perivascular cells leads to a broad spectrum of disorders. New molecular signaling mechanisms and new levels of complexity between seemingly similar cellular structures expand our understanding of how blood vessels are maintained and tissue-specific disorders arise.

Keywords: Endothelium, Smooth Muscle, Vascular Malformation, Vascular Anomaly, ELMO2

Applications of mrecision medicine in reproductive medical practice

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Deciphering the relationship between clinical phenotypes and genes has changed the diagnosis, treatment, and follow-up algorithms of diseases. By using the advantages of genomic medicine approaches, we can classify the patients not only with their clinical phenotypes but also with their genetic background, and we can also provide personalized medical care options. The first application of personalized medicine was pharmacogenetics which showed us genetic variants are able to affect individuals' responses to drugs. The tailored medical approach is now being used in reproductive genetics to provide an opportunity for families to have healthy babies. Several applications of precision medicine in reproductive evaluation of families will be discussed during the presentation.

Keywords: Precision Medicine, Reproductive Genetics, Personalized Medicine

Unsatisfactory results in bariatric surgery: Is there any correlation with genetics?

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Obesity is a disease affecting energy intake, energy expenditure, metabolic efficiency, and reward pathways. Than it is a metabolic disorder resulting from behavioral and heritable causes. An overview of the genetics and epigenetics are associated with responses to obesity treatment, since the study of this field of medicine is constantly and exponentially growing with an evolution. We can see that genetic and epigenetic factors affect the outcomes of obesity treatment and transmission of the disease. At the same time, the current results are contradictory and far from conclusive because of ignorance of surgeons who don't follow the genetic knowledge trends causing failing to recruit data. Despite having a long way to go, the prospects are promising. With more and more studies being conducted, the introduction of precision obesity treatment is brought nearer. We can predict that, in the future, when receiving a new patient in our obesity department, we will be able to determine the patient's personal responses to the different treatments through genetic testing, so that we can choose the most appropriate method, from non-invasive to invasive. Also, in the future, genetic factors may provide a reliable pre-operative method of profiling patients who will successfully sustain weight loss. For today behavioral interventions and pharmacotherapies targeting the obesity mechanisms have had limited long-term success. In contrast, hard surgical treatments affects multiple physiological pathways, leading to substantial and sustained weight loss. Although the mechanisms underlying the clinical response to this procedure are not well understood, emerging evidence indicates that the observed effects result from surgery-induced changes in neuronal and hormonal regulation of energy balance rather than from physical restriction of food intake or malabsorption of ingested macronutrients.

After "HARD SURGERY METHOD" choices, the studies tell us that patients lose an average of 70% of their excess body weight, maintaining approximately 80% of this weight loss over decades. Such a prediction the genetic risk scores would be used for choosing the optimal surgical treatment for patients, avoiding unnecessary adverse effects and costs. Moreover, understanding of the profound response to the prevention and treatment should illuminate key features of the normal regulation of energy balance and body weight. Identifying these genetic mechanisms will facilitate the development of precision combined (pharmaceutical – genetics – surgical) obesity treatment.

Keywords: Genetic, Epigenetic, Bariatric, Surgery

Genetics of Parkinson's disease

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Parkinson’s disease is a complex and heterogeneous progressive disorder which is growing a health-care problem. It is the second most common neurodegenerative disorder after Alzheimer's disease. The estimated prevalence of the disease is 0.3 % in the general population. The incidence increases with age and the prevalence is 1% in people over 60 and 3.0 % in people older than 80 years. The mean age at onset is 60 years and it is more common in males. The condition is described as early-onset disease if the symptoms begin before age 50 and juvenile-onset Parkinson disease before age 20.The disease is characterised by bradykinesia, resting tremor, rigidity and postural instability. Parkinson's disease is caused by a progressive loss of the midbrain dopamine neurons in the substantia nigra. The aetiology in most of the cases still unknown and the majority of patients are classified as idiopathic Parkinson's disease cases, but different genetic causes have been identified in approximately 5%–10% of cases. Familial forms of the disease are highly penetrant and usually related with the early onset of the disease and atypical symptoms. Family history is an important risk factor and the relative risk in first-degree relatives increases nearly three times compared to control groups. Up to date, a total of 23 loci and 19 causative genes have been reported to cause Parkinson's disease. There are autosomal dominant and autosomal recessive forms of the disease, the inheritance patterns differ depending on the genes involved. *LRRK2*, *SNCA*, *PINK1*, *PARK2*, *PARK7*, *PLA2G6*, *FBXO7*, and *ATP13A2* genes are the most common known genetic cause of the disease. By the help of the genetic researchs, understanding of the etiology of the disease and besides etiology based therapeutic approaches will improve.

Keywords: Parkinson’s Disease, Genetic, SNCA, Parkin, LRRK2

Mechanisms of chromatin remodeling

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Chromatin is a highly conserved molecular structure that provides genetic information to regulate cellular functions. Being composed of DNA, histones and interacting proteins, chromatin is inherently dynamic and subject to remodeling processes. These include reconstruction of nucleosomes, enzyme-induced covalent modifications of histones, and repositioning of nucleosomes. In the human genome, approximately 3% of all the genes (>500 genes) are annotated with gene ontology terms: chromatin binding, chromatin remodeling, and chromatin modification. Therefore, it is not surprising that chromatin remodeling plays an important role in the regulation of many physiological functions such as development and maintenance of cell identity and function. Impairments of chromatin remodeling machinery caused by inherited or acquired mutations is observed in a wide range of human disorders including intellectual disabilities, neurodevelopmental and neurodegenerative disorders, immunodeficiencies, and cancer. In this talk, general overview will be provided about the nature and basic mechanisms of chromatin remodeling, which is an active area of discovery in genetic research. In addition, the influence of chromatin structure on gene expression will also be discussed.

Keywords: Chromatin Remodeling, Epigenetics, Mechanism

Chromatin remodeling in the development process of haematologic malignancies and related therapy targets

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Hematological malignancies make up an important part of human malignancies. Leukemias due to their easy sampling property are genetically one of the most studied malignancies in human beings. Leukemias are classified basically according to their cell origins and consequently to subtypes based on cytogenetic and molecular genetic alterations that are important in the diagnosis and follow-up of patients. Even in the leukemias with well-known underlying molecular mechanisms, subclonal alterations or unresponsiveness to the treatment agent can be seen. In the last decade epigenetic studies of hematological malignancies have successfully revealed genetic alterations which affect chromatin packaging and hence expression levels of oncogenes or tumor suppressor genes. These new markers have the potential to be used in the combination therapies as a target.

Studies in this field mainly consist of haematologic counterpart of basic epigenetic mechanisms which could affect chromatin remodeling, like histone modifications, DNA methylation, non-coding RNAs. Some selected researches related with different mechanisms are mentioned below;

Acetylation and methylation of transcription factors STAT3 and STAT5 proteins modify other transcription activating or repressing proteins which they contact, and as a result gene transcription is regulated by chromatin remodeling. Demonstration of mutations affecting SWI-SNF nucleosome remodeling complex associated with unresponsiveness to ibrutinib treatment in mantle cell lymphoma, led to the discovery of new therapy targets for relapse/refractory states of the disease.

Histone H3 Lysine 4 presenter protein WDR5, interacting with MLL, activates the transcription of a number of oncogenes as a consequence of its effect on chromatin remodeling. Several MLL/WDR5 protein-protein interaction inhibitors have been confirmed to reduce H3K4 trimethylation.

Combined therapy with HADC (histone deacetylase) inhibitor and menin-MLL interaction inhibitor was shown to have high-synergistic anti-tumor activity against human MLL-rearrangement AML cells invitro and invivo.

Poor prognosis related to iAMP21 could be related to chromatin remodeling genes CHAF1B and SON. The clinical differences between NPMc+ and t(3;5)NPM-MLF1 translocation have been explained with different chromatin remodeling effects of each.

The oncogenic effects of core binding factor leukemia are related with chromatin remodeling which is shown to change oncogenic transcription. Also the expression profile diversity between RUNX1-RUNX1T1 and CBFB-MYH11 fusion proteins could be explained with their core complex organizations which have different connections with various regulatory proteins.

BET proteins are subgroup of BRD proteins which are reader proteins of histone modification. They are important regulators for critical oncogenes related with haematological cancers. MYC and CCND1 expressions are mediated by BET proteins. For this reason some leukemias which have the chromosomal rearrangements related with these oncogenes are candidates for BET inhibitor therapies.

The researches in this field have accumulated rapidly. Regarding the point of improvement in haematological malignancies, reevaluation of well-known mechanisms of many genetic alterations with their potential effect on chromatin remodeling and on indirectly altered gene expression profile, should guide the pathway in the development of new molecular therapy targets especially in the unresponsive leukemias.

Keywords: Chromatin Remodeling, Haematologic Malignancies, Therapy Targets

Genetic etiology of epilepsy

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Epilepsy is a chronic neurological disease characterized by spontaneous and recurrent seizures resulting from abnormal and excessive electrical discharge in cortical neurons. An epileptic seizure manifests itself in sudden changes in sensory-motor functions, behavior, memory and consciousness. It is stated that epilepsy is the most common neurological disease in childhood and adolescence, and the second most common in adults after brain vascular diseases. Epilepsy is a common disease that affects 4% of people in a certain period of their life. The incidence of lifetime epilepsy development is reported as 3% and its prevalence is around 0.5%. Although there is no exact data on the prevalence of the disease in our country, it has been reported that it is observed in the society in general at a rate of 0.4-1%. Epilepsy is a disease with clinical heterogeneity.

Epileptic seizures are classified into three different types according to clinical course as follows; Partial (partial-focal) seizures, in which only a certain part of the brain is affected and not always accompanied by loss of consciousness,: generalized seizures and unknown (unclassifiable)-Genetic, in which always progress with loss of consciousness. Idiopathic generalized epilepsies (IJE) are a group with variable phenotype, characterized by age-related absence, myoclonic (atonic) and generalized tonic clonic seizures. IJEs cover about a third of all epilepsies, most of which begin during childhood or adolescence. Absence of attacks (petit mal) are shaped by sudden stops in activity, loss of expression on the face, and disappearance of consciousness. Myoclonic epilepsy refers to involuntary, sudden and rapid contractions of muscle groups. These seizures can only be on the face, one or more limbs in the trunk or generalized. Generalized tonic-clonic seizures are also known as 'grand mal' seizures. This form of seizure comes to mind when talking about epileptic seizure among the public. The tonic period of the seizure is when the person is stiff. After a minute, the clonic period begins. This period progresses as the muscles contract and relax.

Genetic Epilepsy; This group, previously referred to as 'idiopathic', is now considered the single gene or complex inheritance that causes epilepsy, with the development of next generation genome analysis methods. Its incidence in the population has been reported to be 0.3-0.5%. The best example of the relationship between single gene defects and epilepsy are mutations that occur in genes that encode ion channels subunits. The most important of these are reported as *KCNQ2*, *KCNQ3*, *SCN1A*, *GABRA1*, *GABRA2*, *SCN1B*, *SCN2A*, *SCN9A*, *SLC2A1* genes.

However, with the emergence of developing technology, hundreds of new genes and mutations associated with epilepsy have been identified. With next generation DNA sequencing systems, ultra fast sequencing can be done with high accuracy. The genomic data obtained by this method provides researchers with rich and unique information that cannot be obtained by any other experimental method.

Keywords: Epilepsy, Genetic, Seizures, Next Generation Sequencing,

Genetics of schizophrenia

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Schizophrenia is a complex disease that have both genetic and environmental factors etiologically and characterized psychosis, cognitive disorder and negative symptoms. It involves young adults with ages between 16 and 30. It is common as 1 % of populations in worldwide. The adoption and twin studies have been clearly proposed the role of genetic factors in the etiology of schizophrenia. The observed familial risk patterns suggest that multiple genes play main role in the predisposition to schizophrenia. Single locus contribution seems like minimal. On the other hand, the heritability is higher as 0.80 in the schizophrenia. However, the highest risk is in the identical twins, the contribution of the candidate genes to increase risk is minimal and about 2-3-fold of population risk. The recent strategies in the studies of schizophrenia genetics have been evaluated in this presentation. It has been emphasized that manageable environmental factors of schizophrenia.

Keywords: Genetics, Schizophrenia, Etiology

Monogenic and polygenic obesity

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Obesity is a worldwide epidemic with rates nearly doubling over the last 30 years. Recent World Health Organization (WHO) data from 2016 estimates over 1.9 billion adults are overweight or obese. In addition, more than 41 million children under the age of five were overweight or obese. Studies of twins, adoptees, and families all suggest the existence of genetic factors in humans with obesity. Obesity is a heritable trait, but the genes that contribute to the more common forms of obesity have been a challenge to identify. The heritability of obesity estimated from twin studies is high, ranging from %60-90 with only slightly lower values in twins raised apart compared with those raised together. Similarly, in adoptees, the body mass index (BMI) correlates with that of their biologic parents rather than that of their adoptive parents.

There are several types of obesity. The most common is a polygenic type of obesity, which is caused by a combination of genetic and environmental factors such as high-fat diet and sedentary lifestyle, with alarming prevalence and serious complications. This type of obesity is called common or complex obesity. In polygenic obesity multiple gene defects interact with the environment.

The first GWAS-derived loci to be reported were intronic variants in FTO (fat mass and obesity associated) and a variant 200 kb downstream of MC4R. To date, genome-wide association studies (GWAS) identified more than 90 loci related to complex obesity that account for approximately 2.7% of BMI variation.

Conversely, Monogenic obesity is described as rare and severe early onset obesity with abnormal feeding behavior and endocrine disorders. This is mainly due to autosomal recessive mutations in genes of the leptin-melanocortin pathway which plays a key role in the hypothalamic control of food intake. Melanocortin 4 receptor defects (MIM *155541) are the most common but are still rare, contributing to obesity in approximately 2 to 6 percent of individuals with early-onset obesity. Mutations causing deficiencies in leptin (MIM #614692) or its receptor (MIM #614963) are rare and usually are associated with consanguinity.

Symptoms of LEP and LEPR include hyperinsulinemia and intense hyperphagia coupled with aggressiveness if food is denied. These patients have undetectable serum leptin levels, as well as other endocrine abnormalities such as hypogonadotropic hypogonadism and hypothalamic hypothyroidism, abnormal puberty, low blood pressure and final adult height is shorter than normal.

MC4R mutations are reportedly the most common monogenic cause of dominantly inherited severe early-onset obesity in humans. Carriers of pathogenic MC4R mutations present with severe early-onset obesity, hyperinsulinemia with euglycemia, a higher prevalence of MetS (as high as 68%), increased use of antihypertensive medications, and oftentimes binge eating disorder, among other clinical phenotypes. Interestingly, the severity of these phenotypes seems to partially decline as subjects age.

Proopiomelanocortin (POMC) deficiency in humans has the following characteristics: Severe early onset obesity, adrenal insufficiency, red(ginger) hair, skin hypopigmentation, neonatal hypoglycemia, seizures, cholestasis and voracious appetite and increased frequency of metabolic syndrome (MetS).

Syndromic monogenic obesity is rare and featuring obesity and mental retardation, dysmorphic features and organ-specific abnormalitiesUp to now over 25 syndromic forms of obesity have been identified. Prader Willi (Like) Syndrome, Bardet Biedl Syndrome, Fragyl X syndrome, Cohen syndrome Albright's hereditary osteodystropia, Carpenter Syndrome, Alström Syndrome etc.

Genetic forms of obesity are important to diagnose because they need a specific management based on multidisciplinary teams which is to be set up as soon as possible. There are several medications in trials for individuals with genetic causes of obesity. Bariatric surgery currently remains the most successful therapy for morbid obesity (with long-term follow-up initially in the expert surgical centre, essential for nutritional adequacy)

Keywords: Obesity, Monogenic, Polygenic

Molecular autospy: Importance of postmortem genetic testing
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A significant portion of unexplained death from the early developmental stage and sudden death cases result from an underlying genetic etiology, which may be determined through postmortem genetic testing. The application of genomic sequencing to investigate unexplained death during early human development and unexplained sudden deaths have been limited and have some challenges and difficulties. The diagnostic power of exome sequencing is well established. Even with a powerful exome sequencing technique; to have successful postmortem genetic results; an appropriate sample should be saved.

Clinical phenotyping is an essential clinical skill that is often aided by supplemental diagnostic approaches. During embryonic and fetal stages, detailed phenotyping can be challenging. Because of this reason fetal phenotyping is extremely important for accurate diagnosis. In our center if we do have a good quality fetal DNA we perform trio clinical or whole exome sequencing. Where no DNA was available from the fetus (fresh or frozen blood/tissue or paraffin embedded tissue), we perform molecular autopsy by proxy, i.e., through parental testing.

Inherited heart diseases can cause sudden unexplained death (SUD) in older and younger individuals. Our focus is cardiac channelopathies, which are characterized by lethal arrhythmias in the structurally normal heart, incomplete penetrance, and variable expressivity. Due to a lack of structural changes in the heart, channelopathies are often considered as potential causes of deaths in unexplained forensic cases. SUD comprise a normal heart at postmortem examination and negative toxicological analysis; therefore called ‘negative autopsy’. In our center we perform routinely extended-cardio panel sequencing in these molecular autopsy samples of the SUD cases.

Our Bursa Uludag University Genetic Diagnosis Center experience suggests that molecular autopsy in pregnancy losses and SUD cases is a practical and high-yield alternative to traditional autopsy, and an opportunity for bringing precision medicine to the clinical practice of perinatology and forensic medicine.

Keywords: Molecular Autospy, Genetic Testing, Unexplained Death

Targeting chromatin remodeling for solid tumors
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Epigenetic modifications alter gene expression. Epigenetic dysregulation is linked to the pathogenesis cancer. Unlike sequence changes, epigenetic alterations modify chromatin structure. This changes the accessibility to the DNA, modifying transcriptional activity and gene expression. The modification process of "epigenome" leads silencing of tumor suppressor genes or the increased expression of oncogenes. By high throughput techniques, mapping epigenetic alterations on a genome-wide scale became possible. Since epigenetic modifications are reversible, they can be targeted in chemotherapy sensitization and immune system modulation. FDA has approved various epigenetic drugs such as a DNMT1 inhibitor 5-azacitidine and a HDAC inhibitor vorinostat. This review will overview the epigenetic targets particularly in solid tumors and the clinical implications of targeting chromatin remodeling events.

Keywords: Epigenome, Solid Tumors, Chromatin Remodeling, Cancer Therapy

Genetic counseling models for different disease groups

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Genetic Counseling has now entered its 50th year as a profession. Despite its limited job description in the past it is now expanding and evolving to integrate into many different aspects of the genetics profession. Genetic counseling is the name of the process performed by the Clinical Geneticists and the Genetic Counsellors. In order to become a Genetic Counsellor, you must obtain a master's degree in Genetic Counselling. In Turkey, Genetic Counselling is performed by Clinical Geneticists.

Genetic counsellors will help patients in different ways which includes risk assessment, preparing for testing, communicating results, assisting in managing the disease and preparing them for communicating the information with their family. There are two main models of genetic counselling. One is the teaching model where the main goal is to educate the client. This model simplifies the human behavior and psychology and has a standard way of delivering information to all clients. On the other hand, the counselling model, brings about a client centered process where the process is tailored to the needs of the individual client. According to this model human behavior and psychology is complex and because of that we must understand each client separately and adjust genetic counseling accordingly. The Counselling model tends to produce better outcomes for the patient.

Most of the genetic counsellors work as general genetic counsellors and tend to be involved with all the diseases that come to the Genetics Clinic. On the other hand, other genetic counsellors specialize in a specific field of genetics, such as cancer, and sometimes a specific disease, such as Huntington's Disease (HD).

Huntington's Disease predictive testing guidelines were established as early as 1994. These guidelines were used as a standard for other predictive testing guidelines including other neurodegenerative diseases, other late onset diseases and even hereditary cancers. HD testing protocol requires neurological testing, pre-testing genetic counselling, with extensive list of topics to cover and result giving session where the results are given to the person face to face and a post-test follow-up to see how the person is coping with the result, even if the results were negative.

Genetic counseling for hereditary cancer syndromes is one of the most investigated areas of genetic counseling as cancer related issues make up at least 50% of the workload of a general genetic counsellor. Most of the testing guidelines are established for BRCA 1/2 as they get of the attention. FAP, Li Fraumeni and HNPCC are also more established. The list of hereditary cancer syndromes is growing everyday as our understanding improves. However, genetic counselling in this field also has to adopt to the new circumstances created by the NGS technology. Data is being compiled to shape the new guidelines. New guidelines are also in progress for genetic testing in childhood cancers.

Chromosomal and Mendelian disorders make up another large portion of the genetic counselling field. Complex testing options, limited time and information could lead to consent with poor understanding of what is going on, especially in prenatal testing setting. Appropriate non-directive genetic counselling becomes very crucial in many of these testing circumstances to safeguard the rights and the interests of the patients.

In conclusion, Genetic counsellors are key professionals in the field of clinical genetics. They perform keys functions in patient support, communication of key information and coordination of healthcare services. Genetic counsellors would elevate the quality of service both for the clinical geneticists and the patients bringing about the best possible course of action for all.

Keywords: Chromosome Disorders, Clinical Genetics, Genetic Counseling, Hereditary Cancer Syndromes, Huntington's Disease

Molecular basis of the oocyte development in females with polycystic ovaries

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Polycystic ovary syndrome (PCOS) affects approximately 4-18% of premenopausal women. PCOS is characterized by disorders in gonadotropin levels, increased androgen levels, insulin resistance, chronic anovulation and abnormalities of the normal menstrual cycles. Typical features include ovaries with presence of multiple cysts. In addition to reproductive anomalies, there is an increased risk of developing several diseases, including type II diabetes and cardiovascular diseases (CVD). The underlying pathophysiology of PCOS has not been fully elucidated. Increased androgen levels and insulin resistance are thought to play a role in the development of PCOS leading to fertility problems. One of the underlying causes of anovulation is thought to be due to an increase in androgen levels. Thus, hyperandrogenism may cause anomalies in follicular development, anovulation due to low oocyte development and maturation. In this study, we aimed to investigate the gene expression levels of a number of genes that is functioning in steroidogenesis and in the maintenance of chromosomal end integrity.

The spare oocytes were collected from NEU Hospital IVF Center following controlled ovarian stimulation cycle. Antral follicle counts were reported following transvaginal ultrasound between days one to three before commencing the stimulation cycle. The collected oocytes were grouped into two, in such oocytes obtained from donors with polycystic ovaries were grouped into one and oocytes obtained from donors with no polycystic ovaries were assessed as the control group. DNA and RNA were extracted using RNA/DNA Purification Kit (Norgen, Canada) according to manufacturer's protocol. Each sample was quantified using NanoDrop technology. Reverse transcription of RNA obtained from oocytes was performed using TruScript First Strand cDNA Synthesis Kit (Norgen, Canada) according to manufacturer's protocol. Real time PCR was conducted using LightCycler® 480 SYBR Green I Master (Roche, UK). The expression levels of three mRNAs, TERF1, TPP1 and POT1, were analyzed in human MII stage oocytes obtained from oocyte donors aged between 18 to 30 years. The numbers of follicles and oocytes collected in the PCOS group were slightly higher compared to the control group. For each mRNA analysis, *ACTB*, the housekeeping gene, was analyzed as a control. PCRs with no cDNA samples were performed as negative controls. The results of this study showed that all three genes were expressed in human MII stage oocytes. Overall, the expression levels of TERF1 and TPP were similar between the two groups. However, the expression levels of POT1 gene was shown to be statistically different in the oocytes obtained from the patients who do not have polycystic ovaries ($p<0.05$).

Polycystic ovaries origin from complex mechanisms that involve both environmental and genetic factors. The results of this study showed that the expression levels of genes involved in the maintenance of chromosome integrity vary in the oocytes obtained from females with polycystic ovaries compared to the controls. The extrapolation of the results indicates that the differences in the expression levels of POT1 may cause anomalies in the chromosome integrity and may contribute to the formation of aneuploidies.

Keywords: Polycystic Ovaries, Gene Expression, Oocytes, Steroidogenesis

Developments for target treatment in breast cancers: FOXM1 signal pathway

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Forkhead transcription factor M1 (FOXM1) is a member of Forkhead family of transcription factors and it acts as transcription factor like the other FOX protein members. Transcription factor FOXM1 is involved in a wide range of biological processes including proliferation, apoptosis, and tumorogenesis. While in normal cells FOXM1 is mainly responsible for cell proliferation, in cancer cells it contributes to all hallmarks of cancer including cell survival, proliferation, migration, angiogenesis and resistance to apoptosis. So, FOXM1 is described as an oncogenic transcription factor and over-expressed in the majority of human cancers, especially triple negative breast cancer (TNBC).

Studies so far showed that over expression of FOXM1 induced malign phenotype by directly upregulation cell cycle related genes such as cyclin-D and cyclin-B in cancer cells. However, it is still unknown its exactly oncogenic activity in cancer cells. Therefore, we investigated roles of FOXM1 in TNBC cell biology. As different from literature findings, we found that FOXM1 is critical driver of breast cancer progression through regulating EF2K expression, Integrin-β1 expression and autophagic processes in TNBC cells.

According to our findings, considering role of FOXM1, it regulates multiple oncogenic pathways in aggressive breast cancer cells. Therefore, we believe that targeting FOXM1 may provide multiple effects and lead to more powerful therapeutic effects in patients with TNBC.

Keywords: FOXM1, EF2K, Integrin-, autophagy, triple negative breast cancer cells

Genetic pathogenesis of neuro-cardiac channelopathies

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Channelopathies occur when one of the proteins forming the channels does not function properly, either due to pathogenic genetic variant or acquired malfunction. Neuro-cardiac channelopathies refers to pathophysiological interplays of the neurological disorders and cardiac arrhythmias. Cardiac channelopathies are a group of clinical syndromes (including Long and Short QT Syndromes, Brugada Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia and Arrhymogenic Right Ventricular Cardiomyopathy) that affect the cardiovascular electrical system, specifically the cardiac ion channels (including Na+, K+, and Ca2+). Pathogenic variants in genes that either encode or regulate specific cardiac ion channels underlie different forms of inheritable arrhytmogenic disorders that occur in structurally normal hearts. Genetic neurological channelopathies cause many different neurological diseases (Epilepsy sydromes, ataxias, pain syndromes, motor and sensory neuropathies and skeletal muscle channelopathies) and are generally an autosomal dominant inheritance. Pathogenic genetic variants in ion channels are linked to cardiac arrhythmia syndromes, neurological syndromes, sudden infant death syndrome, and sudden unexpected death in epilepsy (SUDEP). Epilepsy is one of the most common neurologic diseases. Epilepsy patients are at an increased risk of mortality compared with the rest of the population. Standardized mortality rate in epilepsy patients is shown to be 1.6–9.3 times higher in this population. The leading cause of epilepsy-related premature mortality is SUDEP. Cardiac arrhythmia is the major cause of sudden unexplained death in the general adult population. During seizures (ictal phase), abnormal heart rhythms (mostly tachycardia, presumed sinus in origin) and various electrocardiographic changes have been observed in epilepsy patients.

In recent studies, the interaction between neurological and cardiac arrhythmias is becoming increasingly important, as the underlying mechanisms might be better explained. Ion channel genes such as *SCN5A*, *SCN1A*, *KCNQ1*, *HCN* (hyperpolarization activated cyclic-nucleotide gated channel genes) are expressed in the heart and brain, and the functional variants in these genes may contribute to SUDEP in epilepsy by predisposition to cardiac arrhythmia (5,6). In this report, the common genetic pathogenesis underlying neuro-cardiac channelopathies will be shared with the literature details and research experiences.

Keywords: Channelopathies, Arrhythmias, SUDEP, Gene Variants

Cloning, expression and function of human growth hormone

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Growth hormone (GH) is a 22 KDa hormone consisting of 191 amino acids released from the anterior pituitary gland. GH which has an effect on postnatal growth in mammals, is also involved in development, differentiation and protein, fat, carbohydrate metabolism. BH shows its functions through the Growth Hormone Receptor (GHR), located on the surface of bone, liver, muscle and adipose tissue cells. One of GH abnormalities is Growth hormone deficiency (GHD) which is caused by insufficient or lack of production of growth hormone in children and adults and the treatment with synthetic GH is applied for GHD patient. GH treatment is an expensive and it is imported from abroad.
Human GH (hGH) gene has been cloned in order to produce rGH and use as drug for GHD patients for first time in our country. hGH was expressed in both mammalian and bacterial cells. GH cDNA gene with or without signal peptide was synthesized from RNA isolated from blood leukocytes instead of pituitary gland tumor of acromegaly patients, cloned and expressed. GH genomic DNA was also cloned from human and the biological activity of GH encoded by GH genomic and GH cDNA genes was determined by luciferase assay. Also, GH-GST fusion protein was produced as rGH, purified, and the biological function of the fusion protein has been proven in cell culture. This project was supported by Marmara University research fund BAPKO.

Keywords: Human Growth Hormone, Expression, Recombinant.

The relationship between autism and *CC2D1A*

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Autism is defined as a complex neuropsychiatric disease. Although new information about the etiology has been acquired as a result of many studies conducted until today, the unknown on the subject is the most important factor affecting the treatment of the disease. The *CC2D1A* gene is a gene associated with intellectual disability that took its place in the literature for the first time in 2007 with a large homozygous deletion. This gene, which is shown to be expressed in various parts of the brain, is thought to have very important functions. In particular, it acts on the NF-κB signaling pathway and as a suppressor of the serotonin receptor gene. In our study conducted in 2016, it was determined that *CC2D1A* gene expression increased in patients and the expression of the *HTR1A* gene regulated by this gene decreased in patients. Thus, *CC2D1A* gene expression profile is differently regulated in autism. In the literature, both animal knock-out models of candidate genes and many animal model studies such as VPA models are found. However, the number of studies in the *Cc2d1a* knock-out mouse model is very limited. *Cc2d1a* was tested by behavioral experiments (open field, new object, tail-suspension, whole board, social interaction, Y-maze) where knock-out mice show autistic behavior differently from normal mice. How is autophagy regulated by the studies in this mouse model? How does the *CC2D1A* gene affect autophagy? How is autophagy regulated in different brain regions? How does the gender difference in autism reflect on autophagy? We aimed to find answers to such questions. When we investigated the transgenerational inheritance of autophagic markers in the hippocampus to compensate for the deficiency in this area, it was shown that there was a dysregulated autophagy mechanism. As a continuation of this study, it was determined that LC-3, Beclin expression levels significantly changed in different brain tissues (hippocampus, prefrontal cortex, cerebellum, hypothalamus) in the *Cc2d1a* mouse model, which was followed for three generations. Our study results indicate that neuronal autophagy is regulated differently than normal and differs in particular gender, while the *CC2D1A* gene acts as a new biological pathway in autophagy.

Keywords: Autism, Autophagy, *CC2D1A,* Mouse Models

Inherited retinal diseases and recent advances in therapy

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Inherited retinal diseases (IRDs) are a group disorders, which can result vision impairment or blindness. To date, more than 200 genes have been identified in this group. Common types of IRDs include Retinitis Pigmentosa, Leber Congenital Amaurosis, Choroideremia, Stargardt's Disease, and Achromatopsia. Although each disease in this group is rare, they are common totally. They affect individuals of all ages. Patients and families seek for treatment options and often demand preimplantation genetic diagnosis. Until recently, misdiagnosis and mismanagement of IRDs weren't rare due to lack of proper diagnostic evaluation. Advances in genetics changed approach to IRDs and treatment options are more promising for patients.

Eye has multiple advantages for drug trials: it is small, easily accessible and immune privileged. Besides, IRDs are slowly progressive, which provides time for genetic diagnosis and choosing the right treatment. Food and Drug Administration approved gene augmentation therapy Voretigene Neparvovec-rzyl for an IRD in 2017. It was also important for being the first gene therapy that was approved by FDA. It is an adeno-associated virus vector-based gene therapy to compensate the cells for the *RPE65* mutation. In addition, numerous other gene therapies are currently under development. Since there are many genes responsible for IRDs, more general treatment modalities will have to be developed such as deceleration of photoreceptor degeneration, stem cell and artificial retina.
Briefly, this presentation focuses on monogenic retinal disorders and therapeutic approaches with examples from our clinical experience.

Keywords: Inherited Retinal Diseases, RPE65, Therapy,

Problems encountered in array applications accompanied by sample cases and solution suggestions

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Cytogenetics, molecular cytogenetics and a-CGH / microarray techniques are complementary tools, operated within the sophisticated combination of equations in connection to clinical indications, time-frames, availability of resources, experienced specialist, and the accessibility of the family members if required to be included into the investigation for meaningful results; should not be considered within the irrational hopes.

In the last 40 years, diagnostic sensitivity of chromosomal anomalies has increased from megabases (mb) to kilobases (kb), with the use of new techniques applied in parallel to novel technological developments. In particular, the development and clinical application of a-CGH in the recent years have revolutionized the diagnostic management of patients and greatly facilitated the identification of the molecular basis of many genetic diseases. Due to these developments, molecular karyotyping began to replace the classical cytogenetic techniques in patients with mental retardation and / or congenital anomalies and in prenatal cases with abnormal ultrasound findings. Besides all these diagnostic advantages, there are some disadvantages such as erroneous or incidental probe hybridization or unexplored results of detections. In this context, it is necessary to develop appropriate algorithms for our country and to know the limitations of the technique thoroughly.

In this presentation, discussion environment will be conceived, and experiences will be shared along with the case illustrations.

Keywords: Array Application, Copy Number Variant, CNV, Deletion, Duplication

Digenic inheritance and mutational effects

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Genetic diseases can be classified into 5 major categories which are single gene disorders, mitochondrial disorders, chromosomal disorders, polygenic disorders and somatic cell genetic disorders. Single gene disorders result from mutations in a single gene of the nuclear DNA. They effect almost nearly 2% of all people while 0.7% of live births suffer from chromosomal anomalies which result from entire or segments of the chromosomes. On the other hand, somatic cell mutations which are mostly observed in cancer cells are caused by the mutations gene/s or chromosomes. There are also many monogenic disorders apart from typical simple Mendelian inheritance which include trinucleotide repeat disorders, uniparental disomies, mosaicism and genomic imprinting. Polygenic disorders, the most common genetic based situations, occur as a result of variations in a number of genes interacting with the environmental factors. They constitute nearly 5 to 60 percent of the population depending on age.

However, some abnormal conditions could not be explained by neither monogenic nor polygenic inheritance. Recent work revealed oligogenic disorders, describing diseases which are caused by mutations due to the mutations in more than one gene simultaneously which could be accepted as a bridge between monogenic and polygenic diseases.

Digenic inheritance is the simplest form of oligogenic inheritance. It may happen as diallelic, triallelic or tetraallelic fashion. For a digenic disease to occur, there should be two unlinked genes in which at least one allele of these two gene loci must contain a mutation. These two genes may code different subunits of a protein or they may act in different steps of the same functional pathway which result with abnormal phenotype as a consequence of mutations. Retinitis pigmentosa is the first human disease described with digenic inheritance. However, there are 54 diseases and 169 distinct genes which can be explained by digenic inheritance. Almost 67% of those variant combinations occur as diallelic, 30% triallelic and the rest tetraallelic. Very well known examples of this type of inheritance are Bardet Biedl syndrome, Deafness, long QT syndrome, Hirschsprung disease, Facioscapulohumeral muscular dystrophy and nephrotic syndrome.

It should be kept in mind that there are some clues to suspect from digenic inheritance. One of the most important of those is the observation of more than one affected individual in the same generation although there is no consanguinity between the parents. Nevertheless, coincidental occurrence of 2 separate entities or modifier genes which contribute to the severity of the phenotype can not be attributed to the oligogenicity as well.

In this review, basic information about digenic inheritance and two common examples such as retinitis pigmentosa and Bardet Biedl syndrome will be given.

Keywords: Digenic Inheritance, Oligogenic Inheritance, Phenotype

Genetic approach to neuromuscular disorders

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Neuromuscular disorders are a wide group of genetic conditions characterized by muscle weakness and pain due to progressive muscle degeneration. The mutations related genes display autosomal recessive, autosomal dominant and X-linked inheritance with clinical and genetic heterogeneity. By development of genetic technologies majority of the genes caused neuromuscular disorders are discovered so the DNA based diagnosis is essential for the patient with neuromuscular disorders instead of muscle biopsy. Elucidation of molecular pathogenesis of the neuromuscular disorders is important for follow up, treatment options and also prenatal diagnosis. In this lecture particularly latest genetic information besides briefly clinical features of the more common neuromuscular disorders which are muscular dystrophies, periodic paralyses, myotonia congenita, metabolic muscle disorders examples related with muscular findings will be mentioned.

Keywords: Genetics, Muscular Dystrophies, Neuromuscular Disorders

The role of mosaicism in false positive and negative cfDNA testing results

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Mosaicism is most important issue in fetal karyotyping. It is observed 0,2-0,4% in amniocentesis (AC) samples, but higher (1-1,5%) of chorionic villus (CV) samples. This difference is based on mosaicism confined to the placenta (confined placental mosaicism=CPM), where the anomalies found in placenta could not be confirmed in fetal tissues. CPM is classified as CPM I (anomaly restricted to cytotrophoblasts), CPM II (anomaly restricted to mesenchymal core cells), and CPM III (both cell layers showing the anomaly).

cf-DNA is the most sensitive prenatal screening test especially for trisomy 21 (T21). The scope of the test is expanded to the whole genome, and the problem of mosaicism in CVS is carried over to cfDNA testing. If cfDNA test result is not confirmed cytogenetically (false positive), it is explained by biological factors (CPM or maternal mosaicism) or technical failures.

Here, we report the cytogenetic follow up studies of 17 cases, in which the mosaicism was found as causing factor of discordant cf-DNA results. Out of 3 mosaic trisomy 21 (T21), one case was mosaic T21 in AC, which was performed due to the pathological fetal ultrasound findings (PatFUF), whereas cf-DNA test result was normal. Mosaic T21 was confirmed in the placental samples after the termination of the pregnancy (CPMIII). In the second case, CVS revealed normal result, but AC mosaic T21 (False negative CVS), which was confirmed in term placenta. Third case investigated by CVS due to the risk for T21 was mosaic for T21 in cytotrophoblasts by using direct preparation (DP), but long term culture (LTC) of the mesenchymal core and AC revealed normal results (CPMI), and healthy baby is born. In 2 cases, cfDNA test was positive for T13. In one case investigated by CVS, where DP revealed nonmosaic and LTC mosaic T13, but AC was normal (CPMIII). Second case was a twin pair with normal cf-DNA test result, but PatFUF in one twin pair. AC revealed T13 in affected fetus. Term placenta work-up exhibited mosaicism (True Mosaic). Out of 2 cases positive for T16, one was true mosaic, where both techniques of CV showed nonmosaic T16, and AC revealed mosaic trisomy. Second case had mosaicism in CVS, where DP revealed nonmosaic and LTC mosaic T16, but results of AC were normal (CPM III).

Out of 2 cases positive for T22, in one of them DP and LTC of CV showed nonmosaic, but AC mosaic T22 (true mosaic), and pregnancy was terminated. Second case was nonmosaic in DP, mosaic in LTC for T22 and normal in AC by karyotyping and I-FISH investigation (CPM III). Fetal growth retardation was observed in 3. trimester of pregnancy and delivered at 36 gestational weeks.

One case positive for T10 by cfDNA was nonmosaic by DP and normal by LTC of CV and AC (CPM I). One case positive for T4 was normal in AC. Due to the fetal growth retardation, pregnancy was delivered at 32. weeks of gestation and placental studies showed nonmosaic T4 in 3 regions, but mosaic T4 in one region closed to umbilical cord (CPMIII).

Keywords: Cell Free DNA, Confined Plasental Mosaicism, False Positive, False Negative

Combined PGT-M and PGT-A applications

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Preimplantation genetic diagnosis process for single gene diseases has started to be called PGT-M with new terminology. PGT-M protects the mother from medical abortion and shortens the time to reach a healthy baby. It allows simultaneous aneuploidy screening, which is one of its most important advantages. PGT-M is also preferred for the prevention of low-penetration conditions such as some familial cancers, and it also provides an advantage in preventing the late onset diseases, such as Huntington corea. In embryo transfer, if the priority is given to homozygous normal embryos, elimination of this recessive disease can be achieved in the next generations. Suspicious risks can be eliminated by eliminating class 3 variations with PGT-M. Performing WGA (whole Genomic Amplification) during PGT-M application allows aneuploidy screening simultaneously. However, it increases the risk of ADO (allele drop out) and thus the risk of false diagnosis simultaneously. Among the reasons that increase the risk of miss diagnosis, mosaicism, wrong embryo transfer, contamination, etc. can also be counted. The most effective way to eliminate ADO risk is to add informative marker (STR or SNP) analysis to the test. Preferring trophectoderm biopsy on day 5 instead of blastomere biopsy on day 3 is another important measure that reduces the risk of ADO.

Also, the addition of PGT-M primers to amplification during WGA is called the “Targeted Enrichment Protocol” and stands out as another application that reduces the risk of ADO. In the new terminology, the PGT-A process is an abbreviation used instead of aneuploidy scanning. Today, after PGT-M application, aneuploidy can be screened using array or NGS-based platforms from the existing WGA product. NGS-based aneuploidy screening has become the most preferred method since it provides monitoring of the mosaics and has higher sensitivity, specificity and reliability rates. It is of great importance to monitor the mosaics in embryos, as mosaic rates in general can reach very high rates in embryos, especially during the cleavage stage. Before these embryos are transferred, the patient should be informed about the risks in accordance with the relevant risk scoring and guideline recommendations, and then embryo transfer should be done. Because mosaic embryo transfer can cause mosaic aneuploid fetus risk as well as IUGR and UPD. Considering all these, very important benefits are provided by combining PGT-M and PGT-A processes. With the addition of PGT-A, the implantation rate and pregnancy success increase, the risk rate of pregnancy resulting with abortion decreases and thus, the time to reach a healthy baby is shortened. The risk of a baby with chromosomal anomaly is eliminated and also multiple pregnancy is prevented.

Keywords: Preimplantation Genetic Diagnosis, PGT-M, Aneuploidy Screening

Recombination effect and mutation accumulation in the human genome

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Meiotic recombination is essential for accurate chromosomal disjunction and maintenance of genomic stability during meiosis in eukaryotes. During meiosis, the recombination process is initiated by the introduction of DSBs at specific locations across the genome. High-resolution recombination maps revealed molecular characterization of recombination events through single and pooled sperm genotyping led to the identification and characterization of individual hotspots. With sperm genotyping, such areas were shown to correspond to clusters of recombination breakpoints spanning 1 -2 kb. Linkage disequilibrium (LD), the non-random association of alleles among different loci, is mainly driven by local rates of recombination. Furthermore, LD-based methods led to the identification of thousands of recombination hotspots genome-wide, whose location is associated with the distribution of a degenerate 13-mer sequence motif crucial in recruiting crossover activity in at least 40% of the human recombination hotspots and associated with genomic instability and disease-causing breakpoints. The 13-mer motif was inferred to be the binding site of a zinc-finger (ZnF) protein-the PR domain-containing 9 (PRDM9), a histone methyltransferase. Polymorphisms in the ZnF domain of PRDM9 were shown to be associated with alternative sequence motifs and underlie differences in the location of hotspots in human populations.

In humans, altered meiotic recombination is associated with large structural rearrangements, aneuploidies and infertility. DSBs at sites of recombination will sometimes be aberrantly repaired with non-homologous loci, in a process called non-allelic homologous recombination (NAHR), which results in structural rearrangements. NAHR can result in chromosomal inversions, translocations, duplications and deletions. These rearrangements are likely to dramatically disrupt genes and are for the most part deleterious. Genomic disorders associated with NAHR include Charcot–Marie–Tooth disease type 1A, neurofibromatosis type 1, Williams–Beuren syndrome, Smith–Magenis syndrome, hereditary neuropathy with liability to pressure palsies, DiGeorge syndrome, Prader–Willi syndrome, childhood spinal muscular atrophy and the 17q21.31 microdeletion syndrome. Many lines of evidence also suggested that PRDM9 variation correlates with instability in minisatellite repeats and with recurrent pathological rearrangements, such as 17p11.2 deletions/duplication events and 7q11.23 microdeletions. Additionally, PRMD9 A allele has been associated Charcot-Marie-Tooth, Hunter and Potocki-Lupski / Smith-Magenis syndromes. PRDM9 deficiency has been reported in two independent cases of azoospermia in Japan. This contrasts with the Pakistani woman with the homozygous null mutation, which is still fertile in PRDM9. Deciding whether these differences are gender-related or whether they reflect human variation in the presence of an alternative recombination route will require more data. However, PRDM9 C allele was found in the parents of children with B-cell acute lymphoblastic leukemia.

As recurrent microdeletions are associated with unusual specific patterns of meiotic recombination, we aimed to evaluate the role of PRDM9 variants as a risk factor for recurrent genomic disorders. Our results are compatible with previous findings which showing that variation in the ZF array of PRDM9 has a major effect on the frequency with which recurrent deletions. In conclusion, our study provides suggestive evidence that carriers of rare PRDM9 alleles may be predisposed to produce an increased frequency of offspring with deletions of Prader–Willi syndrome.

Keywords: meiotic recombination, mutation accumulation, PRDM9, Prader-Willi syndrome, microdeletion

Next Genereation Sequencing (NGS) applications in practice of clinical oncology

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Molecular genetic testing methods have become the most powerful tools for omics sciences. Among all the molecular genetic testing methods, next generation sequencing is the most reliable and frequently used in routine health care applications. NGS plays a significant role in a lot of diseases' diagnosis and treatment, particularly in the oncology field. NGS method has increased its popularity by providing high sensitivity and reliable sequencing with DNA and RNA which are extracted from a broad range of starting materials such as peripheral blood, tissue and liquid biopsy samples and also fusion studies. Moreover, it enables to sequence hundreds of genes and samples simultaneously. However, the correct choice of the patients and the testing with the right testing method and instrument is crucial in terms of personalized medicine. Concordantly, the results of NGS are analyzed in two steps; they are primarily evaluated for the technical sequencing quality controls independently with patients' clinical findings. Then secondary analysis is performed in terms of starting material and patients' clinical background. So that all the laboratory applications and the bioinformatics analysis together with the clinical reporting process requires to have a qualified technical team and geneticists. All the applications starting from bioinformatics analysis to clinical reporting should be performed due to international guidelines.

Within the scope of genomic medicine, multi-gene panels which are designed for different cancer types and genes that are possible therapy targets are essential. Determining personalized therapy options and alternative treatments regarding the possible resistance pathways are only applicable by NGS outcomes in routine health care services. In addition, these studies are not only limited to treatments, they can also provide important information about diseases' progression and possible disease predispositions. Thus, it becomes possible to counsel and follow-up not only the index cases or the patients but also the whole family and sometimes siblings.

Advantages of next generation sequencing cannot be underestimated when compared to conventional methods. As conclusion, increased biomarker and therapeutic studies and also more comprehensive and faster genetic testing with lower costs in routine health care services are provided as results of advanced NGS technologies.

Keywords: Cancer genomic profiling, precision oncology, molecular oncology, cancer genetics, NGS testing

Latest developments in NIPT tests

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Since the treatment method for genetic diseases is not yet available, the early diagnosis of these diseases is very important. Down syndrome is the most common chromosomal disorder. Its frequency is about 1: 700. Parallel to the increase in maternal age, the frequency of Down syndrome increases. The risk for a 40-year-old expectant mother increased to an average of 1:70. Amniocentesis is the most commonly used method in the prenatal diagnosis of Down syndrome. In addition, this method is the best known method for the prenatal diagnosis of Down syndrome. The classic reported complication rate for this method is 1: 300.

Indications for prenatal diagnosis:

- Advanced maternal age> 35,
- Positive result in maternal serum screening,
- Anormal ultrasound finding(s),
- Pregnancy history with aneuploidy,
- Parental translocation,
- Pregnant mothers who want to avoid invasive diagnostic tests.

Thanks to next generation technologies, the trisomies can be detected non-invasive. There are two main methods for detecting cfDNA: Massive parallel sequencing (Whole-genome sequencing, Targeted sequencing, SNP sequencing) and microarray.

Advantages of MPPS method: Test failure rate is low, analysis is done faster - results can be reached earlier, new content can be easily added to the test, high number of readings (10-30 M).

Disadvantages of Targeted MPPS method: High rate of failure, complex workflow and giving results in a longer time, adding new content to the test is difficult. It cannot be applied in egg donation and surrogacy cases, low numbers reading numbers (500K-6.4M).

Reasons for not getting results and getting wrong results for these tests. Low amount of cfDNA, Placental or maternal mosaicism, vanishing twin syndrome, cancer, some germline or somatic variants that may be interfere the analysis, and unknown twin pregnancy.

Over seven thousand genetic disorders can be evaluated with NIPT. Disorders that can be evaluated with newly developed panels are increasing day by day.

Keywords: NIPT, Non-invasive prenatal test, cfDNA, Massive parallel sequencing

Oral Presentation Abstracts

OP-20-101

The sexual and psychological conditions of male patients with klinefelter syndrome and vasal agenesis

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Klinefelter syndrome (KS) is characterized by azoospermia, small testes, gynecomastia, tall structure with eunochoidal body proportions and hypergonadotropic hypogonadism. Affected males carry an extra X chromosome, which result hypogonadism, androgen deficiency, and broken down of spermatogenesis. Congenital absence of the vas deferens is a post-testicular disease which may affect one or both vas deferens associated with agenesis of the seminal vesicles, and epididymal malformations. The congenital bilateral absence of vas deferens (CBAVD) can be suspected after scrotal examination and on the basis of semen analysis: semen volume <1.0 ml with an acid pH (<7) and absence of spermatozoa and of immature germ cells in semen. Patients with KS and CBAVD have similarities with their low ejaculate volumes. While this is due to testicular failure in patients with KS, the main reason is obstruction in patients with CBAVD. It is a matter of wonder that how low semen volume affects sexual functions in these patients' groups. The aim of this study was to investigate the sexual and physiologic conditions of patients with KS and CBAVD and compare them with the normal fertile healthy individuals using validated sexual function questionnaires.

Keywords: Klinefelter Syndrome, Vasal Agenesis, Sexual Dysfunction, Depression, Ejaculation Dysfunction

OP-20-102

Family screening of a child with Werdnig-Hoffman's disease by MLPA

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Spinal muscular atrophy is a group of autosomal recessive neuromuscular disease characterized by the loss of motor neurons. We determined telomeric deletion of exon 7-8 in *SMN1* gene by RFLP in a 5-month-old boy who was referred to medical genetics with a preliminary diagnosis of spinal muscular atrophy. In MLPA analysis, homozygous deletion was detected in *SMN1* gene of this child and SMN2 gene appeared normal. MLPA method showed heterozygous deletion of both *SMN1* and *SMN2* gene in his father, while *SMN1* and *SMN2* gene appeared normal in his mother. In order to explain this discrepancy, we applied MLPA analysis to the parent of the child's mother. Heterozygous deletion was detected for *SMN1* and 3 copies were detected for *SMN2* in the grandmother. Grandfather had 3 copies of *SMN1* gene and homozygous deletion for *SMN2* gene. Based on these results, we thought that his mother had inherited a single duplicated allele from her father for *SMN1* and she was the carrier (heterozygous deletion). This child had inherited deletive alleles from his mother and father (homozygous deletion) and he was diagnosed with Werdnig-Hoffman's disease. On the other hand, the child's condition quickly worsened. Respiratory distress developed and tracheostomy was performed. He did not respond to treatment. His mother had heterozygous deletion for *SMN2* due to inheriting a single duplicated allele from grandmother and the child had also heterozygous deletion for *SMN2*. This situation is likely to contribute to the clinical course of the disease.

Keywords: Werdnig-Hoffman's Disease, *SMN1*, *SMN2*, Deletion

OP-20-103

Lethal skeletal dysplasias

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Skeletal dysplasias comprise a wide group of diseases that can be classified in more than 400 types and 40 groups. They may be due to intrinsic / extrinsic causes and mainly divided into two major categories namely, lethal and non-lethal ones. Genetic causes have been identified in more than 70 % of cases. With the era of modern sonographic screening the prevelance seems to be increased during gestation reaching 7.5 in 10,000 pregnancies.

They are responsible for nearly 0.9 - 1.0 % of neonatal deaths and 5 % of the genetic defects diagnosed in the newborn period. The mainstay of diagnosis is ultrasound examination but further diagnostic modalities (MRI, CT etc.) may be useful. Second trimester is the ideal time for examination but late first trimester scan can be rewarding. Correct diagnosis is possible for more than 2/3 of cases. If the partially correct diagnoses are included this ratio reaches > 90 %. The most common lethal dysplasias are thanatophoric dysplasia, achondrogenesis and osteogenesis imperfecta type 2 which comprise 40 – 60 % of all lethal ones. There are four main sonographic features that have to be paid attention in order to perform optimal differential diagnosis after the criteria for lethality are met. These are bone mineralization, presence of macrocrania, short trunk and fractures. Thanatophoric dysplasia, the most common lethal one, should be suspected in case of a macrocranic fetus without bone demineralization, short trunk and fractures. Considering the wide specturum of these dysplasias, it is crucial to keep in mind that exceptional and overlapping findings may be present and may affect the precise diagnosis.

Chorionic villus sampling (performed transcervically at 11 to 14 weeks of gestation or transabdominally after 11 weeks of gestation) or amniocentesis (performed at ≥15 weeks of gestation) are methods for obtaining fetal DNA for molecular diagnostic testing for diagnosis of these approaches.

The role of molecular studies for diagnosis of a specific skeletal dysplasia in an ongoing pregnancy with no personal or family history is controversial since the time necessary for DNA analysis can be lengthy and a negative result or failure to identify a specific mutation does not change the clinical implications derived from the ultrasound findings.

Furthermore, mutations in the same gene can cause different forms of skeletal dysplasia and mutations in different genes can cause similar skeletal abnormalities. However, the use gene panels for fetal skeletal dysplasia, and the use of whole exome sequencing (WES) or whole genome sequencing (WGS) when there is no family history of a specific condition and when no specific diagnosis can be made based on fetal imaging makes molecular analysis an important diagnostic tool in cases suspected of skeletal dysplasia. Since the detailed fetal ultrasound has a high detection rate for lethal skeletal dysplasia, the molecular analysis in these cases is mainly needed for prenatal and preimplantation genetic testing for future pregnancies rather than for prognostication in the affected pregnancy.

Keywords: Lethal, Musculoskeletal Disease, Prenatal Diagnosis, Thanatophoric Dysplasia

OP-20-104

WES in a Family with vestibular problems and hearing loss

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Hearing impairment (HI) is quite heterogeneous genetically which hinder genetic counseling and molecular diagnosis. As anatomically there are lots of fibers in the vestibular system in the structures of the inner ear that sense equilibrium, such as the utricle and the saccule. The fluid in this area of the ear can sense where the head of the person is in relation to the gravitational pull. Organ of Corti is responsible for hearing. The cochlear system is the section that assists in hearing, and the vestibular system assists in maintaining and identifying equilibrium. Vestibular system is mainly responsible for balance and helps us when we stand and ensures us straight posture.

There are some vestibular system disorder in literature. Vestibular problems can be link to Meniere`s Disease, Migraine, Benign Paroxysmal Positional Vertigo, Anxiety Disorders, Cerebellopontine Angle Tumors (Vestibular Schwannomas), Lateral Medullary Infarction (Wallenberg's syndrome), Ototoxic Drug Exposure (aminoganglioside antibiotics, cisplatinum), Hearing Loss. Vestibular system impairment does not have to accompanied with these disorders but occurs mostly. To evaluate vestibular impairment in these disorders: caloric, rotational and positional tests are applied. Abnormal (increased or reduced, bilateral or unilateral) eye movements are investigated by specialist. *OTOG, PTPRQ, GRXCR1, GJB6, PJVK, SLC26A4, CLIC5, TMPRSS3, COCH, MYO7A, KCNQ4* genes are responsible for hearing loss and vestibular impairment in medical genetics literature. The genetics of vestibular impairment still not well-known. Last three genes are located in different DFNA (autosomal recessive) loci-family and while the others in DFNB (autosomal dominant) loci. Some mutations (not all) in these mentioned genes can cause vestibular disfunction and hearing loss (HL). In a family with hearing loss, balance problem and early motor delay, we performed Whole Exome Sequencing (WES) in two family members (II.1 and III-2) in order to find causative genes. Clinical features of family have been shown in pedigree in detailed. Hearing loss, early motor delay and balance problem were monitored in this family. Hereditary pattern was compatible with autosomal dominant inheritance. We filtered variants based on their phread 1 and 2 scores ≥80, total reads ≥5, % variation reads ≥20, %SNP/non causative ≤0.5, synonymous (false), gene component as exon, splicing acceptor and splicing donor at first. Then for missense variations, we filtered following; phylop ≥2.7, Houston %≤1.5 and included 29 out of 313 of all filtered missense variations. In candidate gene databases we confirmed 2 out of 15 and selected 8 genes out of 14 because of their deleterious features.

As to 303 splice sites variants after filtering Houston %≤1.5 and +8/-20 (donor/acceptor), among the 6 candidates only one gene is found to be as a candidate gene. In out of 392 indels, after filtering Houston scores ≤1.5%, only one out of five candidate genes included. Lastly among 3 stops none of found to be causative.

As a result, 4 different candidate genes' variants are found as causative for hearing loss and they all were all segregated and confirmed by sanger sequencing. In this family in terms of their filtering step results, condel and etc., exom variant server (EVS) values and their functions in the cell metabolisms.

The genes and their roles and their adventures in hunting process will be shared in this oral presentation.

Keywords: Gene Hunting, WES, NGS, Hearing Loss, Medical Genetics.

OP-20-105

A case with recurrent pneumonia and cystic lung disease

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Recurrent pneumonia is a life threatening condition in pediatric population having many risk factors as aspiration, immunodeficiency, and asthma. Having numerous different etiologies, it is hard to the diagnosis. Herein we had a case referred to our center with a preliminary diagnosis as surfactant deficiency syndrome having recurrent pneumonia and localized cysts at lung tissue.

A 6-year-old male patient who had recurrent pneumonia and a cystic lesion formation at his right lower lobe. His previous sweat chloride tests and genetic analysis for cystic fibrosis were normal. He was analyzed for immunodeficiency state and evaluated as normal and his vaccination schedule was complete. The patient had no atopic background and no family history.

A biopsy was planned for the patient to find the underlying pathology and at the biopsy material extensive emphysema, cystic changes, lymphoid aggregations, and lymphocyte infiltration were detected. The primary ciliary dyskinesias and surfactant deficiency were considered at the differential diagnosis and the patient was included in clinical exome sequencing.

For his molecular analysis, after DNA isolation from peripheral blood, exons and intronic regions proximal to exons were sequenced at the Illumina NovaSeq Platform using Agilent SureSelect V5 kit. The data obtained were analyzed by Sophia DDM data analysis software. The results were confirmed by Sanger analysis. We have analyzed a panel of genes effective at cystic lung pathologies including; *DICER1, SFTPB, SFTPC, SFTPD, SFTPA1, AKT1, FLCN, A2M* and *RSPH4A* genes. Among his variants heterozygous c.2620 G> A p. (Ala874Thr) variant at the *A2M* gene and heterozygous c.731 G>A p.(Arg244His) variant at *RSPH4A* gene were detected and there was no copy number variation (CNV) at the target genes. *A2M* gene mutation is not defined in UpToDate variant databases but using in-silico analysis we have predicted that it could be pathogenic. To confirm the diagnosis, serum alpha 2 macroglobulin level was measured and found at normal range. We planned to perform segregation analysis. We could not detect any genes mutations at causing surfactant deficiency at our panel. Also, for PCD differential diagnosis since we had only one heterozygous variant of unknown significance we could not confirm the clinical condition.

After completion of segregation analysis of *A2M* and CNV analysis of *RSPH4A* gene mutations, we will follow up our patient's clinical condition.

Keywords: Cystic Lung, Recurrent Pneumonia, Primary Ciliary Dyskinesias

OP-20-106

Novel *RAB3GAP1* mutation causing Warburg Micro syndrome in Turkish girl

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Warburg micro syndrome (WARBM) is a rare, genetically heterogenous, autosomal recessive syndrome characterized by postnatal microcephaly, hypotonia, spasticity, hypotalamic hypogonadism, brain anomalies especially corpus callosum hypolasia and cortical gyrus anomalies and ocular anomalies including congenital cataract, optic atrophy and microphthalmia. Approximately, 150 families with Warburg Micro syndrome and about less than 100 mutations have been identified to date and its true incidence is not known. The four WARBM subtypes are *RAB3GAP1*, *RAB3GAP2*, *RAB18* and *TBC1D20*. Of these, *RAB3GAP1* mutations are most common and account for about %50 of WARBM patients.

A five-year-old girl was referred to our clinic because of hypotonia and congenital cataract. She was born at 40 weeks of gestation by cesarean section after an uneventful pregnancy. She was diagnosed with bilateral cataracts in the first months of life, and cataract surgery was performed on her. On clinical examination microcephaly, microphthalmia, strabismus, arched eyebrow, hypertrichosis, anteverted nares, short neck, atonic pupils, hypoplastic labia minora, lower limb spasticity were detected. she couldn't control her head. Electroencephalogram (EEG) was abnormal with isolated sharp waves. Cerebral magnetic resonance image (MRI) showed hypoplasia of corpus callosum and bilateral frontal polymicrogyria. Sequence analysis of RAB3GAP1 gene revealed a novel homozygous c.258_261delAGAA (p.Gly88Argfs*5) mutation at exon 4. Both of the parents were heterozygous carrier. This mutation was evaluated as pathogenic according to ACMG 2015 criteria.

The *RAB3GAP1* gene encodes RAB3 GTPase-activating protein catalytic subunit 1, which has an imported role in the regulation of intracellular vesicle transport. Expression of *RAB3GAP1* plays role in normal development of the eyes and brain. In the most of Turkish patient has been detected c.748+1G>A splice-site mutation in literature. We identified novel homozygous frame shift mutation of *RAB3GAP1* in a Turkish patient. Although our patient has clinodactyly on 4th toes and arched eyebrow, there does not appear to be specific phenotypic findings associated with this mutation. Molecular diagnosis has a clinical significance because it allows accurate genetic counseling and appropriate management.

Keywords: Congenital Cataract, *RAB3GAP1*, Warburg Micro Syndrome

OP-20-107

The frequency of *CCR5* Δ32 gene variant in the Turkish Cypriot population and Nigerian and Zimbabwean populations living in North Cyprus

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Human Immunodeficiency Virus (HIV) is a serious health problem which affects millions of people globally despite of the advances in antiretroviral therapy. As reported by the Joint United Nations Program on HIV/AIDS (UNAIDS), there are presently more than 37.9 million people living with HIV universally, approximately 70 percent of whom are in Sub-Saharan Africa. Interactions between the viral envelope glycoprotein gp120 and the cell surface receptor cluster of differentiation 4 (CD4) are important for the entry of HIV-1 into the host cells in most of the cases. Moreover, the C-C chemokine receptor 5 (CCR5) which is expressed on potential HIV target cells is the primary co-receptor which also plays a critical role in viral entry during initial transmission and through the early stages of infection. Previous studies have shown that there is a direct relationship between a 32-base pair deletion in the *CCR5* β-chemokine receptor gene (*ΔCCR5* mutant allele) and resistance to HIV-1, Acquired Immune Deficiency Syndrome (AIDS) onset and long survival of HIV-1 infected individuals. Importantly, it has been demonstrated that individuals who are naturally homozygous for the *CCR5* gene variant Δ32 are resistant to CCR5-tropic HIV infection due to the absence of cellular *CCR5* surface expression. These findings shed light on investigation of *ΔCCR5* allele distribution in human populations. In our study, we aimed to detect the CCR5-Δ32 allele frequency in different populations living in North Cyprus. 326 Turkish Cypriot subjects, 141 male (43.1%) and 185 (56.9%) female, 103 Nigerian subjects, 60 male (58%) and 43 (42%) female and 108 Zimbabwean subjects, 56 male (52%) and 52 (48%) female living in North Cyprus were tested. In order to achieve our aim, the region of the CCR5 gene containing the Δ32 deletion was amplified using flanking primers. The results showed that the allele frequency of the wild type *CCR5* was 0.97 and CCR5Δ32 was 0.03. The CCR5Δ32 variation was only detected in heterozygous individuals. No homozygous ΔCCR5 individuals have been detected in the Turkish Cypriot population in the studied cohort. Furthermore, the allele frequency of the CCR5Δ32 variation was calculated as 0% in Nigerian and Zimbabwean populations. To our knowledge, this is the first study to demonstrate the allele frequency of the ΔCCR5 deletion in the Turkish Cypriot population. In addition, this study also revealed the lack of CCR5-Δ32 deletions in Nigerian and Zimbabwean population living in North Cyprus, indicating loss of genetic advantage in HIV infection and potential rapid development of AIDS, if other protections are not performed. We hope that our present study could be a point of discussion for this subject and a warning for people to take HIV infection more seriously. Lastly, a more serious discussion about this topic is required between the physicians, the government officials and the public which can be helpful to raise the awareness of the public against HIV.

Keywords: CCR5 Δ32, HIV, North Cyprus

OP-20-108

Serum expression level of miR-15a and miR-190b were significantly lower in delirious state when compared with non-delirious state with similar underlying diseases

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Delirium is a neuropsychiatric syndrome with an estimated incidence of 20% among hospitalized patients in general medicine and with an increasing incidence among patients in other medical settings including geriatric, post-operative, intensive care units while similar incidence was detected in psychiatric inpatients. MicroRNAs (miRNAs) are a class of small non-coding, single stranded RNAs that can modulate a target expression levels of mRNA. MiRNAs are suggested to have roles in many biological processes including dendritic patterning, synaptic plasticity, and apoptosis. In this study, we aimed to compare serum miRNA levels in patients with delirium and in patients with similar underlying diseases without delirium and to investigate correlation between serum miRNA levels and delirium severity.

Blood samples from patients with delirium and blood samples from patients who had similar diseases without delirium from various inpatient clinics were obtained. To explore putative biomarkers, we compared the miRNA profiles of saliva samples obtained from 4 patients with delirium and 4 patients with similar disease without delirium using Agilent miRNA microarray (V19). Differentially expressed miR-15a, miR-190b, miR-377, miR-323-3p, miR-485 were selected for further confirmation using qRT-PCR in 30 patients with delirium and 30 patients who had similar disease without delirium. The results showed that the expression level of mir-15a and miR-190b were significantly downregulated in blood samples of patients with delirium in comparison to patients without delirium ($p=0.004$ and $p=0.01$, respectively), and the remaining miRNAs could not be validated. In addition, there was a strong positive correlation between miR-15a and miR-190b (R ¼ 0.439, $P < 0.0001$) expressions. Moreover, delirious score was negatively correlated with both miR-15a (R ¼ -0.295, $P < 0.05$) and miR-190b (R ¼ -0.302, $P < 0.05$). There is no knowledge about the relationship between delirium and serum miRNAs in human beings, we considered that low miR-190b levels might cause behavioral symptoms in delirium while low miR-15a might lead neuroprotective efforts in brain but associated with mortality. Thus findings of miRNA in the current study might be important to understand the underlying mechanisms of delirium and might give opportunity to have different/innovative treatments by using antagonist or agonist above mentioned miRNAs.

Keywords: Delirium, miR-15a, miR-190b,

OP-20-109

Genetics of coronary atherosclerosis; A case report

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Atherosclerosis is a complex process that involves a number of cellular processes and molecular mechanisms. The relationship of genetic mutation to atherosclerotic cardiovascular disease in humans provide important information on the pathophysiology of atherosclerosis. Familial hypercholesterolemia (FH) is characterized by severely elevated LDL cholesterol levels that lead to atherosclerotic plaque deposition in the coronary arteries and leading to an increased risk for cardiovascular disease. Genome-wide association studies have had a great success in the identification of common DNA sequence variants associated with complex human diseases. In this way, a large number of candidate genes, genetic variants and susceptibility loci associated with atherosclerotic diseases have been identified in recent years.

Heterozygous pathogenic variant in one of several genes (APOB, LDLR (%60-80), and PCSK9) cause Familial hypercholesterolemia. Also, *MEF2A* gene is related autosomal dominant coronary artery disease and acute myocardial infarction. A 40 years old woman with familial hypercholesterolemia was referred to our clinic. We detected a great number of patient with hypercholesterolemia and coroner artery disease in her family history. As well as she had muscle pain and cramps of unknown cause. We have identified heterozygous mutations in LDLR (low-density lipoprotein receptor), *MEF2A* (mads box transcription enhancer factor 2) and *LIPC* (lipase, hepatic) genes with clinical exome analyses. The c.1478_1479delCT pathogenic variant in the LDLR gene has been reported multiple times in association with FH. However, detection of *LDLR*, *MEF2A* and LIPC mutations at the same time is a rare condition. C.830 C>T genomic variant in *MEF2A* and c.1214 C>T genomic variant in *LIPC* classified as likely pathogenic according to ACMG guidelines. Besides all this we surprisingly identified a homozygous mutation (c.1 A>G) in PYGM (glycogen phosphorylase, muscle) gene that related with McArdle disease. The disease (glycogenosis type V), one of the most common metabolic myopathies, is characterized clinically by exercise intolerance, myalgia, muscle cramps, and, in some patients, recurrent myoglobinuria. This case confirm that clinical or whole exome analyses is very useful for multidirectional and correct diagnosis.

Keywords: Familial Hypercholesterolemia, Coronary Artery Disease, McArdle Disease, Clinical Exom Sequencing

OP-20-110

A large Tangier family with a pathogenic *ABCA1* gene variant

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We report here a novel mutation in the adenosine triphosphate-binding cassette transporter A1 (*ABCA1*) gene causing Tangier Disease (TD) in a Turkish family. Tangier is an autosomal recessive disease with high intrafamily variability, and most of the patients present symptoms in the second decade. Tangier families are typically associated with pathology in the cholesterol esters mechanism, while *ABCA1* is most often associated with reticuloendothelial tissues. Genomic studies based on linkage analysis and sequencing revealed that the defect is related to mutations in chromosome 9q31 locus, the genomic region containing the *ABCA1* gene which is characterized by enlarged, orange-colored tonsils, peripheral neuropathy, abnormal lipid profiles, including very low plasma high-density lipoprotein cholesterol (HDL-C, frequently under 5 mg/dL) and apolipoprotein A-I (apoA-I) levels; but also peripheral neuropathy is seen in only 50% of adults affected by this gene. We are presenting 16 members of a possible *ABCA1* mutant family due to TD which is generally presents with neuropathies in adulthood of varying severity. Thus, we would like to emphasize the importance of *ABCA1* gene mutations in the patients with undiagnosed peripheral neuropathy and unexplained plasma HDL-C levels to identify any underlying genetic cause.

Keywords: Tangier, *ABCA1*, Neuropathy, Mutation, 9q31 Locus

OP-20-111

Clinical utility of a multigene panel for hematologic malignancies

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Molecular profiling helps to diagnose, classify and guide the treatment of hematologic neoplasms. Thus, NGS is the most powerful diagnostics tool to serve clinical management needs. In this study, we analyzed a multigene panel for genes associated with diagnostic, prognostic and therapeutic utilities for hematologic neoplasms.

A total of 37 samples of myeloid and lymphoid were analyzed in GeneReader NGS system through a targeted multigene panel consisting of *ASXL1, CALR, CBL, CEBPA, CSF3R, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, RUNX1, SETBP1, SF3B1, SH2B3, SRSF2, TET2, TP53, U2AF1, ZRSR2*. QCI-Analyze and QCI-Interpret were used for bioinformatic analyses. Each sample generated 2.176.058 million reads on average, and minimum of 99.5 % mapped reads to the reference reads. Total of 38 reportable variants of 16 genes were detected in 21 patients. The positivity rate was 70.5% (12 of 17) in myeloid group while its 90% (9 of 10 patients) in lymphoid group.

In conclusion, our study shows the high sensitivity and specificity of the NGS technology that facilitates the identification of actionable genetic alterations on multiple genes simultaneously to avoid time-consuming multi-step procedures in hematologic malignancies.

Keywords: NGS, Hematology, Malignancy

OP-20-112

Investigation of miR-145 target genes in multiple myeloma cell lines

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Reduced expression of miR-145, a well-known tumor suppressor microRNA, directly or indirectly affects a large number of proto-oncogenes in cancer cells. It is known that decreased miR-145 expression in tumors contributes to carcinogenesis processes by targeting various genes, including *JAG1, CDK4* and *CDK6.*

In this study, we aimed at investigating the involvement of miR-145 and *JAG1*, *CDK4* and *CDK6*, which are direct targets of miR-145, by performing functional studies on RPMI8226 and U266 multiple myeloma (MM) cell lines. We initially transfected miR-145 to those cells and explored the effect of ectopic miR-145 expression on cell proliferation using WST-8 technique. We then evaluated the expressions of *JAG1*, *CDK4* and *CDK6*, as well as certain epithelial mesenchymal transition (EMT) markers upon miR-145 transfection with quantitative real-time PCR. A significant decrease was observed in cell proliferation capacity of miR-145 transfected cells when compared to the control group cells. Expression level of *JAG1* was significantly reduced in miR-145 transfected cells compared to control group cells, although no significant alteration was found in the expressions of *CDK4* and *CDK6*. According to the literature, *JAG1*, a ligand of the Notch signal pathway, is known to have increased expression in many cancers, including MM. In addition, it is thought that the over-expression of *JAG1* could have an important role in the transition from monoclonal gammopathy of undetermined significance (MGUS) to MM, therefore *JAG1* may serve as a marker for prediction of poor prognosis and metastasis in this cancer type. Several studies have shown that *JAG1* is targeted by miR-145, however this is the first study about the relationship between miR-145 and *JAG1* in MM cell lines.

We would like to share our study results and our experiences as an oral presentation on functional studies about miRNAs and their target genes in the cell culture models.

Keywords: microRNA, miR-145, Multiple Myeloma

OP-20-113

A case of myhre syndrome with a very rare finding: Severe constipation

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Myhre syndrome is an extremely rare connective tissue disorder, described by intellectual disability, fibrosis (thickening and scarring of connective tissue), characteristic facial features (blepharophimosis, short philtrum, thin lips, maxillary hypoplasia and prognathism), striking muscular build and typical skeletal anomalies (short stature, limited range of joint motion, broad ribs, iliac hypoplasia, brachydactyly, platyspondyly and thickened calvarium). Additional findings are congenital heart defects, restrictive pulmonary disease, gastrointestinal abnormalities (pyloric stenosis, duodenal strictures), severe constipation, autistic-like behaviors and hearing loss. This syndrome was first defined by Myhre at al. in 1981 in two unrelated males with intellectual disability, short stature, a skeletal muscular hypertrophy, decreased joint mobility and mixed hearing loss. To date, more than 60 individuals have been reported to the medical literature. Myhre syndrome, inherited in an autosomal dominant manner, occurs sporadically. In majority of cases, de novo mutation in the *SMAD4* gene cause this disorder. We presented a 13-year-old boy who had short stature, mild intellectual disability, dysmorphic facial features (short palpebral fissures, deeply set eyes, maxillary hypoplasia, prognathism, short philtrum with downturned nasal tip and small ears), short neck, brachydactyly, 2-3 syndactyly, muscular build and thickened skin. He had also congenital heart defect and digestive problems such as severe constipation. In patient, next generation sequence analysis revealed a recurrent p.Ile500Val mutation in the *SMAD4* gene. Here, we present a rare finding: severe constipation in a patient with Myhre syndrome due to a heterozygous mutation in the *SMAD4* gene.

Keywords: Constipation, Myhre syndrome, *SMAD4* mutation

OP-20-114

Identifying new players in fetal haemoglobin expression, from cell cultures' bioinformatic to benchtop.

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Beta Thalassemia Major is the most common monogenic inherited blood disease caused by beta globin gene mutations. Lack of globin production or total insufficiency, due to the mutations, effects the clinical severity of the disease. 2 chains of four globin are alpha globins haemoglobin molecule. In fetal and first couple of months in postnatal term, alpha and gamma globin chains are collocated but in adulthood beta globin is replaced instead. Thus, haemoglobin molecule can manage its' functional duties physiologically.

In order to enhance HBF, lots of molecules are experimented in cell culture studies. Among the FDA approved drugs there have been some molecules like short chained fatty acids (SCFA) and histon deacetylase (HDAC) inhibitors in treatment of thalassemias. Lastly, by using some antioxidant molecules like resveratrol, it is shown that it is possible to increase the amount of fetal haemoglobin in cell lines and primary erythroid cell cultures of patients.

HBF production may also occur naturally, without any induction. Clinics of thalassemia, is variable, due to the increment of HBF production, and thanks to the mutations in modifier genes. Up to now, there are three loci may clarify the variability of fetal haemoglobin. These locus harbours X*mnI* polymorphisim, HBS1L-MYB intergenic region and *BCL11A* variations. After 2011, relationship between *KLF1* mutations and high HBF amounts have also been shown. In recent scientific literature with publications related to the *ZBTB7A /LRF/* Pokemon gene, which I hypothesized that the K562 cell line caused high HbF expression based on its' cell line whole genomic bioinformatic data, suggest that one of the major players in high HBF induction is *ZBTB7A / LRF*. Similarly, Vienna Lab Beta Thalassemia Modifier Assay serves 5 genomic alterations' situation at the same time with reverse dot blot hybridization (RDBH) analyses.

For these reasons we evaluated role of major modifiers of globin switch with sanger sequencing in case of Pokemon gene's specific variation, and RDBH analyses of *BCL11A*, X*mnI* polymorphism, HBS1L-MYB intergenic regions' specific alterations in 60 Beta Thalassemia patients with increased fetal haemoglobin levels based on their haemoglobin electropheresis results.

All patients were have different transfusion needness and increased fetal haemoglobin levels. Their *HBB* gene mutation profile were recorded but we took in account their fetal hemoglobin amounts into and tried to evaluate whether genomic alterations are causative or not. We found the heterozygous mutation, for the first time to the best of our knowledge, what we hypothesised in Pokemon gene in 1 out of sixty patients by sanger sequencing. This patient is a child of a couple with second degree consanguineous marriage and evaluated as beta thalassemia major in terms of her homozygous beta globin gene mutation status and monthly transfusion needness profile. Haemoglobin F level was 4.0 for this patient and was found to be splenectomized on anamnesis form. This 24-year-old female patient has beta thalassemia trait child and is pregnant now.

In one out of 60 patients, a very rare synonymous variant found heterozygous and this one is also first report from Turkey. Her fetal haemoglobin level were higher than the previous one and spleen was normal respectively. As to RDBH analysis results, we finished genotyping fourty out of 60 patients. Several existence of different combinational mutational profiles have been detected both compound heterozygously and/or homozygously mutated and will be presented after remaining ones' status clarified exactly.

Our relatively large beta thalassemia patient cohort with 60 patients' genomic profiles with two different methods at the same time, will be discussed and it could extend the understanding what is the new player and how they may have a role in increasing fetal haemoglobin levels.

Keywords: Pokemon//LRF/ZBTB7A, RDBH, Fetal Haemoglobin, Beta Thalassemia, Medical Genetics, Haemotology.

OP-20-115

Is I-FISH competing with metaphase FISH and cytogenetics, in the diagnosis of prenatal interchange trisomy 21
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The incidence of balanced reciprocal translocation is 1 in 500. There is no risk for the carrier himself or herself, but unbalance karyotype can be occurred on the progenies because of the constitution of pachytene quadrivalent configuration instead of bivalent pachytene form. Interchange trisomies and monosomies are the 3:1 segregation products of this erroneous configuration. Most of the cases have no chance to live and the pregnancies are ended with the wastages of gestation in intrauterine period. The ones related with the chromosomes 13, 18 and 21 can live in intrauterine or natal periods depending on the gene content of the partial trisomies/monosomies. Here we report an interchange prenatal trisomy 21 case due to the mother's balanced reciprocal translocation consisting chromosome 1 and 21.

Chorionic villus sampling was performed at 13rd gestational week due to the fetal ultrasonographic anomalies and due the presence of parenteral translocation carrier. The reciprocal translocation carrier mother, consisting the chromosome 1q32.1 and 21q22., has two healthy children with one from spontaneous and one from assisted reproduction. Rapid interphase fluorescence in situ hybridization (I-FISH) analyses with the probes consisting chromosomes 13,18, 21 and X/Y revealed trisomic signals for chromosome 21. Interphase FISH analysis could not rule out whether the trisomy is regular or partial due to the 3:1 segregation, while conventional cytogenetics has given us this opportunity. The obvious configuration of the chromosomes related with t(1;21)(q32.1;q22.1) was seen via chromosome analyses on light microscope. The fetus had two normal chromosome 21s and a single derivative chromosome 1. Metaphase FISH analyses detected the intact parts of 21q22.13 and 21q22 on the derivative chromosome 1. Parents had given genetic counselling due to the all results, and prenatal and preimplantation genetic diagnosis were recommended.

Depending on the breakage locus of the translocated chromosome, I-FISH can seize the aneuploidies or can miss the aneuploidies while conventional cytogenetics and metaphase FISH can give apparent chromosome configurations. In sum cytogenetics has great value to detect the interchange and tertiary trisomies besides the balanced chromosomal rearrangement in prenatal period.

Keywords: Interchange Trisomy, Trisomy 21, 3:1 Segregation

OP-20-116

Autosomal recessive form of clouston syndrome?
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Clouston Syndrome is an autosomal dominant, childhood-onset form of ectodermal dysplasia associated with missense mutations in *GJB6*. Here, we describe a child with Clouston syndrome, whose parents were consanguineous, and who we found to be homozygous for a novel missense mutation (p.G45R) in *GJB6*, which encodes Cx30. Her parents and unaffected siblings were heterozygous for this mutation. This missense mutation has not previously been reported in any SNP database. In contrast to wild-type Cx30, ectopically expressed p.G45R mutant protein rarely formed gap junctions when expressed in cultured cells but often led to increased cell death We conclude that a p.G45R missense mutation in GJB6 alters the in vivo function of Cx30 and causes an autosomal recessive form of Clouston syndrome.

Keywords: Clouston Syndrome, Hidrotic Ectodermal Dysplasia Type-2, Autosomal Recessive Inheritance, Connexin 30, *GJB6*

OP-20-117

From pediatric emergency to genetics

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Although current technology has led significant advances in health sciences, clinical evaluation, physical examination findings and accurate anamnesis remain to be important in diagnosis. A detail taken into account during evaluation of patient's complaint can direct future of patients or his/her family. This study aimed to emphasize importance of referral to appropriate units in establishing diagnosis based on data acquired from anamnesis.

A 2-years old girl presented to pediatric emergency department with findings of upper respiratory tract infection. It was observed that there was visual abnormality in the patient in whom physical examination findings were established and history was taken. In family history, it was seen that there were individuals with similar findings in the family. After treatment for upper respiratory tract infection, the patient was referred to Medical Genetic department in order to evaluate etiology of familial vision loss. In Medical Genetic department, it was found out that the patient had vision-related complaints which had begun as nystagmus at 4 months of age and progressed with strabismus and vision loss.

In the ocular examination, no finding other than photophobia and nystagmus were detected. In the anamnesis, it was found that there was consanguinity between parents (third-degree relatives) and consanguinity was common in the family with members having similar clinical Picture. Whole-genome sequencing (WES) was performed as the karyotyping and micro-array analysis were normal in the patient but similar findings were present in the family members. In WES analysis, a homozygous c.1004+1 G>A splice site mutation was detected at intron 6 of *PDE6C* gene. This variant has not been defined in the literature so far. This mutation, which is not present in homozygous form in the open-access databases (ExAC, EVS, dbSNP, 1000GP), is considered as a high-probability disease factor based on in silico databases. This variant detected in PDE6C gene is classified as "Class 1 Pathogenic (P)" based on 2015 ACMG criteria.

PDE6C c.1004+1 G>A splice site mutation causes CONE DYSTROPHY 4; COD4”e (# 613093 OMIM), a progressive cone disorder. It is an autosomal recessive disorder characterized by poor visual acuity, photophobia, nystagmus and severe color vision deficiency. Although patients may have cone function, there may be increased loss of visual acuity in the electroretinography, photophobia, color vision deficiency and decreased cone responses in the first and second decades of life. Normal rod cell functions and unresponsiveness of cone cells are observed on electroretinography. Either disruption or death of cone receptor cells is cause of unresponsiveness and major clinical feature of the disease.

In this autosomal recessive disease, a segregation study was performed as there were complaints in family members. In the Sanger sequencing, homozygous mutation was detected in 4 of 11 cases while heterozygous mutation in 7 cases. No clinical disease was detected in the heterozygous individuals. Genetic counseling was provided to family about results. In addition, the family was informed regarding prenatal diagnosis and pre-implantation diagnosis in the future pregnancies. Again, they were informed about preventability of the disease in the future generations.

In conclusion, the patients could have been referred to appropriate units and the diagnosis could have been achieved by vision disorder taken into account in the anamnesis together with positive family history, providing preventive genetic counseling for next generations. In the patients from all fields, it may be possible to achieve appropriate diagnosis and treatment by careful history taking and appropriate referrals. In this study, it was aimed to emphasize importance of careful history taking and physical examination.

Keywords: Vision Disorder, Autosomal Recessive, Cone Dystrophy 4

OP-20-118

A rare cancer predisposition disorder: DICER1 Syndrome

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DICER1 is a RNaseIII endoribonuclease essential to generating microRNAs (miRNAs). It is required for RNA intervention and produces the small active RNA component that suppresses gene expression. In addition DICER1 is crucial for embryogenesis and early development. Pathogenic germline *DICER1* mutations cause a hereditary cancer predisposition syndrome increased cancer risks for pleuropulmonary blastoma (PPB), cystic nephroma (CN), ovarian sex cord-stromal tumors, and multinodular goiter (MNG). Pleuropulmonary blastoma (PPB), the most common primary lung cancer in children, is the hallmark of this syndrome. On the other hand, *DICER1* mutation has been detected in some cystic diseases of lung. In these cases, an increased risk of malignancy has been shown in patients with a germline mutation. Herein we will discuss a patient with a cystic adenomatoid malformation whose surgical operative desicion depended on detection of *DICER1* mutation.

Our case is an 8-year-old Turkish boy with cystic formations in his lung that are detected at the fifth month of gestation prenatally. During the postnatal period, he had no signs and symptoms of respiratory system. Due to his current condition, the operation was not deemed necessary and his cystic structure was followed up. The patient's developmental milestones were normal. In September 2018, he admitted to the hospital with persistent cough. As a result of physical examination, imaging and blood tests, his cough was not linked to infection. At the radiological analysis, cystic adenomatoid malformations and bronchiectasis were detected in the left lower lobe. Because it has been shown that malignant potential is higher if germline *DICER1* mutations are present in patients with cystic lung disease, to decide operation and removal of the malformation patients molecular results are crucial. In our patient, we found the heterozygous c.4084 A> G p. (Lys1362Glu) variant of the *DICER1* gene. This variant was pathogenic in in-silico analysis although it was not reported in uptodate mutation databases. Due to this novel variant, we have decided the surgical removal of the cystic structure.

The removal decision of pulmonary cystic malformations is a challenging issue for physicians. It is pivotal to detect *DICER1* mutation to manage these patients with this clinical entity.

Keywords: Cystic Lung Disease, DICER1, Pleuropulmonary Blastoma

OP-20-201

Reanalysis of trio whole exome sequencing (WES) data with a novel variant prioritization workflow reveals a de-novo missense variant in *EBF3* gene associated with hypotonia and developmental delay

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Clinical whole exome sequencing (WES) is considered as a powerful approach for identifying disease-causing variants, despite it yields a diagnosis in 25-30% of patients. While some of these undiagnosed patients have a pathogenic variant in already sequenced exome, it may not be identified in the initial analysis. The main challenge in this field is the data analysis and interpretation, in terms of detecting the causative mutation from thousands of variants of unknown significance. A recent study reported that 10% of the undiagnosed patients could get a precise diagnosis through the reanalysis of the same WES data, using different workflows and with the help of growing knowledge in the literature.

We developed a variant prioritization workflow taking into account distinct symptoms of patients and the variants in the genes that can give rise to those symptoms. In this study, we present a reanalysis of trio WES, which was left as unsolved through several attempts. To identify disease-causing variants, WES was performed on genomic DNA extracted from samples submitted from the proband, biological mother, and biological father. We have applied our internal workflow to WES raw data. After the variant annotation step, homozygous and compound heterozygous variants with minor allele frequency (MAF) <0.1% in the databases, i.e. gnomAD and 1KGP were filtered. Heterozygous variants, which were found in at least one of these databases, were excluded. The intronic variants that were further away from ±10 bases of exon-intron boundaries were eliminated. Then, the variants were prioritized based on the symptoms of the proband via using inhouse variant prioritization workflow and collecting evidence from various resources and literature. Via integrating several computational analyses, a de-novo heterozygous mutation, c.C487T (p. Arg163Trp), in *EBF3* gene (OMIM *607407) was prioritized as the most prominent variant. *EBF3* gene encodes a member of the early B-cell factor (EBF) family transcription factors that has crucial roles in neurogenesis and development. Heterozygous mutations in *EBF3* are associated with Hypotonia, Ataxia, and Delayed Development Syndrome; HADDS (OMIM #617330), which is a neurodevelopmental syndrome characterized by congenital hypotonia, delayed psychomotor development, variable intellectual disability with speech delay, ataxia and variable dysmorphic facial features. Although the pathogenic mechanisms of *EBF3* mutations remain unclear, a number of missense, nonsense, and intronic variants, and copy number variations are described so far. Interestingly, all of the reported missense variants are located in the DNA binding domain, which is highly conserved in EBF3 protein. Five of these missense variants affect the same amino acid residue (Arg163), which is in the Zn2+ finger Collier/Olf/Ebf (COE) motif. In this respect, a recent study conducted molecular dynamics simulations and demonstrated that p.(Arg163Trp) can cause decreased DNA binding affinity and differential transcriptional activation. The overlapping phenotypic features of our proband with all previously reported cases include generalized hypotonia with global developmental delay, mild facial dysmorphisms such as frontal bossing and low-set ears, speech delay, decreased pain response, hyperactive deep tendon reflexes, strabismus and bilateral esotropia. As it is the case for some of the reported cases, our proband had normal evaluations for brain magnetic resonance imaging (MRI), electroencephalography (EEG), chromosomal microarray, and comprehensive biochemical metabolic testing.

In conclusion, by employing our internal WES data analysis and variant prioritization pipeline on a previously unsolved exome, we identified a pathogenic de-novo missense variant in EBF3 gene. Targeted Sanger sequencing was used to confirm the variant in proband and to show the absence of the alteration in parental samples. Hence, the proband is diagnosed with HADDS. To sum up, here we highlight the potential of reanalysis of WES data for undiagnosed individuals.

Keywords: *EBF3*, Hypotonic Ataxic Developmental Delay Syndrome (HADDS), Reanalysis, Unsolved Exome, Whole Exome Sequencing (WES)

OP-20-202

Developing evidence based computerized diagnostic tools for breast cancer early prediction

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Early diagnosis as the initial step of medical practice. This has given rise to evidence based computerized diagnostic tools, intended to aid the physician in making primary medical decisions and hence an early diagnosis which helps reduce the treatment time or may save lives. The complicated clinical decision making which is usually accompanied with the degree of ambiguity and uncertainty. Since uncertainty is the inseparable nature of medicine, fuzzy logic methods have been used as one of the best methods to decrease this ambiguity. Some of the most important areas in medicine research are related to cancer and cardiovascular diseases. Specifically, heterogenous disease breast cancer, is the cause of the most common cancer death in women globally, early detection of the breast cancer is an effective method to reduce mortality. The majority (~70%) of breast cancer cases are sporadic. Familial breast cancers (~30%), often seen in families and have been associated with a number of susceptibility genes. Family-linkage studies have identified high penetrance genes (*BRCA1/2*, *PTEN* and *P53*) that are responsible for inherited syndromes. Additionally, a combination of family-based and population-based approaches revealed that genes involved in DNA repair associates with breast cancer risk. *BRCA1* and *BRCA2* are involved in maintaining genome integrity, at least in part, by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps. Thus, the complete loss of function of either protein leads to a dramatic increase in genomic instability. Thousands of different disease-associated variations of *BRCA1/2* genes have been detected. The estimated *BRCA1/2* mutation carrier frequencies in the general population are between 1/300-800. Several studies have estimated the penetrance associated with *BRCA1/2* mutations. Female carriers of deleterious *BRCA1/2* mutations are predisposed to high lifetime risks of breast, ovarian cancer or probably other cancer types. Therefore, identification of genetics variations within the *BRCA* gene family is crucial for early diagnoses. Thus, the aim our study to develop a variant selection method based on a fuzzy logic and neural network selections and classification algorithms, and to validate the variant signatures obtained on *BRCA1/2* positive breast cancer patient cohorts. Sixteen different risk factors were determined as inputs for 268 different *BRCA1/2* positive breast cancer patients. These input parameters were age, sex, consanguinity, family history, number of family member, tumor size, lymph node, degree of malignancy, tumor position, estrogen receptor, hormone progesterone hormone, *BRCA1* gene, *BRCA2* gene, other genes (68 genes), diagnosis and classification. A total of 61 *BRCA1*, 128 *BRCA2* and 11 both *BRCA1* and *BRCA2* genes associated breast cancer patients' data were used to train the system. MATLAB is a multiple paradigm digital computing software and a fourth-generation programming language. MATLAB is a proprietary programming language developed by MathWorks and is a high-performance language for technical computing. It combines computing, visualization and programming in an easy-to-use environment where problems and solutions are expressed in familiar mathematical notations. The MATLAB, the software of the fuzzy logic and neural network systems, was used in this study. It is a logic form that proves that human values and experiences can be any real number between 0 and 1 with its fuzzy logic approach. The results from developed system were very similar. We achieved excellent results as train success was 99.9%, validation success was 99.6%, test success was 99.7% and whole system was success 99.9%. Even the developed softwares showed 95.5% accuracy when we tested new patients.

Overall, our developed models will provide the early prediction for *BRCA1/BRCA2* related breast cancer cases and will improve to be beneficial for preventive medicine and a unique example for today's genetic-based personalized medicine software.

Keywords: *BRCA1*, *BRCA2*, Fuzzy Logic, Neural Network, Artificial Intelligence, Early Diagnosis

OP-20-203

***ZBTB24* novel mutation identified in Turkish ICF syndrome patient**

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The ICF syndrome is an ultra-rare autosomal recessive condition comprised of Immunodeficiency, Centromeric instability, and Facial anomalies. The ICF is a group of primary immunodeficiencies, which encompass a group of more than 350 inherited disorders. Therefore, these result in the specific impairment of normal immune development and function. Intellectual disability also frequently occurs. Additionally, mild facial dysmorphism and failure to thrive can be part of this syndrome. Instability most frequently involves the vicinity of the centromeres of chromosomes 1, 16 and often 9. DNA methyltransferase 3 beta (*DNMT3B*) and zinc finger and BTB domain-containing 24 (*ZBTB24*) genes are the well-known genes for patients with ICF syndrome.

DNA was isolated from peripheral blood and genes sequence analysis was done via Next-Generation Sequencing (NGS). 24 genes examining at all exons and nearby intron regions were studied as multi-gene panel. By evaluation of clinical findings, the case was diagnosed as ICF and discussed in the light of literature.

19-year-old boy was referred to our clinic because of recurrent lower respiratory tract infections and low levels of immunoglobulin. Any pathological condition is not detected in prenatal, natal and postnatal histories. His parents were consanguineous (second-degree cousin). He was thought to have primary immunodeficiency because of recurrent otitis media, lower respiratory tract infections and low B cell rate at first 6 months of age. In his physical examination failure of thrive, length and weight below the 3rd percentile were detected. His dysmorphic features were hypertelorism, flat face, flat nasal bridge, low set ears and crowded teeth. His hearing examination was normal at birth. However, hearing loss was observed and tympanic membrane perforation was found after recurrent infections at 18 months of age. The patient had an intellectual disability and difficulty in speaking. His levels of immunoglobulins: IgG:12,64 g/L(5.5-14.4), IgA: <0,06 g/L(0.4-3.5), IgM: 0,1 g/L(0.5-3), IgE: <1 IU/mL(6.8-39.6). There is no family history in terms of immunodeficiency. There were two miscarriages of his mother and undiagnosed two dead cases of his mother's brother and sister before 2 years of age. His karyotype (100 metaphase) was 46, XY (57 metaphase) and deletion in chromosome 16 (43 metaphase). Homozygous mutation in *ZBTB24* c.156delA (p.Ala53Profs*12) and homozygous variation in *DNMT3B* c.1833C>T (p.Phe611Phe) were found in patient and they are pathogenic based on silico analysis.

Autosomal recessive deficiencies of *DNMT3B* or *ZBTB24* account for two-thirds of ICF cases. Lots of variable genes cause primary immunodeficiency. Therefore, analysis of more genes supplies identification and classification well. Our patient has typical clinic features of ICF. We reported our patient to contribute to genotype-phenotype correlations in ICF.

Keywords: Facial Anomalies, Immunodeficiency, Mental Retardation

OP-20-204

Is autosomal dominant hyperlipidemia genetic testing crucial for risk analysis?

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Autosomal dominant hypercholesterolemia (ADH), characterized by an isolated elevation of plasma low-density lipoprotein (LDL) is one of the major disorder. In case hyperlipidemia, a wide range of organ systems are affected and this situation causing different mortality and morbidities. Diagnosis of the disease depending on biochemical values are not always potent to counsel the family as a whole.

We had thirty patients with hyperlipidemia who admitted to our center at years between 2018-2019. The age of our patients were 22 to 82 and 10 were males, 20 were females. DNA of patients was isolated from peripheral blood and analyzed with Next Generation Sequencing Illumina MiSeq platform. The targets analyzed in the gene panel are *PCSK9*, *APOE*, *LDLR*, *APOB* and *ABCG8*.

There were nineteen patients with mutations/variations of sequence genes. *PCSK9* gene mutations were detected at 2 patients, and 3 patients with variations, while *APOE* mutations and variations were present in 2 and 5 patients respectively. Seven patients have *LDLR* mutations, and 2 patients have variants of that gene. *ABCG8* gene mutations detected at only 1 patient, whereas no variations of that gene were detected.

The diagnosis of hyperlipidemia has been challenging before the genetic analysis. Genes effective in cholesterol pathway should be characterized for those patients with high levels of lipids. Thus, genetic counseling and risk analysis of genetic testing is pivotal in the diagnostic work up.

Keywords: Autosomal Dominant Hypercholesterolemia, Hyperlipidemia, Next Generation Sequencing

OP-20-205

A case with multiple reciprocal balanced translocations with primary infertility

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Cytogenetic analysis of peripheral blood of patients who suffer from infertility can reveal the balanced translocations. Balanced translocations may be innocent for the carriers but abnormal gonadal segregation may cause recurrent pregnancy loss or primary infertility. Here, we present a patient with multiple balanced translocations (t(1;17)(q10;p10), t(14;17)(q10;q10), t(15;19)(p10;q10), trc(5;1;14)(q33;p34p10;p10)). For male primary infertility, other genetic abnormalities like CFTR gene mutations that lead to congenital absence of the vas deferens or Y chromosome microdeletions that cause isolated spermatogenesis defects can be responsible. Chromosomal microarray is performed for this patient to indicate if there are small chromosomal disruptions as consequence of translocations or Y chromosome microdeletions and it reported as normal. More surprisingly his only complaint was azoospermia and infertility except communicating hydrocephalus incidentally diagnosed by MRI scan. He had not any dismorphological feature or major health problem. This case is interesting because it points that balanced translocations can be responsible for male infertility or azoospermia and translocations in large quantities are able to be compatible with life, even sometimes they do not cause any major health problems.

Keywords: Azoospermia, Infertility, Translocations, Reciprocal

OP-20-206

Molecular genetic characterization of *ABCA4* gene in Stargardt disease

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Stargardt disease (STGD), which is also called Stargardt macular dystrophy, juvenile macular degeneration, or fundus flavimaculatus, is an inherited disorder of the retina. The disease typically causes vision loss during childhood or adolescence, although in some forms, vision loss may not be noticed until later in adulthood. Although mutations in five genes (*ABCA4, ELOVL4, PROM1, CNGB3, PRPH2*) have been associated with STGD, *ABCA4* mutations are the most common cause of the disease.

Keywords: Stargardt Disease, *ABCA4*, Vision Loss

OP-20-207

Effect of histon deacetylase inhibitor vorinostat on gene expression in polarized macrophages

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Monocyte and macrophage cells are essential components of the innate immune system. Macrophage cells can be polarized into subtypes with different phenotypes and physiology depending on the cytokines in their environment. As a result of this polarization, macrophage cells may have different phenotypes characterized by producing pro-inflammatory or anti-inflammatory cytokines.

In recent years, histone deacetylase inhibitors(HDACi) have been used in cancer treatment. Studies have shown that HDACis also have anti-inflammatory properties. However, the epigenetic mechanisms of the immune system have not yet been fully elucidated.

In our study we investigated the effects of vorinostat in RAW264.5 mouse macrophage cells which we polarized into different phenotypes for evaluating the expression levels of *COX2, CXCL9, TNF-α, NOS2* and *Arg2* genes that play a role in macrophage activation.

In cells that are polarized to the inflammatory M1 phenotype with stimulation of LPS and IFN-γ, the expression levels of *COX2* and *NOS2* have found to be increased when compared to the LPS-induced macrophages, especially in combination with LPS and vorinostat. The expression of chemokine *CXCL9* expressed by IFN-γ stimulation in macrophages has been found to be significantly increased by vorinostat treatment. TNF-α expression was found to be decreased by vorinostat treatment while the expression of Arg2 which is a marker for M2 macrophages did not. In addition, in the cells which were polarized into the M2 macrophage phenotype with the stimulation of IL-4, vorinostat treatment did not change the expression of *COX2* and *CXCL9* while TNF-α expression was found to be decreased. *NOS2* expression was increased when M2 macrophages were treated with the combiantion of LPS and Vorinostat. It was seen that the vorinostat treatment alone decreased the Arg2 expression by approximately 80%. LPS treatment alone was significantly increased the Arg2 expression in M2 cells, but in the combination of LPS and vorinostat, there was a significant decrease in Arg2 expression. Vorinostat, a histone deacetylase inhibitor, has been shown to produce differences in the expression of important genes for macrophage activation in polarized mouse macrophage cells. Further functional studies are required to determine the effects of these changes in gene expressions on the characteristic features of macrophage cells. The results of this study contributed to the literature to elucidate epigenetic mechanisms in macrophage polarization.

Keywords: Macrophage, HDACi, Vorinostat, Macrophace Polarization

OP-20-208

A rare disease: Ullrich congenital muscular dystrophy

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Ullrich congenital muscular dystrophy (UCMD) forms the subgroup of collagen VI-associated myopathies. Starting from birth or early infancy, it is a very rare congenital disorder characterized by progressive muscle weakness, contractures of the proximal joints and hypermobility of the distal joints and normal intelligence. UCMD is caused by mutations in the *COL6A1*, *COL6A2* or *COL6A3* gene, thus leading to collagen VI deficiency in the extracellular matrix. Less than 50 molecularly confirmed cases have been reported worldwide. In this case report, we aimed to present a 10-year-old patient with a new pathogenic mutation in the *COL6A2* gene, clinically and genetically. It was learned that the patient, who was brought to the pediatric neurology outpatient clinic with the complaint of progressive walking difficulty, was hypotonic in the neonatal period, congenital hip dislocation and scoliosis. The case was the third child of the mother and father (third-degree cousins) who was relatives. It was learned that one of his brothers had similar complaints and died when he was 11 years old. On examination, there were contractures in the elbow and ankle joints, hyperlaxity in the distal joints, scoliosis, exophthalmus, and keratosis pilaris on the front of the bilateral leg. The patient had a normal sensory examination, and his blood CK level was within the normal range. Sequence analysis of *COL6A1*, *COL6A2* and *COL6A3* genes from the patient who was referred to the medical genetic outpatient clinic with a preliminary diagnosis of congenital muscular dystrophy was studied. The patient was found to be homozygous for a single nucleotide change (G> T) resulting in an early STOP codon at position c.2293 on exon 26 of the *COL6A2* gene. The C.2293G> T variant was classified as a pathogenic variant according to the ACMG guidelines. To the best of our knowledge, this variant has not been reported in the scientific literature to date. In the segregation analysis for family members, heterozygosity was detected in terms of existing mutation in the mother, father, and brother. The family whose family tree was drawn was given detailed information about the prognosis of the disease. With this case report, it is aimed to emphasize that the genetic spectrum of the disease expands, but a correct and rapid combination of genetic and clinical data in collagen VI-related diseases guides clinical treatment and provides useful information to families to provide genetic counseling.

Keywords: Ullrich Congenital Muscular Dystrophy, Collagen Type VI, *COL6A1*, *COL6A2*

OP-20-209

Clinical impact of a targeted next-generation sequencing gene panel for immunodeficiency- Our first results

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Primary immunodeficiency disorder (PID) refers to a large heterogeneous group of disorders that result from defects in immune system development and/or function. PIDs are broadly classified as disorders of adaptive immunity (i.e., T cell, B-cell or combined immunodeficiencies) or of innate immunity (e.g., phagocyte and complement disorders). Although the clinical manifestations of PIDs are highly variable, many disorders involve an increased susceptibility to infection. More than 250 different disorders have been genetically identified to date, with new disorders continuously being recognized. From the genetic perspective, over 400 genes have been identified as monogenic causes of PIDs. Early consultation with a clinical immunologist is essential, as timely diagnosis and treatment are imperative for preventing significant disease-associated morbidity. Genetic testing is required to make a definitive diagnosis.

Keywords: Immunodeficiency, NGS, Panel

OP-20-210

A novel mutation of infantile epileptic encephalopathy type 9; a rare genetic disorder with an interesting inheritance pattern

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Early infantile epileptic encephalopathy type 9 (EIEE9) also known as epilepsy and mental retardation restricted to females is a rare genetic disorder which has an interesting inheritance pattern. Although it is inherited in X linked manner, heterozygous females and somatic mosaic males are affected, whereas hemizygous males are asymptomatic. This intriguing condition is explained by mechanism of cellular interference. EIEE9 caused by heterozygous mutation in *PCDH19* gene which encodes protocadherin 19 protein that plays an essential role on neuronal adhesion and organization. Mutations of *PCDH19* gene cause cellular interference due to impairment of neuronal organization and disease occurs in patients with mosaisism; combination of the cells with and without of *PCDH19* mutations. *PCDH19* gene is one of the common pathogenic genes in epilepsy. To date about 150 mutations in *PCDH19* gene have been reported in the literature. EIEE9 characterized by seizures onset in infancy, mild to moderate entellectual disability and behaviroural phenotype including aggressive, obsessive and autistic features. We report a 17 month old girl referred to our clinic with epilepsy onset in infancy. Whole exome sequencing revealed a novel heterozygous variant in *PCDH19* gene. This mutation was not reported previously in the literature. It is a frameshift mutation leads to premature stop codon. In-silico bioinformatic analysing tools indicates the mutation as disease-causing mutation. Here, we report a novel mutation of a rare genetic disorder inherited by an interesting manner.

Keywords: Cellular Interference, EIEE9, Novel Mutation, *PCHD19*

OP-20-211

A patient with two de novo variants, one causes recessive and other causes dominant disorder

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Hyperphosphatasia with mental retardation syndrome (HPMRS) is a heterogeneous group of disease. It shows a broad spectrum of symptoms which includes varying degrees of intellectual disabilities, dysmorphic facial features, brachytelephalangy, and hyperphosphatasia. HPMRS is caused by an impairment of synthesis or maturation of the glycosylphosphatidylinositol (GPI)-anchor.

Meanwhile *GRIN2B* -related neurodevelopmental disorder is another rare genetic condition characterized by developmental delay, intellectual disability, muscle tone abnormalities, epilepsy and autism spectrum disorder. Developmental delay, microcephaly and epilepsy are common findings of both syndromes. Herein, it is aimed to present a case diagnosed with two de novo variants: one is causing a dominant and the other is causing a recessive disorder by Whole exome sequencing (WES). Physical examination of seven-month-old girl with hydroureteronephrosis and seizure history revealed microcephaly, brachycephaly, coarse face, metopic ridge, up-slanting palpebral fissures, inverted nipples, umbilical hernia and bilateral hypoplastic 5th fingernails. There was no consanguinity of her parents. Her laboratory findings revealed high ALP values. EEG showed focal epileptiform discharges. Cranial MRI and echocardiography results were normal. On the hand radiography hypoplasia, aplasia or duplication of different distal phalanges were observed. Pelvic USG displayed grade 4 hydronephrosis and IVP confirmed this finding. Denver developmental screening test demonstrated developmental delay. Array CGH analyses revealed 507 kb de novo duplication of Xp11.22 and interpreted as CNV with unknown significance. Even if the clinic of patient indicates the HPMR syndromes, it was hard to make differential diagnosis among subtypes of HPMR basing only those clinical findings. Therefore, WES analysis was planned.

Two rare variants in *PIGO* (NM_032634.4) gene; c.1944C>G (p.Cys648Trp) and c.2708_2710delTCT (p.Phe903del) were shown by WES analysis. Segregation analysis by Sanger sequencing revealed that mother was heterozygous carrier of *PIGO* c.1944C>G (p.Cys648Trp) variant and father did not show the presence of both mutation. The c.2708_2710delTCT (p.Phe903del) variant was de novo, while the c.1944C>G (p.Cys648Trp) variant was inherited. Additionally, heterozygous variant (rs505297) in 173 base pairs distance of c.2708_2710delTCT and 1158 bp distance of c.1944C>G was used to determine the allele positions (either cis or trans). The variants were evaluated as in trans position. Moreover, a rare variant was detected in *GRIN2B* gene: c.1852G>A (rs1428234478) (p.Val618Ile). Since both parents were non-carrier for the variant mentioned here, this variant was also de novo. To confirm parentage STR markers were used. In conditions with multiple genetic diagnoses, phenotypes can be separated or can be overlapped. When phenotypes overlap, as in the case presented here, it is not possible to distinguish it only with clinical diagnosis. If one of multiple genetic diagnoses is overlooked, this would completely change the management options of the disorders and genetic counseling to the family.
Nowadays with the usage of next generation sequencing (NGS) based techniques, it is started to be unveiled that the underestimated number of dual molecular diagnoses of conditions that may be mistakenly interpreted as new features of known single-gene disorder if single gene investigations had performed instead of NGS methods. In a retrospective study Posey et al. showed 4.9% of cases of whom Whole-Exome Sequencing was informative had multiple molecular diagnoses. And in a cohort study Balci et al. found 3.5% of their cases has multiple genetic diagnoses. Especially when differential diagnosis is hard or a phenotype with multiple molecular diagnoses is suspected, it would be wise to prefer comprehensive genome-wide techniques instead of single gene investigations because of its multilocular analysis capability.

Keywords: Multiple Genetic Diagnoses, Dual Phenotype, Hyperphosphatasia With Mental Retardation Syndrome, *GRIN2B*, Next Generation Sequencing, NGS.

OP-20-212

A single center experience: Challenges and advices in reporting of incidental findings in Whole Exome Sequencing

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In comprehensive genetic tests such as clinical exome, whole exome and whole genome analysis, we are unsure whether to report the clinically unrelated pathogenic / likely pathogenic variants we encounter. At this point, the list of incidental genes determined by ACMG helps us. Based on WES data of our center from the last one year, we aimed to share the incidental genes we reported, frequency, encountered problems and our suggestion for our community.

83 (13,9%) of 594 patients did not approve of reporting these genes. We detected pathogenic or likely pathogenic variant in the ACMG incidental genes in 24(%5) of 594 patients. In 24 patients, we reported 26 variants, 3 of which were pathogenic and 23 of which were possible pathogenic. The vast majority of reported genes were those associated with cardiomyopathy and long QT syndrome. Less frequently reported phenotypes were Wilson disease and arrhythmogenic right ventricular dysplasia, hereditary nonpolyposis colon cancer.

Although there are suggestions for reporting of these genes, different centers may display different approach styles such as reporting VUSs, heterogeneous variants in OR phenotypes. It is even possible to report other genes not recommended by ACMG in some centers, Different societies may display different attitudes regarding incidental genes to be reported. The content of these genes may vary depending on time and society due to reasons such as frequency of consanguineous marriages and diseases and new treatment possibilities. For our community, it can be recommended to report diseases such as Thalassemia and FMF, which are high frequency in our society In addition, reporting of heterozygous variants in OR phenotypes can be discussed for our country where consanguineous marriage is common.

Keywords: American College of Medical Genetics, Incidental, WES, Thalassemia, FMF

OP-20-213

The utility of whole exome sequencing in the diagnosis of rare skeletal dysplasias: Ege experience

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Skeletal dysplasia is a group of genetic diseases involving 461 diseases in 42 groups and involving more than 437 genes. Identifying genetic etiology in skeletal dysplasias is important in determining the carrier status for a recessive disease and identifying other family members at risk for the disease found in the same family and this is of great importance in terms of prenatal diagnosis and possible treatment options in this group of patients with genetic and phenotypic heterogeneity. Skeletal dysplasias are seen in the population in the frequency of 1/3000-5000, although they are rare when examined separately. Considering the fact that the high rate of consanguineous marriages in our country increases the frequency of many diseases that are expected to be rare, the importance of the situation is better understood. Whole exome sequencing (WES), which is one of the successful applications of Next Generation Sequencing NGS, stands out as a very important technique in establishing molecular diagnosis for diseases with known genes and in identifying novel genes in diseases with unknown molecular etiology.

21 variants were found in 19 different genes (*NEK1, LIFR, TP63, COL1A1, PIGV, COL5A1, NSD1, FBN1, GNTPAB, IFITM5, CASR, PIK3CA, COL1A2, COL11A2, GNS, MECOM, GDF5, ARSE, DOCK6*). Autosomal dominant inheritance, autosomal recessive, X-linked recessive inheritance are observed respectively in 9,7 and 1 genes. Also, somatic mutation is observed in 1 gene. In addition, autosomal dominant and recessive inheritance patterns can be seen together in *COL11A2* and *GDF* genes. Ten of the 21 variants identified are novel and 11 of them have been reported as defined. 8 missense, 7 nonsense, 3 splicing, 2 frameshift deletions and 1 synonym variants were detected. Moreover, WES has an important place in making a definitive diagnosis in rare diseases such as skeletal dysplasia with clinical and genetic heterogeneity, where it is difficult to determine the subtypes clinically.

Keywords: Skeletal Dysplasia, Whole Exome Sequencing, WES

OP-20-214

Evaluation of clinical, cardiological and possible causes of inherited thrombophilia risk of patients with Down Syndrome

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Down syndrome (DS) or Trisomy 21 is the most common genetic cause of mental retardation, immunodeficiency and congenital heart defects. To our knowledge, there are no studies about the possible causes of inherited thrombophilia and cardiological examination in DS patients. So, we performed the current studies. Total of 53 patients with DS (32 male and 21 female) were included in the current study.

Physical examination of cases were performed. 12-lead Electrocardiogram (ECG) was done for each case at rest. All of the patients were evaluated with transthoracic echocardiography. Additionally, possible causes of inherited thrombophilia including MTHFR *A1298C*, MTHFR *C677T*, Factor II *G20210A*, Factor V Leiden *G1691A*, Factor V Cambridge *G1091C*, Factor XIII, *APOB*, *ITGB3*, *FVHR2*, *FGB*, *PAI-1* and *ACE* genes were evaluated.

Mean age of cases was 5.164±4.428. Mean length and weight of cases were 96.955±29.293cm and 22.056±21.482kg, respectively. Mean birth weight of cases was 2955.283±397.122 gr. There is no family history of cases for DS. Twenty-two of cases (79.2%) had delay in holding their head, 43 of cases (81.1%) had delay in unsupported sitting, and 41 of cases (77.4%) had delay in walking. Twenty-eight of cases (52.8%) had hypotonia. Twenty of cases (37.7%) had mild developmental delay, 23 cases (43.4) had moderate developmental delay and 7 (13.2%) cases had severe developmental delay but 3 (5.7%) cases had no developmental delay.

Forty-four (64.1%) patients had system anomalies. Twenty-seven (51%) patients had hypothyroidism and three patients (5.7) had hyperthyroidism, conversely twenty-three of cases (43.3%) had normal. Twelve of cases (22.6%) had hearing problem and seven of cases (13.2%) had vision problem. Only two cases(3.8%) had convulsion history. Three cases (5.7%) had aortic regurgitation(AR) and two of them had mild AR and 1 of them had moderate AR, six cases (11.4%) had mitral regurgitation(MR) and four of them had mild MR, 1 of them had moderate MR and 1 of them had severe MR. Sixteen cases (30.3) had tricuspid regurgitation(TR), 11 of them had mild TR and 5 of them had moderate TR. Two cases (3.8%) had mild pulmonary regurgitation. Thirteen of cases (24.5%) had ASD, nine cases (17%) had VSD. Eight of cases (15.1%) had operation history. Five cases (9.4%) had thinned interatrial septum. Fourteen of cases (26.4%) had Pulmonary hypertension, 2 of them had stage I, 11 of them had stage II and 1 of them had stage III. Seven of cases (13.2%) had incomplete right bundle branch block in their ECG.

Twenty one patients (39.6%) had heterozygous MTHFR A1298C carriers and ten patients (18.9%) had homozygous MTHFR A1298C carriers. One patient (1.9%) had heterozygous Factor II G20210A carriers. Nine Patients (17%) had heterozygous Factor V Leiden G1691A carriers. Three patients (5.7%) had heterozygous Factor V Cambridge G1091C carriers. Twenty-one patients (39.6%) had heterozygous MTHFR C677T carriers and one patient (1.9%) had homozygous MTHFR C677T carriers. Twenty-three patients (43.4%) had 5G/5G carriers and eighteen patients (34%) had 4G/5G variation carriers for PAI. Twelve patients (22.7%) had heterozygous FactorXIII carriers and one patient (1.9%) had homozygous FactorXIII carriers. All patients were normal for APOB and FVHR2. Six patients (11.3%) had heterozygous ITG carriers. Twenty-six patients (49.1%) had ins/del carriers and twenty patients (37.7%) had del/del variation carriers for ACE. Two patients (3.8%) had heterozygous FGB carriers. All patients had homozygous and/or compound heterozygous variation carriers for inherited thrombophilia.

In addition to developmental delay and system anomaly, thyroid failure, hearing loss, ocular abnormalities etc, cases with DS may have increasing cardiac problems and possible causes of inherited thrombophilia risk. Therefore, these cases should be regularly evaluated and followed for cardiac problems and inherited thrombophilia risk.

Keywords: Down Syndrome, Inherited Thrombophilia, Cardiological Examination

OP-20-215

Hypohidrotic ectodermal dysplasia: A novel mutation in the *EDA* gene

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Hypohidrotic ectodermal dysplasia (HED) is a genetic disorder characterized by the cardinal features hypohidrosis, hypotrichosis and hypodontia. The estimated incidence is approximately 1 to 2 in 10,000 live births. HED is caused by mutations in the *EDA, EDAR, EDARADD, or WNT10A* genes. In approximately 65-75% of HED cases is inherited as an X-linked pattern, with the rest of the cases showing autosomal recessive or autosomal dominant inheritance. X-linked hypohidrotic ectodermal dysplasia (XLHED) is caused by mutations in the *EDA* gene, which encodes a transmembrane protein, called ectodysplasin A. This protein is part of a signaling pathway that plays an important role in the development of ectodermal tissues. Some people with hypohidrotic ectodermal dysplasia have distinctive facial features, including a prominent forehead, thick lips, and flattened bridge of the nose. A five years old male patient was referred to our clinic because of hypodontia and dysmorphic features. He is the seventh child of non-consanguineous parents. At the clinical evaluation his weight was 10,5kg (<3rd centile), height 90cm (<3rd centile) and head circumference 47cm (<3rd centile). The physical examination findings included fine and sparse scalp hair, high forehead, mild wrinkles and hyperpigmentation around the orbits of the eyes, depressed nasal bridge, hypoplastic alae nasi, missing and abnormal teeth. Chromosomal analysis revealed a normal 46,XY male karyotype. Clinical diagnosis was compatible with hypohidrotic ectodermal dysplasia on the basis of these typical manifestations. Molecular analysis revealed a novel hemizygous c.644G>T (p.Gly215Val) mutation in the *EDA* gene. In this study, we describe the clinical features and molecular characterization of a novel mutation identified in a patient with XLHED. Our finding expands the spectrum of *EDA* mutations and may contribute a better understanding of the molecular basis of HED.

Keywords: *EDA* gene, Hypohidrotic Ectodermal Dysplasia, Novel Mutation

OP-20-216

An extremely rare condition Rhizomelic chondrodysplasia punctata type 5 in a large kindred Turkish family

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Numerous rare genetic conditions are difficult to diagnose, sometimes the diagnoses can take decades. Thus, patients and families get delayed diagnosis or undiagnosed during their lifetime. Clinical features can broadly be used to discriminate one condition from another. In some cases, these clinical features overlap with some other genetic circumstances. On the others, it is very difficult to diagnose due to insufficient clinical knowledge or technologies. However, a recent high-throughput DNA sequencing approaches give the easiest and the most accurate molecular diagnosis. Rhimozelic chondrodysplasia punctate type 5 (RCDP5; MIM# 616716) is an extremely rare autosomal-recessive genetic condition with an estimated incidence of 1/1000000. RCDP5 is generally characterized by dwarfism, broad nasal bridge, epicanthus, high-arched palate, dysplastic external ears, micrognathia, congenital contractures, ocular involvement, cutaneous lesions, and severe mental retardation. 16-years-old male patient was admitted to pediatric policlinic with complaints of joint pain. He was the second child of consanguineous parents. According to his mother, he started to show first symptoms due to chondrodysplasia around two-years-old. Despite the family went to several hospitals, since then the child could not get accurate diagnosis. The other siblings were healthy, however his great uncles and nephews also from consanguineous marriage are affected with similar clinical symptoms. During clinical examination, his height (169 cm) and weight (69 kg) were recorded normal. Shortness of the femur and humerus, broad nasal bridge, epicanthus, high-arched palate, dysplastic external ears, micrognathia, congenital contractures, cafe au late stain were observed. Whole Exome Sequencing analysis revealed a homozygous frameshift variant (c.151delA; p.Ser51Valfs*21; rs1302004687; MAF: 0.00001) within the *PEX5* (MIM# 616716) gene. In silico prediction software were indicated the variant as likely pathogenic. This variant has been detected as heterozygous statues in two individuals who has South Asian origin according to GnomAD browser. The other affected members also show same clinical phenotype, thus direct re-sequencing analysis have been carried out those family members as well as non-affected family members as well. This study contributes one more variant to the growing list of reported mutations for this syndrome giving an importance of gene-gene and gene-environment interactions. Overall, in the light of the fact that the genotype and phenotype correlation of RCDP5 is still uncertain, the present outcome can enhance our knowledge on this rare and severe genetic disorder.

Keywords: Rhizomelic Chondrodysplasia Punctata Type 5, PEX5, Rare Disease, RCDP5

OP-20-217

Transaldolase deficiency in a patient with hypergonadotrophic hypogonadism: Novel mutation in the pentose phosphate pathway

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The pentose phosphate pathway (PPP), also known as the hexose monophosphate shunt, is an alternative way for glucose oxidation and branches off from glycolysis. This pathway consists of oxidative and non-oxidative phases and acts as an important component of cellular metabolism in maintaining carbon homeostasis. Firstly, during the oxidative phase it produces nicotinamide adenine dinucleotide phosphate (NADPH), which is important for protection against oxidative damage. Secondly, it synthesizes ribose-5-phosphate (R5P), which is used in nucleotide synthesis. The non-oxidative phase of the pathway reversibly reconverts pentose phosphates into glycolytic intermediates, such as fructose-6P and glyceraldehyde-3P. Several disorders including glucose-6-phosphate dehydrogenase deficiency, R5P isomerase deficiency and transaldolase deficiency have been identified in the pentose phosphate pathway. Translaldolase (TALDO) is a rate-limiting enzyme of the non-oxidative pentose phosphate pathway. Lack of TALDO enzyme causes accumulation of seven carbon chain sugars and scarcity of antioxidative NADPH and glutathione. Additionaly, TALDO is suggested to disturb the mitochondrial metabolism by affecting other metabolites involved in the tricarboxylic acid (TCA) cycle.

TALDO deficiency (OMIM 606003) is a rare autosomal recessive multi-systemic disease of carbohydrate metabolism. TALDO deficiency has a vast phenotypic spectrum ranging from neonatal liver failure to slowly progressive liver cirrhosis and characterized by intrauterine growth restriction, hepato(spleno)megaly, bicytopenia, nephrolithiasis and congenital heart disease. Coagulation defects and skin manifestations consisting of telangiectasias or hemangiomas could also be seen in the patients due to the liver failure. This condition was first described in 2001, in a Turkish patient presenting with neonatal liver failure and coagulation disorder.

Since the first description in 2001 approximately 39 patients with 16 different genetically confirmed mutations have been reported. We report on a patient with a late on-set form of TALDO Deficiency characterized by hypergonadotrophic hypogonadism in whom the molecular diagnosis could be established through the application of reverse genetics with the use of clinical exome sequencing (CES). Illumina TruSight One panel was used for clinical exome sequencing. Libraries were pooled together and underwent two rounds of hybridization and capture, and additional quantification and size assessment.

In conclusion, we further expand the mutational and phenotypic spectrum of TALDO deficiency and we show that TALDO deficiency is a pleiotropic disorder that should be considered in the differential diagnosis of unexplainable elevated AFP levels and hypergonadotropic hypogonadism with microlithiasis.

Keywords: Alpha Feto Protein, Hypergonadotropic Hypogonadism Deficiency, TALDO1, Transaldolase Deficiency

OP-20-218

Diagnostic efficiency of clinical exome solution panel in patients with deafness/hearing loss

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Hearing loss is a heterogeneous disorder in which multiple genes are implicated in the disease etiopathogenesis. Genetic diagnosis is highly important for Hearing Loss (HL) patients to ensure the etiology of the condition and counsel the patients properly. NGS is considered to be the best practice for diagnosis. Large gene panels also can evaluate non-prevelant genes and candidate variants specific to populations.

Keywords: Hearing Loss, Hereditary Deafness, Next-Generation Sequencing, CES

OP-20-219

A novel *EDAR* gene variant causing autosomal dominant hypohidrotic ectodermal dysplasia

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Ectodermal dysplasias (EDs) are rare, heterogeneous genetic disorders characterized with primary defects of skin, hair, nail, sweat gland and teeth that are tissues derived from embryonic ectoderm. There are more than 100 types of EDs. The most common ED is hypohidrotic ectodermal dysplasia (HED) with 1/20.000 incidence and present with hypotrichosis (sparse hair), hypohidrosis (reduced ability to sweat) and hypodontia. It's caused by *EDA* (MIM *300451), *EDAR* (MIM *604095), *EDARADD* (MIM *606603), *TRAF6* (MIM*602355) and *WNT10A* (MIM* 606268) gene variants. Phenotype- genotype correlation isn't clear today. Most of the patients with HED have the X-linked inherited *EDA* gene variants. Ectodysplasin 1 anhidrotic receptor (*EDAR*) gene has an important role in embryogenesis and these gene's variants are inherited either autosomal recessive or dominant manner.

We evaluate a patient with clinical signs of hypohidrosis, hypodontia and hypotrichosis. For the investigation, we performed clinical exome sequencing and found a novel heterozygous variant in exon 12 of the *EDAR* gene [NM_022336 c.1119_1123delinsA p.(Trp374Alafs*9)]. Next, we performed Sanger sequencing to the patient, her mother and father and confirm the de novo variant.

Our study reports a novel variant in the *EDAR* gene associated with HED. Also, it confirmed previous studies showing that autosomal dominant inheritance *EDAR* variants result in milder clinical manifestations and contributing to the phenotype-genotype correlation.

Keywords: *EDAR* gene, Hypohidrotic Ectodermal Dysplasia, Hypodontia, Case report

OP-21-301

Targeted next-generation sequencing for Limb-Girdle Muscular Dystrophies achieves a high diagnostic yield

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Limb-Girdle Muscular dystrophies (LGMD) are a heterogeneous group of neuromuscular disorders with multigenic etiology. There are more than 30 subtypes of LGMD that have both autosomal recessive and autosomal dominant inheritance. Many myopathies or metabolic diseases can simulate the muscle weakness observed on LGMD, therefore, whole-exome sequencing has been discussed several times to be the most powerful method for the molecular diagnosis in patients with muscular dystrophy- myopathy clinic, previously.

In terms of cost-effectivity, a panel with 47 genes including *ANO5, CAPN3, CAV3, CLCN1, COL6A1, COL6A2, COL6A3, DAG1, DES, DMD, DNAJB6, DYSF, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GMPPB, GNE, HNRNPDL, ISPD, LAMA2, LIMS2, LMNA, MYOT, PLEC, POMGNT1, POMGNT2, POMK, POMT1, POMT2, SEPN1, SGCA, SGCB, SGCD, SGCE, SGCG, SMCHD1, SYNE1, SYNE2, TCAP, TNPO3, TRAPPC11, TRIM32, TTN, VCP* genes was designed as a first-tier genetic approach. This panel includes not only LGMD related genes but also some metabolic disease and myopathy associated genes that have overlapping clinical findings. This test was performed to 40 patients who were consulted at the Medical Genetics Clinic of Ankara City Hospital between March and December 2019 due to muscular dystrophy. Dystrophin gene deletion/duplication analyses were also performed to the patients with a pre-diagnosis of Duchenne muscular dystrophy.

Molecular etiology of 21 patients was solved (21/40-%52,5) with this panel which was resulted as normal for 13 patients. There were three patients who had a variant of unknown clinical significance (*FLNC* gene (2) and LMNA gene (1) mutations) while a heterozygous pathogenic variant was detected in 3 patients for an autosomal recessive disease (*CAPN3*, *SGCA*, *ANO5*), thus we planned MLPA (multiplex ligation probe amplification) for any possible deletion on the other allele. Causal variants were identified in 12 genes including *DYSF (4), LAMA2(3), CAPN3(2), LMNA(2), SGCA(3), TTN(2), COL6A1, ANO5(2), POMGNT, TCAP, POMT1, POMT2,* and *CAV3*. Two of the patients had compound heterozygous mutations (*SGCA* and *ANO5* genes), and also the molecular etiology of a patient, who had both *POMT1* and *POMT2* mutations, thought to be clarified by digenic inheritance.

Molecular diagnosis in muscular dystrophies is essential to arrange the treatment options, reproductive choices, and predictions about the prognosis. Targeted NGS is a cost-effective method that reduces the whole-exome sequencing requirements by %50 approximately, and provides a significant diagnostic rate in the patients of LGMD.

Keywords: Next Generation Sequencing, Muscular Dystrophy, Genetic Heterogeneity

OP-21-302

Retrospective evaluation of pgd-hla cases for diverse genetic diseases

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The combination of preimplementation genetic diagnosis (PGD) with human leukocyte antigen (HLA) matching has appeared as a remarkable tool for the therapy of single-gene or acquired diseases in affected individuals. The technique (PGD-HLA) provides the parents whom have affected child with disease-free and HLA-matched embryos that are compatible with the affected child, offering an unaffected newborn and a donor for affected child.Embryo biopsy samples of the cases were evaluated by Sequence method using STR marker and linkage analysis method.The present retrospective evaluation covers 64 couples who had undergone 131 PGD cycles in total for both HLA matching and elimination of the mutation(s) associated with different diseases, including acute lymphoblastic leukemia (n=2), aplastic anemia (n=1), Diamond-Blackfan anemia (n=2), Fanconi anemia (n=2), Griscelli syndrome (n=2), Hermansky-Pudlak syndrome (n=1), hyper IgE syndrome (n=1), hyper IgM syndrome (n=3), myelodysplastic syndrome (n=1), Morquio syndrome (n=1), severe combined immunodeficiency (n=1), thalassaemia (n=55), Wiskott-Aldrich syndrome (n=1), chronic granulomatous disease (n=1) and amyotrophic lateral sclerosis (n=1). Amongst the total embryos (n=1217), 250 embryos (20%) were wild type in terms of scanned mutation(s) and 206 embryos (17%) were found to be HLA-matched.64 patient with 125 embryos in total were transferred and 33.8% clinical pregnancy rate per transfer was achieved. 27% of these pregnancies were born healthy. The present study underlines the importance and efficacy of PGD-HLA method in the treatment of related diseases.

Keywords: Genetic Diseases,HLA Matching, PGD-HLA, Single Gene

OP-21-303

Next-generation sequencing based panel testing for primary myelofibrosis

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Primary myelofibrosis is a type of disorder among Philadelphia negative myeloproliferative neoplasms, presents with bone marrow fibrosis and pancytopenia. Genetic and epigenetic alterations could result in impaired clonal hematopoietic stem cell proliferation in addition to bone marrow micro-environmental factors. Although the molecular mechanism of myelofibrosis is still not clearly understood; the effect of hematopoietic stem cells, stromal cells and their surrounding signal molecules on the progression of myelofibrosis and development of malignancy is known. In addition to conventional diagnostic methods such as morphological evaluation and flow-cytometry, next-generation sequencing (NGS) based panels has been added recently. Several myeloid panels are now available from evaluation centers of genetic diseases. In this context, we performed Myeloid SolutionTM by Sophia Genetics to six myelofibrosis case for describing the somatic driver mutations. The samples were taken from peripheral blood for five patients and bone marrow for one patient. The panel covers complete coding sequence including ± 25 bp of exon-flanking regions of the 30 most relevant genes (*ABL1, ASXL1, BRAF, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1, ZRSR2*). The sequencing process was performed on the Illumina MiSeq system (Illumina Inc., San Diego, CA, USA). The data analyses were performed on Sophia DDM software (Sophia Genetics, Saint-Sulp). According to the results, the number of the somatic alterations is higher in the sample, which was taken from bone marrow, as expected. The most mutated gene is RUNX1, which is detected in four patients. The variation is common for all patients (RUNX1:c.1265A>C p.(Glu422Ala) NM_001754). RUNX1, a transcription factor involved in hematopoietic differentiation, is altered by mutation or chromosomal rearrangement in various hematologic malignancies. Other mutations have been detected in *CEBPA, TET2, ASXL1, NRAS, U2AF1, ETV6* genes. None of the detected mutations offered targeted therapy alternatives. In addition, there are no informative findings in terms of prognosis determination. In conclusion, with the elucidation of molecular changes in myelofibrosis and the expansion of targeted therapy opportunities, the data obtained from patients who received myeloid panel will be more functional. Collaboration of medical geneticists and hematologists is important in this regard.

Keywords: Primary Myelofibrosis, Next Generation Sequencing, Myeloid Panel

OP-21-304

Clinical, electrodiagnostic, and genetic features of Kennedy disease (spinal and bulbar muscular atrophy) in a patient with proximal muscle weakness

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Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare, X linked inherited, lower motor neuron disease characterized by progressive muscle weakness. SBMA is important in differential diagnosis of myopathies with motor proximal muscle weakness and other motor neuron disorders.

Herein we report a case of 68 year- old- man presented with complaints of worsening gait and dysphagia for several years. Physical examination revealed grade III gynecomastia. Muscle strength was 4/5 in the proximal muscles of both lower extremities. Also, there was postural tremor in both upper limbs. Laboratory tests revealed elevated serum creatinine kinase (CK) with decreased serum creatinine levels. Electrophysiological examination revealed decreased sensorial conduction velocities and sensory nerve action potential (SNAP) amplitudes. Insertion activity was commonly increased and fibrillation potentials were detected in proximal muscles of both lower extremities. In addition, interference pattern of all muscles were incomplete and motor unit action potentials (MUAP) were detected as high amplitude, prolonged and polyphasic. The diagnosis of SBMA was confirmed by detecting increased CAG repeat on genetic examination.

SBMA should be kept in mind in male patients in the presence of perioral fasciculation and gynecomastia presenting with proximal muscle weakness. In laboratory tests there may be moderate serum CK increase and serum creatinine levels may correlate inversely with disease progression. Electrophysiological studies and genetic investigations play a critical role in distinguishing SBMA from other motor neuron disorders. Anti-testosterone therapies are promising in SBMA and further studies using biomarkers such as serum creatinine are needed to address the beneficial effects of new treatments.

Keywords: Kennedy Disease, Creatinine Kinase, CAG Repeat, Motor Neuron Disorder

OP-21-305

An unexpected patient with recently named mental retardation. The report of the very first case of GATAD2B-related neurodevelopmental disorder in Turkey

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GATAD2B-associated neurodevelopmental disorder (GAND) is an autosomal dominant inherited infantile-onset disorder characterized by impaired language development and typical facial dysmorphism. GATA zinc finger domain-containing 2B (GATAD2B) gene encodes a subunit of the MeCP1-Mi-2/nucleosome remodeling and deacetylase complex which thought to be involved in the stem cell differentiation and neurodevelopment. We herein report a patient with GAND, a newly defined rare genetic disease, in contrast to previously reported cases. The patient was a 5-year-old male, child of healthy and nonconsanguineous parents, accepted to our center with the complaint of speech delay. He was born at 41 gestational weeks via Caesarian section. At birth, he weighed 3,600 g and had head circumference greater than average. He hospitalized in his early neonatal period because of nutritional deficiency and jaundice. He was able to sit without support at 10 months of age and was able to walk unaided at 1.5 years of age. He described as floppy in his infancy and his gait was ataxic. He never attained toilet training. He had dysmorphic facial features, those are a high wide forehead, prominent supraorbital ridges, an elongated wide nose, a bulbous nasal tip, a short philtrum, and a pointed chin. In the neurological assessment, the patient had good eye contact. He could not speak a single word and showed a tendency toward hyperactivity. The MRI demonstrated prominent perivascular spaces in the parieto-occipital region. Chromosome analysis confirmed normal karyotype (46, XY) and PTEN gene sequence analysis was normal. Chromosomal microarray analysis identified microdeletion on 1q21.3, encompasses *INTS3*, *SLC27A3*, and *GATAD2B* genes. The latter gene is known to be related to GAND however, alterations of the other two genes are not associated with any known disorder. Only 60 GAND cases have reported by this time. This is the very first GAND case reported in Turkey. Despite the heterogenic causes of intellectual disability makes it more challenging for genetic and clinical diagnosis, accurate identification of the etiology will make proper management and accelerated reintegration of patients into the community.

Keywords: Chromosomal Microarray, GATAD2B-Associated Neurodevelopmental Disorder, Microdeletion

OP-21-306

A unique cytogenetic progression pattern of a chronic myeloid leukemia patient

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Chronic myeloid leukemia (CML) is a hematologic malignancy and mostly affects elderly people. The Philadelphia chromosome is shown approximately at 90% of blood cells with CML patients. We demonstrate a very young patient at the age of 32 who has been diagnosed with CML. His complaints were weight loss, weakness and loss of appetite. His physical examination revealed splenomegaly, and laboratory analysis showed leukocytosis. He was diagnosed by bone marrow biopsy. He has been treated with imatynib/dasatynib for several years. Six years later, he went into acute transformation. Patient developed erythematous nodular skin lesions and pancytopenia. Skin biopsy was performed, and it reported as granulocytic sarcoma and bone marrow biopsy confirmed acute myeloid leukemia (AML). More interestingly, while acute phase, he has had very complex karyotype with classic Philadelphia chromosome and a marker chromosome later identified as Philadelphia chromosome by FISH analyses. The cytogenetic pattern were 50,XY,+8,+8,+9,+der(22)t(9;22)(q34;q11),t(9;22)(q34;q11),i(17q). He had two extra chromosomes 8 which is one of the most frequent abnormalities aside from Philadelphia chromosome in CML and in very rare cases it is associated to the development of myelodysplastic syndrome (MDS) or AML. All cytogenetic findings are confirmed with FISH analyses. Two additional findings like monosomy of *PDGFRB* gene at the 5q32 and trisomy of PML gene at 15q24 locus were found.

Keywords: Leukemia, Philadelphia, Cytogenetics, Tetrasomia

OP-21-307

Missense rarely mutation, c.435 T>G, on *MSH2* gene of breast cancer

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Breast cancer is the most commonly occurring cancer among women. A family history of breast cancer is one of the main risk factors for developing the disease. It is currently estimated that approximately 5–10% of breast cancers are due to an inherited predisposition, and approximately 20–25% of this risk is explained by many high-penetrance susceptibility genes: *BRCA*, *PALB2*, *RAD51C* etc. The NGS analysis of the *PALB2* and *MSH2* genes is described as follows. The sequencing data were analyzed with bioinformatics software: The Sophia DDM® software version 5.6.0 (Sophia Genetics SA, Saint Sulpice, Switzerland) was used to confirm point mutations and is also used to identify copy number variants (CNVs). Proband has a triple negative breast cancer and has found to carry heterozygous c.1704_1707 deletion mutation in *PALB2* gene which is a frameshift mutation that causes protein termination at codon 598 as a result of NGS analysis and to carry heterozygous c.435 T>G missense mutation in MSH2 gene which this variant was also identified in a patient with triple negative breast cancer, in co-occurrence with a pathogenic *PALB2* variant. Therefore, as proband was carrying mutation, other sisters and mother were also screened for carrying c.1704_1707 deletion mutation due to having a family history of breast cancers. Therewithal probands daughter was carrying c.1704_1707 deletion mutation in *PALB2* gene and c.435 T>G missense mutation in *MSH2* gene. But proband's daughter does not developed breast cancer. So we informed about it and take her on screening program on breast cancer. c.435 T>G missense mutation in *MSH2* gene mutation was classified as Uncertain significance in literature but Spugnesi et al. (2016) was described triple negative breast cancer, in co-occurrence with a pathogenic *PALB2* variant. Our result coincides with Spugnesi 2016. However c.435 T>G missense mutation in *MSH2* gene is a classified as Uncertain significance by analysis of more cases, any relation could be found between this mutation and disease in near future and could be added to databases.

Keywords: Breast Cancer, MSH2, PALB2

OP-21-309

Submicroscopic insertion of PML segment into RARA on chromosome 17q resulting a very rare variant of PML-RARA fusion in acute promyelocytic leukemia

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Acute promyelocytic leukemia (APL) which is a subtype of acute myeloid leukemias (AML) represents 5-10% of AML and is characterized by t(15;17)(q24;q21) resulting in a fusion protein of the PML (15q24.1) and RARA (17q21.2) genes. Rapid diagnosis of APL is crucial as this genetic alteration is specific to APL and it has been associated with favorable prognosis in terms of an availability of an effective therapy. The presence of PML-RARA fusion may be confirmed by various methods. The classic fusion pattern is present in 90-95% of the cases; however other variants are observed in minority of patients. Here we report a 30-year-old male patient who admitted to the emergency department with weakness, bleeding in the mouth and high fever. In the physical examination, pale skin, bleeding from the gum mucosa and splenomegaly was observed. Hematological parameters revealed leukocytosis, thrombocytopenia and anemia. Coagulation studies were consistent with disseminated intravascular coagulation. In the peripheral smear, dense granulated promyelocytic blastic cells with Auer rods were noted. The leukemic cells expressed CD33, CD117 and MPO, and were negative for CD123, CD163, CD3, CD34, CD79a and TdT detected by flow cytometry. Bone marrow biopsy showed a hypercellular marrow with 100% cellularity, 90% involvement by blasts. t(15;17)(q24;q21) was suspected in the karyotype analysis obtained from bone marrow and fluorescence in-situ hybridization (FISH) analysis using dual color, dual fusion PML-RARA probe showed a different pattern of hybridization. One fusion, two *PML* and one *RARA* signals were detected. It was interpreted that a small *PML* fragment was translocated to *RARA* locus on chromosome 17, demonstrating an interstitial insertion of PML into RARA gene. The patient was diagnosed as APL and all-trans-retinoic acid (ATRA), idarubicin and cytarabine treatment was started. The patient underwent cranial tomography due to sudden memory loss and lack of orientation and multiple hemorrhagic areas were detected in brain structures. Subsequently, he lost consciousness and was intubated. The patient died on the 5th day of chemotherapy. Among the reported rare cryptic PML-RARA rearrangements, most of the variants were insertions of *RARA* gene into PML locus. Submicroscopic insertion of *PML* gene into *RARA* locus is extremely rare and to our knowledge, there are less than ten cases reported in the literature. According to those literature, response to treatment and relapse rates were found to be similar compared to classic t(15;17) however, prognosis was poor in most of the cases. Our report highlights the importance of cryptic PML-RARA rearrangements in APL diagnosis. Careful investigation of atypical FISH data may help in characterizing the exact mechanism of this rearrangement and it surely supports the aspect that the reported non-reciprocal single PML-RARA fusion is the primary fusion product for APL pathogenesis.

Keywords: Acute Promyelocytic Leukemia, PML, RARA, Submicroscopic Insertion

OP-21-310

Therapeutic approach to DMD with HSP70-hom and HSP70-2

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Duchenne muscular dystrophy (DMD), which is a X-linked recessive disease, vigorous and progressive muscle wasting disorder formed by mutations in dystrophin gene. It is leading to stroke in the adolescence and usually resulting with death in the third decade from cardiopulmonary problem. With regret, there is no precise cure for these patients yet, and existing therapies are unsuccessful. HSPs are vital for the repairing of faulty proteins resulting from different stresses including inflammation, toxic metals, oxidative free radicals. *HSP70* gene family have three members and these are; HSP70-1, HSP70-hom and HSP70-2. HSP70-1 and HSP70-2 similar protein. Polymorphism within *Hsp70-hom* and *Hsp70-2* genes has been characterized in 1992. Polymorphic Pst1 site at location1267 A>G[=1249A>G, (GI=5123454)] of the Hsp70-2. Other polymorphic Nco1 site at location [=1630 C>G, (GI=27436929)] of the Hsp70-hom. The aim of the present case-control study was to determine the association between the heat shock protein 70 (HSP70) and risk of DMD in Turkey patients by genotyping gene polymorphism. This study hypothesized that the development and severity of DMD may be reduced with HSPs therapy. A total of 40 DMD (+), 40 DMD (-), 40 control subjects considered for this study. Thereby; the present study was designed to assign whether the polymorphic features of two *HSP70* genes; *HSP70-2* and *HSP70-hom*, are annexed with the severity of DMD. DNA isolations were performed and SNV and CNV analyzes were performed with the new generation sequence system. Cases whose copy number changes were confirmed by MLPA. Genomic DNA was extracted from peripheral blood using commercial DNA isolation kit (QIAamp DNA blood kit). The Quality of DNA (ng/µl) samples were assigned using agarose gel-electrophoresis and exact quantities assessed by spectrophotometry (Nano Drop 1000, Thermo Scientific, Wilmington, NC). Polymorphism was performed using (PCR-RFLP) technique. Pst-1 site within the *HSP70-2* gene and NcoI site within the HSP70-hom gene. As a result; a direct sequencing approach (Company of Sequetech, CA) was performed to confirm the genotypes obtained by PCR-RFLP for some of the different groups. All statistical analyses were examined in SPSS (SPSS Inc., Chicago, IL, USA). The allele and genotype frequencies for HSP70-hom amongst controls and patients were searched by Pearson chi-square test. we found significant association between genotype and presence of DMD patients (p=0.05 The allele and genotype frequencies for HSP70-2 amongst controls and patients were searched by Pearson chi-square test. We found significant association between genotype and presence of DMD patients (p=0.02). The frequency of Hsp70-2A/G or G/G and Hsp70-hom CC haplotype in DMD patients crosscheck to controls come up with them as susceptibility genotypic/allelic variants for DMD patients. Moreover, the important association of high frequency allelic variants of HSP70 genes in DMD, we suggest them as prognostic indictors. Nevertheless, these observations need upward investigations in a bigger controls and relevant patients.

Keywords: DMD, NGS, RFLP-PCR, HSPs

OP-21-311

A novel variant in the *EFTUD2* gene is associated with mandibulofacial dysostosis with microcephaly in a Turkish patient and her mother

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Mandibulofacial dysostosis with microcephaly (MFDM; OMIM:610536), is a rare autosomal dominant disorder. Heterozygous pathogenic sequence variants and exon or whole-gene deletions/duplications in the elongation factor Tu GTP-binding domain containing 2 (*EFTUD2*; OMIM: 603892) gene have been shown to result progressive microcephaly, congenital craniofacial anomalies (malar, mandibular and zygomatic arch hypoplasia, dysplastic ears, micrognathia), cleft palate, hearing loss and choanal atresia. Mutations in *EFTUD2* gene also cause extracraniofacial malformations such as congenital heart defects, esophageal atresia, thumb abnormalities, short stature and developmental delay. Intellectual disability is a significant feature. The disorder is highly penetrant but variably expressive. As most affected individuals have a de novo monoallelic mutations in *EFTUD2* gene, familial recurrence can develop from germline mosaicism or inheritance of the variant from a parent with a relatively mild phenotype. Here, we report a novel heterozygous variant in *EFTUD2*:c.2362-2A>G (p.?) in exon 24 (NM_001142605) in a 4 years old female patient who presented with microcephaly, craniofacial anomalies, cleft palate, dysplastic ears and hearing loss. The patient's mother has also had similar features like microcephaly, mandibular hypoplasia, micrognathia, dysplastic ears. The patient and her mother have had the same splice site mutation in *EFTUD2* gene, identified on clinical exome sequencing. This variant had not been previously reported in the literature and we classified it as "likely pathogenic" according to ACMG criteria.

Keywords: Clinical Exome Sequencing, Dysplastic Ears, Mandibulofacial Dysostosis

OP-21-312

Retrospective evaluation of chimerism analysis after allogeneic transplantation for malignant and non-malignant hematological diseases

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Chimerism analysis is the detection of non-host lymphohematopoietic cells in the blood and bone marrow samples examined. Genetic profiles of donor and recipient are determined by chimerism test after allogeneic hematopoietic stem cell transplantation for malignant and non-malignant hematological diseases. The degree of the mixture found in the peripheral blood, bone marrow or other tissues of the recipient after transplantation is determined. The chimerism test (engrafment analysis) analyzes genetic polymorphisms, often used in DNA identification tests, called the short tandem repeat (STR) locus. These STR loci and *D2S1338, D3S1358, D7S820, D8S179, D13S317, D16S539, D18S51, D21S11, TPOX, THO1, vWA, CSF1PO* and *AMXY* (Amelogenin) regions are examined. By comparing the receiver and donor STR profiles, the percentage of STR loci belonging to the donor in the recipient is determined after bone marrow transplantation. The purpose of this retrospective study is to determine the disease-free and overall survival rates of 260 patients diagnosed with malignancy in Erciyes University Medical Genetics Department between 2016-2019, according to the diagnoses. After the transplant, the suitability STR loci of the recipient was evaluated. In the study, the conditions such as chimeric success rates, survival, 2nd and 3rd transplantations were evaluated. DNA isolation was performed from donor and recipient peripheral blood or bone marrow for chimerism test. STR loci has been replicated using the AMPSTR identifier plus kit. Using the reference sequence with the ABI PRISM 310 genetic analyzer, the STR loci fits were analyzed. When the evaluation is made after analysis, 89 of 260 patients are AML, 47 are ALL and 124 are malign and non-malignant hematological patients. 22% of AML patients died during the follow-up period. It has been observed that the rate of chimerism of patients with Ex gradually decreases. 3 patients have been observed to exhale after the second transplantation. Of 69 patients who were under follow-up, the follow-up of AML patients continues, 10 of these patients were found to have reduced chimerism rates during the follow-up period, and 3 patients were transplanted and 2 were transplanted. 25% of ALL patients were observed to be ex. It has been observed that the rate of chimerism of patients with Ex decreases gradually, and 2 of them have undergone 2nd transplantation. Chimerism rates of 10 of 35 patients who were on the right follow-up decreased and 5 of them were found to have been applied 2nd transplantation. According to the results of chimerism of 260 patients evaluated as a result, the success in allogenic transplantations was not related to the diagnosis of patients. Low donor chimeric levels were observed to be associated with relapse of the disease and mortality of patients. In this respect, chimerism test can potentially be used as an early predictor and prognostic marker. In addition, by looking at the decreased levels of chimerism, survival can be increased by applying immunotherapies to improve in patients as in MRD (Minimal Residual Disease) follow-ups. These findings can be used to design new approaches to prevent relapse and improve post-transplant survival.

Keywords: Chimerism Analysis, AML, ALL

OP-21-313

The evaluation of Th17-related cytokines, IL-6-driven STAT3 phosphorylation in a child with novel *HYOU1* gene mutation

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Hypoxia upregulated 1 (HYOU1) is a chaperone that localizes to endoplasmic reticulum and mitochondria, and participates in cell stress responses, including oxidative stress and unfolded protein response. In the literature, only a single patient with *HYOU1* mutation exhibiting immune deficiency and hypoglycemia has been reported to this day. In this study, we investigated the presence of T cell dysfunction in a patient with a novel *HYOU1* mutation. Whole Exome/Sanger Sequencing was used to identify and confirm the mutation. Peripheral blood lymphocytes were characterized by FACSAria III-based flow cytometric assays with respect to proliferation, apoptosis, cytokine production and phosphorylation. We report a novel, pathogenic compound splice site *HYOU1* mutation (c.2253+6T>G; c.2165+3_2165+6delAAAGT) in a 8-year-old girl who presented with achondroplasia and neutropenia. The patient showed slightly decreased regulatory T cell (Treg) numbers and percentages. There was comparable apoptosis in peripheral blood mononuclear cell (PBMC)s, the *HYOU1* mutation also did not impair phytohemagglutinin, or CD3/28 induced T cell proliferation. Mutant T cells produced elevated Th17-related cytokine IL-17A, while the production of IL-22 and IFN-gamma unchanged. Importantly, *HYOU1* mutant PBMCs showed impaired IL-6-driven STAT3 phosphorylation. In summation, we identified a novel pathogenic mutation in *HYOU1*. This is the first report analyzing Th17-related cytokines (IL-17, IL-22) and showing impaired IL-6 driven STAT3 phosphorylation in a patient with *HYOU1* mutation.

Keywords: Child, HYOU1, IL-6-driven STAT3 Phosphorylation, Th17-Related Cytokines

OP-21-314

A novel variant in the *SLC2A2* gene associated with glycogen storage disease type XI

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Glycogen storage disease type XI is a rare monogenic disorder inherited in an autosomal recessive fashion and is characterized by glycogen accumulation in liver and kidney, proximal renal tubular dysfunction and intolerance to glucose and galactose. It is also called as Fanconi-Bickel syndrome. The responsible gene is *SLC2A2* located in chromosome 3q26.2. The gene encodes the solute carrier family 2 member 2 protein, which is also called as GLUT2 (glucose transporter 2). This transporter is mainly found in hepatocytes, pancreatic islet beta cells, enterocytes, renal tubular cells and facilitates the glucose transport in both directions. Due to its lower affinity to glucose, it works as a glucose sensor. The loss of its function, therefore, leads to the enlargement of liver and kidney, fasting hypoglycemia episodes in addition to postprandial hyperglycemia and diabetes, partial resistance to adrenaline and glucagon, failure to thrive and weakened bones. While the homozygous mutations in this gene are responsible for the Fanconi-Bickel Syndrome, heterozygous mutations may increase susceptibility to non-insulin dependent diabetes mellitus.

We report a case of Glycogen storage disease type XI caused by a novel variant in the *SLC2A2* gene. The patient was a 10-year-old boy when he first admitted to our clinic in February 2019. He became symptomatic in the first days of his life, though. Following a liver biopsy at 12 months of age, he was followed as glycogen storage disease. He was consulted to our clinic to establish the definitive diagnosis. The patient has a younger brother showing similar symptoms and their parents are consanguineous.

We analyzed the patient's DNA using next-generation sequencing. Our analysis yielded a homozygous novel variant (NM_000340 / c.521_527del) in exon 5 of the *SLC2A2* gene causing a frameshift starting from 174th amino acid, changing it from methionine to threonine and forming a premature stop codon 75 amino acids later. Other genes causing glycogen storage disease in our panel showed no significant variants. In order to confirm the result, we performed Sanger sequencing. Both the patient and his younger brother had the same deletion in exon 5. To conclude, we report a novel variant in a very rare metabolic disorder called Fanconi-Bickel Syndrome.

Keywords: Glycogen Storage Disease, Hypoglycemia, Next Generation Sequencing, Novel Variant, *SLC2A2* Gene

OP-21-315

Investigation of *SOX15* gene expression as a new potential tumor suppressor in thyroid carcinoma

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Thyroid cancer is the most common endocrine cancer. *SOX15* gene, located in the p13.1 region of chromosome 17, plays a role in determination of cell fate and the regulation of embryonic development. The aim of this study is to investigate the role of *SOX15* gene in the patients with thyroid cancer. 50 patients who were diagnosed with thyroid cancer in Istanbul Education and Research Hospital General Surgery Clinics were included in the study. Tumor and healthy normal tissues from patients were removed with thyroidectomy operations and *SOX15* gene expression was analyzed by qRT-PCR. Forty of 48 patients (83.3%) were female. Mean age of the patients was 49.75 ± 12.93 years. Expression level of *SOX15* gene was decreased in 31 patients (64.6%), increased in 13 patients (27.1%) and not changed in 4 patients (8.3%). *SOX15* gene expression was decreased by 49% in tumor tissue samples compared to normal tissue samples (p =0.015). No association was found between *SOX15* gene expression and clinical parameters (p>0.05).We found that expression of *SOX15* gene was decreased in thyroid cancer. *SOX15* gene may be a potential tumor suppressor gene in normal thyroid cells.

Keywords: SOX15, Thyroid Cancer, Tumor Suppressor, qRT-PCR, Transcription Factor

OP-21-401

Genetic analyses in understanding of renal tubulopathies

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Renal tubules consist of variable number of different epithelial cells which provide solutes and fluid transmission in nephrons and the renal tubular diseases involve a highly diversity of classification. Anomalies in tubular transport can be divided into two types, primary, or more often secondary to congenital malformations or acquired diseases. Because of the primary tubulopathies are rare and characterized by significant phenotypic variability, clinical diagnosis of these disorders can be difficult. In recent years, advances in sequencing technologies increased the diagnostic rate of renal tubulopathies.

In this study, we aimed to detect the diagnostic yield of our custom designed next-generation sequencing renal tubulopathy panel which includes 50 genes and investigate genotype-phenotype correlation.

We retrospectively assessed 52 patients with renal tubular disease and identified 8 pathogenic variants (15%). Two out of eight mutations were novel. Confirmation and segregation analysis of identified pathogenic and likely pathogenic variants were done by Sanger sequencing. Genotype-phenotype correlation was revealed and used for genetic counseling.

Keywords: Genotype-Phenotype Correlation, Renal, Tubulopathies

OP-21-402

A newborn of fatal surfactant metabolism dysfunction with homozygous mutation in *ABCA3* gene

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ABCA3 (pulmonary surfactant metabolism dysfunction, type 3;MIM 610921) mutations have been associated with lethal neonatal respiratory distress, pediatric and adult interstitial lung disease and surfactant metabolism dysfunction. Most mutations are inherited in an autosomal recessive manner, but cases of uniparental disomy have also been reported. Here we report a newborn of fatal surfactant metabolism dysfunction with homozygous in-frame insertion mutation in the *ABCA3* gene.

Keywords: ABCA3, Homozygous, Surfactant Dysfunction

OP-21-403

A Case of Ovarian Cancer with Double Heterozygous Mutations in *BRCA1* and *BRCA2* genes

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Ovarian cancer is the 7th most common cancer type in women and the prognosis is relatively poor. It is very important to assess the risk of ovarian cancer because of it is being an insidious disease and usually in advanced stages (FIGO stages IIb-IV) when diagnosed. In some families, ovarian cancer could be a member of familial cancer syndrome and seen with other cancers. Although it has been shown various genes in hereditary breast ovary cancer syndrome, the best known genes are *BRCA1* and *BRCA2*. There are lots of reports related with *BRCA1* and *BRCA2* gene mutations, but a relatively small number of papers related with two mutations in both genes are available. Here, we report a case of ovarian cancer with double heterozygosity for *BRCA1* and *BRCA2* genes. A 50-year-old woman with high-grade serous adenocarcinoma in bilateral ovaries diagnosed at 43 years old were referred to our clinics. Recurrence/or metastasis of ovarian cancer has been developed 7 years after first diagnosis. Breast cancer was diagnosed in the patient's both mother and aunt and ovarian cancer was diagnosed in both her grandmother and another aunt. Sequence analysis of *BRCA1*/*BRCA2* genes was performed with the "Qiaseq Human *BRCA1* and *BRCA2* Panel" kit on the Illumina MiSeq platform. Analyzes were done with "Qiagen Clinical Insight (QCI) Analyze Universal Version 1.5.0." pipeline and software. Variants were visualized with the IGV tool. Heterozygous pathogenic frameshift mutations; 858_859delGA (p.N287fs*7) mutation in *BRCA1* gene and c.9682delA (p.S3228fs*21) in *BRCA2*; were detected. The family was consulted in terms of family segregation. In the literature, double heterozygous (DH) mutations in *BRCA1* and *BRCA2* genes have been described in a few papers. DH is seen in 0.22-0.87% of *BRCA* genes and is a rare condition. It has been reported that there is no difference by means of the age of onset, expected life span and development of multiple primary tumors in patients compared to those with a single gene mutation. However, the number of patients identified in the literature is too few for an exact consensus on this issue. Another important issue is genetic counseling of these patients. The risk of carrying mutations in first degree relatives is higher than carriers of single mutations and is up to 75%. Also, generally, DH in *BRCA* genes may have been detected for the first time in the proband and it is more likely to inherit one of the two mutations from the previous generation and also inherit to subsequent generation of the family. So, patient with familial cancer syndromes must be evaluated carefully for all genes studied and double heterozygosity of familial cancer genes should be kept in mind for an appropriate genetic counseling.

Keywords: BRCA1, BRCA2, Double Heterozygosity, Ovarian Cancer

OP-21-404

Multiple neurodevelopmental disorder and *CNTNAP2* gene deletion

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The *CNTNAP2* gene encodes contactin-associated protein-like protein 2, which is a member of the neurexin family and functions as cell adhesion molecules and receptors in the nervous system. This protein is localized in myelinated axons and mediates the interaction between neurons and glia during the development of the nervous system. *CNTNAP2* is one of the largest genes in the human genome localized on chromosome 7q35. This gene has been implicated in multiple neurodevelopmental disorders, including Gilles de la Tourette syndrome, schizophrenia, epilepsy, autism, ADHD and intellectual disability.

The proband two-year-old male patient second child of nonconsanguineous parents was evaluated with delayed speech, crawling, and mild mental retardation. Karyotype analysis was found as 46, XY. In terms of spinal muscular atrophy, analysis of exons *SMN1*, *SMN2* genes 7 and 8 were normal for deletions. As a result of Whole Exome Sequencing (WES) analysis, no pathogenic mutation compatible with the patient's clinic was detected. As a result of Agilent's Array-CGH analysis, arr [GRCh37] 7q35 (146511720_146673090) × 1 result was found. It was observed that *CNTNAP2* gene was found in the region where 161 kb loss (number of markers: 18) was detected in the chromosome 7q35 region. Biochemical studies including thyroid function tests, mucopolysaccharide screen, and urinary amino and organic acids were all normal, as was his cerebral CT scan.

This deletion detected in the *CNTNAP2* gene characterized by multiple neurodevelopmental disorders was found to be compatible with the patient's clinic. The case is presented with the aim of contributing to the literature since it is a rare chromosomal anomaly.

Keywords: *CNTNAP2* Gene, Multiple Neurodevelopmental Disorders, Molecular Karyotyping

OP-21-405

Incidentally identified a *MYL2* gene variant responsible for cardiomyopathy during moleculer analysis of Hermansky Pudlak Syndrome: Evaluation of incidentally detected variants in whole-exome sequencing analysis

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Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease characterized by oculocutaneous albinism and bleeding disorder. In most patients, pulmonary fibrosis, which develops in advanced ages, is the most important cause of death, while a common morbidity is granulomatous colitis. Until today, 10 HPS types resulted from 10 different gene mutations have been identified. Next generation sequencing enables to analyze many genes at the same time, accelerating the clinicians in determining the molecular etiology of genetic heterogeneous diseases. Whether to choose whole exome sequencing (WES) or targeted next-generation panels is a matter of debate due to some ethical problems about the detection of coincidental pathogenic variants that are unrelated to the phenotype. ACMG has recommended that the incidental pathogenic gene variants responsible for 24 different clinical conditions should be reported associated with the results of disease requiring panel or WES. In this study, an HSP patient in whom WES analysis revealed a homozygous mutation in *HPS4* gene and another pathogenic mutation in *MYL2* gene, incidentally, has been presented.

A 39 years-old woman having oculocutaneous albinism, recurrent colitis, bleeding disorder and pulmonary fibrosis was referred for genetic counseling. Her parents were from the same small village. Family history revealed presence of two siblings with albinism. Regarding her clinical findings the diagnosis of HPS was considered. WES was performed for molecular analysis. A homozygous pathogenic c.649C> T (p.Arg217*) variant in *HPS4* gene and a heterozygous c.431delC (p.Pro144fs) variant in MYL2 which is previously defined in hypertrophic cardiomyopathy were detected. Clinical findings and family history of the patient were reevaluated. Family history revealed that she had a mother and maternal grandfather who had been diagnosed to have hypertrophic cardiomyopathy and an echocardiography was planned to evaluate asymptomatic cardiac involvement in her. All potentially affected individuals in the family were also invited for clinical examination and genetic counseling.

This case report emphasizes the importance of WES in the use of genetically heterogeneous diseases and the interpretation of coincidentally detected variants unrelated to the phenotype.

Keywords: Hermansky-Pudlak, Syndrome, WES

OP-21-406

Clinical exome sequencing analysis of a patient with corneal distrophy

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Corneal dystrophies represent a heterogeneous group of genetic diseases that include 22 distinct forms which have predominantly autosomal dominant, although autosomal recessive and X-chromosomal dominant inheritance patterns. A phenotype-genotype correlation has not been reported for the majority of the corneal dystrophies. However, in the diagnosis of corneal dystrophies transforming growth factor, ß-induced gene (TGFBI) mutations were found to be evident for a general phenotype-genotype correlation. Besides, collagen, type XVII, alpha 1 mutation (*COL17A1*) which are causative in the epithelial recurrent erosion dystrophy (ERED) are also found to be important diagnosis of corneal dystrophies.

Here we report a 27-year-old woman who is diagnosed as Bullous keratopathy. At the age of four, she had suddenly lost of vision, having a history of keratoplasty for both eyes but graft was successful only for the left eye. Neurology department is following her in regards to trigeminal neuralgia, continuous headache, pain and tingle in the arms and legs. Besides these symptoms she has an amnesia and exhaustion. There is no history of rheumatic disease. In our laboratory we have performed clinical exome sequencing analysis by Illumina platform covering the exonic and intronic regions of 4500 genes. We have created a panel of 478 genes related to corneal dystrophies by using SOPHIA DDM platform. We have found that our patient was carrying a heterozygous c.121C>T missense mutation on the exon 1 of *PITX2* gene which is classified as potential pathogenic and is very rare among the community. Clinical significance of this variation is not situated in Clinvar.

PITX2 protein is known to play a crucial role in early development, particularly in the formation of structures in the anterior segment of the eye including the iris, the lens of the eye, and the cornea. It is reported in OMIM database that the mutations in the gene can cause ring dermoid of cornea, Axenfeld-Rieger syndrome type 1 ve Anterior segment dysgenesis type 4. Besides these abnormalities *PITX2* gene was also reported to be associated with Peters' anomaly. Clinical findings of our patient were seemed to related with Peters' anomaly. Therefore, genetic counselling was given to her informing that clinical correlations are needed. As we learn lately that her brother has also suffer from the same problem, a family study is planned for detailed analysis.

Keywords: Exome Sequencing, PITX2, Corneal Dystrophy

OP-21-407

The importance of the integrated molecular approach to glycogen storage disease etiology

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Glycogen storage diseases (GSDs) are phenotypically heterogeneous disorders, which can be manifest in various ages from early childhood to adulthood, with different findings such as growth retardation, hepatomegaly, hypoglycemia, and muscle weakness. Classification is made according to the enzyme types whose synthesis is disrupted. However, accurate classification is not always possible with clinical evaluation and biochemical findings. Enzyme replacement therapy is currently available in type 2. GSDs are generally inherited in autosomal recessive manner. Molecular genetic technics are used in the genetic diagnosis of GSDs. The molecular diagnosis provides an opportunity in the management of the disease, especially in patients without clear clinical signs.

In Ankara City Hospital, Medical Genetics Department, a next-generation sequencing (NGS) panel covering 17 genes (*GAA, SLC37A4, G6PC, GYS2, AGL, GBE1, PHKA2, PHKB, PHKG2, PHKA1, PYGM, PYGL, PFKM, PGAM2, LDHA, ENO3, PGM1*) were sequenced using NGS method in 12 patients who were referred for genetic diagnosis of GSDs. Four patients did not reveal a causative variant. Two patients had homozygous pathogenic/likely pathogenic variants in the AGL gene and one patient had hemizygous pathogenic variants in the *PHKA2* gene. One patient had a homozygous variant of unknown significance (VUS) in *PGM1* gene. One patient had a heterozygous likely pathogenic variant in the *PYGM* gene and one patient had heterozygous VUS in the *PYGM* gene. In 2 patients, mutations were detected in different genes suggesting the possibility of digenic inheritance: heterozygous pathogenic/likely pathogenic variants in *GYS2* and *ENO3* genes in one patient and pathogenic/likely pathogenic variants were identified in *GBE1* and *ENO3* in another patient.

Mutations in the *ENO3*, *GBE1* and *GYS2* genes alone are insufficient to explain the patient's phenotype. However, these variants, which can be detected by comprehensive molecular analysis, were thought to explain the patient's clinical findings by digenic heredity. Mutations should disrupt both alleles of a gene to cause disease phenotype in autosomal recessive disorders. Similarly, it should be taken into consideration that in the molecular evaluation of glycogen storage diseases, heterozygous mutations may affect the enzyme level or there may be digenic inheritance in genes with similar function in the same pathway.

The importance of the genetic approach is inarguable in the diagnosis and treatment of GSDs. NGS panels provides a compherensive approach to shorten the diagnosis period.

Keywords: Glycogen Storage Disease, NGS Panel, Digenic

OP-21-408

Investigation of receptor-ligand gene pair mutations in hypogonadotropic hypogonadism

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Hypogonadotropic hypogonadism (HH) is a rare disease that prevents normal pubertal development and causes infertility. To date, more than 50 genes have been reported in HH. Receptors, which are proteins involved in signal transduction, and ligands that bind to them in the biological process are encoded by specific genes. Gonadotropin-releasing hormone receptor (*GNRHR*) and its ligand gonadotropin-releasing hormone 1 (*GNRH1*), tachykinin receptor 3 (*TACR3*) and its ligand tachykinin precursor 3 (*TAC3*), and prokineticin receptor 2 (*PROKR2*) and its ligand prokineticin 2 (*PROK2*) are the main group of receptor-ligand gene pairs which is a HH-related causal genes. In our study, we aimed to evaluate the mutations in the receptor-ligand gene pairs that cause the HH clinic when mutated and to reveal the differences with the literature. In this analysis, the genetic data of 49 HH patients carrying mutations in one of the *TACR3-TAC3*, *GNRHR-GNRH1*, and *PROKR2-PROK2* genes were evaluated. Mutation distribution was determined as 14 *TACR3* (13 missense and one nonsense), two *TAC3* (2 missense), 18 *GNRHR* (15 missense, one splice-site, and two compound heterozygous missense), five *GNRH1* (four frameshift and one missense), 2 *PROKR2* (two missense), and eight *PROK2* (seven missense and one initiation codon change). It is known that receptors have a higher rate of mutation in receptor-ligand pairs. However, in our study, it was observed that the opposite of this situation in our patients carrying mutations in the *PROK* gene group. In detailed *PROK2* mutation analyses, found that the individuals in independent families carry genetic changes in the same amino acid. This repeatedly observed mutation in different patients suggests that it may be a mutation-prone region (hotspot) for this gene. Therefore, it has been demonstrated that giving priority to this region is important in terms of time and cost while screening the mutation responsible for the disease. In addition, we suggest that the detected hotspot data is a guide for ethnic-specific studies and should be specified in public databases.

Keywords: Receptor-Ligand Pair, Hypogonadotropic Hypogonadism, Gene Mutations

OP-21-409

The evaluation of 36 Turner syndrome cases with cytogenetic findings and clinical features of amenorrhea and premature ovarian failure.

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Turner syndrome (TS) is traditionally defined as a chromosomal disorder that affects phenotypic females who have complete or partial monosomy of X chromosome in association with various clinical manifestations. It is the most common sex chromosome disorder in females, occurring in 1 out of 2500 live births. In this study was evaluated the finding of cytogenetic results in turner syndrome's cases.

Keywords: Turner Syndrome, Cytogenetic Findings, Primer Amenorrhea, Premature Ovarian Failure

OP-21-410

A novel *"AMPD2"* gene variant related to pontocerebellar hypoplasia type 9

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Pontocerebellar hypoplasias (PCHs) are autosomal recessive inherited progressive atrophy of the cerebellum and/or brainstem, especially pons. With availability increase of next generation sequencing technologies and whole exome/genome sequencing (WES), detection of new genes and pathogenic variants makes easier to make a diagnosis. There are 21 types and subtypes related to 19 genes (*AMPD2, CHMP1A, CLP1, COASY, EXOSC3, EXOSC8, EXOSC9, PCLO, RARS2, SEPSECS, TBC1D23, TOE1, TSEN15, TSEN2, TSEN34, TSEN54, VPS51, VPS53, VRK1*) in OMIM database describing genetically and clinically heterogeneous phenotypic series of PCHs. In this work we describe a trans positioned AMPD2 gene novel variant with known pathogenic variant.

Seven-year-old male patient from non- consanguineous marriage who has deceased sister with same complaints were referred to our clinic for genetic evaluation because of neurodevelopmental disorders (brain abnormalities in radiology imaging, absent psychomotor development, spasticity and seizures). Examination for dysmorphic features revealed microcephaly, bitemporal narrowing, midface hypoplasia, hypotonic facie, strabismus, poor eye fixation, rotary nystagmus, abnormally shaped ears, arched eyebrows, hypertrichosis, short stature, cryptorchidism. Cytogenetic analysis was normal. Trio WES revealed *AMPD2* gene ENST256578: c.2327T>G; p.Leu776Arg and c.2059C>T; p.His687Tyr variants, father is carrier of p.Leu776Arg variant which is listed as Pathogenic in ClinVar database and mother is carrier of novel p.His687Tyr variant. Unfortunately, it was not possible to find DNA sample of deceased sister. In conclusion, we can say that compound heterozygosity in trans position was first thing we looked for during data analysis as it is perfect explanation for this family history. Specific clinical features overlapping with previously reported (14 patients) few cases made diagnosis easier. Family were warned about 25% probability of same outcome in future pregnancies.

Keywords: Pontocerebellar Hypoplasia, AMPD2, WES

OP-21-411

4 years old boy with Sotos syndrome: A case report

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Sotos syndrome which is an autosomal dominant genetic condition is characterized by primary features including excessive growth during childhood, macrocephaly, advanced bone age, typical facial features and a non-progressive neurological disorder with intellectual disability, and etc. Sotos syndrome is caused by mutations in the NSD1 gene and NSD1 gene mutations are almost identified in 90% of affected patients.

Our patient was born at 38 weeks of gestation with 3730 gr weight. He was suffering from asthma, diagnosed as bilateral sensorineural hearing lost, had a hydrocele in the left testicle, neurodevelopmental retardation and secundum atrial septal defect in the first 5 months of his life. His physical examinations revealed that he had macrodolichocephaly, a receding hairline, long-thin face, frontotemporal thin hair, extremely slanted palpebral fistula, forth and fifth premolar teeth in both sides and upper and lower jaw missing, altogether 8 teeth as well as distinctive mandibula. He referred to our outpatient clinic and we have performed NGS analysis covering the exonic and intronic regions of 4500 genes. We have detected a heterozygous pathogenic frameshift mutation on the exon 5 of NSD1 gene: c.2386_2389del (p.Glu796Ilefs*10).

The *NSD1* gene was found to be responsible for Sotos syndrome, and more than 150 patients with *NSD1* alterations have been reported up to date. In Sotos syndrome, the face is round with unproportional prominence of forehead and continuation of the pointed chin, macrodolichocephaly, receding hairline, apparent hypertelorism with down slanted palpebral fissures, etc. are commonly identified in the infancy. Most patients found to have a non-progressive neurological dysfunction. We have also observed most of the disease symptoms of Sotos syndrome also in our patient. The diagnosis can be confirmed by FISH (fluorescence in situ hybridization) analysis to detect microdeletions, MLPA (multiplex ligation-dependent probe amplification) and also DNA analysis by genome sequencing to determine the specific *NSD1* gene mutations. In order to evaluate phenotype-genotype correlation of the patient we performed clinical exome sequencing revealing that the patient was carrying a pathogenic frameshift mutation. Similarly, to our data, a four-base deletion, c.2386-2389del, was reported in a mother and son of an Israeli family. Besides the importance of evaluating the characteristic clinical Picture of Sotos syndrome, molecular genetic testing is also extremely recommended as well.

Keywords: Sotos Syndrome, NSD1, NGS

OP-21-412

Pathogenic variations of *MUTYH* gene in hereditary cancer cases

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MutY DNA Glycosylase (*MUTYH*) is a base excision repair (*BER*) gene and has 1-2% carrier rate for pathogenic alleles in general population. Pathogenic, biallelic *MUTYH* mutations are associated with autosomal recessively inherited "multiple colorectal adenomas" (MIM no. 608456). The disorder is also called "*MUTYH*-Associated Polyposis (MAP)" and it is characterized by a great risk for colorectal cancer. Generally, MAP cases have ten-few hundred adenomatous polyps, but the phenotype may vary depending on the genotype, in some cases the colorectal cancer may occur without polyposis. In the presence of pathogenic genetic variations, frequently there are adenomas of duodenum and there is increased risk of duodenal cancer. In addition to these cancer-associated clinics, there are increased risks for ovary, bladder, breast and endometrium cancers. Beside these, *MUTYH* associated clinical features include jawbone cysts, and congenital hypertrophy of the retinal pigment epithelium. In the management of MAP cases, colonoscopy, endoscopy, thyroid ultrasonography and dermatology follow up are considered. Polypectomy and other preventive approaches are used in cases with pathogenic variations of *MUTYH*. The relatives of the patients, including the young (10-15 years) and elderly also, are candidates for genetic testing. In our study, we would like to present the clinical findings and the results of 24 *MUTYH* pathogenic variation positive cases, selected from 735 hereditary cancer cases who are investigated between the years 2018-2019 in our genetic diagnosis center. As far as we know, there are case reports describing patients with pathogenic *MUTYH* variations from our country but no series. Therefore, we hope to contribute genotype-phenotype studies in our region.

Keywords: Cancer, MAP, MUTYH

OP-21-413

MODY genetics: Novel variants and genotype-phenotype correlation

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Maturity onset diabetes of the young (MODY) is an autosomal dominant inherited, most common subtype of the monogenic diabetes and responsible for 1-3% of all cases of diabetes. MODY is frequently misdiagnosed because of confused with Type 1 and Type 2 DM. To improve the prognosis of MODY, it is important to identify the affected subjects as early as possible.

Known MODY-related genes can be identified by next-generation sequencing method to predict the clinical disease course and offer the most appropriate treatment. In this sense, candidates for genetic testing may include positive family history of diabetes, nonobese subjects with hyperglycemia, no insulin requirements. Genetic heterogeneity exists, at least 14 genes have been reported. Mutations in *GCK* and *HNF1A* genes are the most frequently identified etiologies that account for 30-60% of the MODY while *HNF4A* and *HNF1B* gene mutations are responsible for approximately 10% of all affected patients in the world.

Since some MODY subtypes are associated with additional manifestations, clinical symptoms may help to identify the disease causing MODY genes. For instance, *HNF1B* mutations are associated with developmental disorders of the kidney, renal cysts, hyperuricemia, hypomagnesemia, and early-onset gout or *HNF4A* mutations associated with the case of macrosomia and congenital hypoglycemia.

In this retrospective study, we analyzed samples that had been obtained from a total of 74 patients with MODY by custom design next generation sequencing panel which includes *GCK*, *HNF1A*, *HNF1B, HNF4A, PDX1, NEUROD1, KLF11, CEL, PAX4, BLK* and *INS* genes.

Pathogenic and likely pathogenic variants were found in 19 (25%) patients. Of these, six mutations (5 missenses and a nonsense mutation) were novel. Similar with the literature, GCK mutations were the most common cause of MODY in our study population. Disease causing variants were confirmed and segregation analysis were performed with Sanger sequencing. Genetic counseling was given.

In this study, new variants have been added to the mutation spectrum in MODY genes and genotype-phenotype correlations have been studied.

Keywords: Maturity Onset Diabetes of The Young, GCK, Next-Generation Sequencing

Poster Presentation Abstracts

PP-001

Cause of craniosynostosis in a monozygotic twin case; Crouzon syndrome

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Crouzon syndrome (CS) is a rare autosomal dominant inherited syndrome characterized by craniosynostosis, proptosis, beak nose, hearing loss, normal intelligence and extremity development. More than 100 syndromes have been reported related with craniosynostosis, which is seen one in 2500 live births. Syndromic craniosynostosis accounts for 15% of cases. Since CS constitutes 4.8% of all cases, it is the most common craniosynostosis syndrome. 70% of cases are familial and 30% are de novo. Disease shows variable expression and incomplete penetrance and is seen one in 60.000 live births. *FGFR2* gene encodes receptor tyrosine kinase, which plays important role in embryonic development. We examined case diagnosed with CS. Seven-month-old monozygotic twins, whose parents were first-degree cousins, were referred for craniosynostosis. Weight, height and head circumferences of the premature twins born at week 36 were found to be smaller than 3 percentiles. Physical examination showed coronal synostosis, proptosis, beak nose. Karyotype analyses reported as 46,XY. Pathogenic c.833G>T (p.Cys278Phe) heterozygote variant detected at seventh exon in *FGFR2* whole gene sequence analyses were associated with CS. There wasn't similar case in family tree. The patients were diagnosed with CS according to clinical findings and genetic test results. Decrease in cranial pressure capacity, insufficiency in protecting the eyes secondary to serious proptosis and obstructive sleep apnea secondary to maxillary hypoplasia are major problems in CS. Therefore, multidisciplinary follow-up of patients is important. Pfeiffer and Apert syndrome are in the differential diagnosis of the disease. Preimplantation genetic diagnosis or prenatal diagnosis should be recommended for the patients.

Keywords: Crouzon Syndrome, Craniosynostosis, Coronal Synostosis

PP-002

Investigation of repeat numbers (CAG, CTG, CGG, GAA, GCC) and variable expression of our patients with trinucleotide repeat disease in Afyonkarahisar

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The trinucleotide repeat disorders (also known as trinucleotide repeat expansion disorders or triplet repeat expansion disorders) are a set of genetic disorders caused by an increase in the number of trinucleotide repeats in certain genes exceeding the normal, stable, threshold. Each gene affected by trinucleotide repeat expansion has a different number of repeats that constitutes the normal threshold and the number that results in manifestation of disease. Once the number of repeats has increased, the tendency to increase the number of repeats increases as they are transferred in the germ line. This condition is known as anticipation and genetic anticipation is a phenomenon in which the signs and symptoms of genetic conditions become more severe and/or appear at an earlier age, as they are passed from one generation to the next. Our aim in this study; AFSU-Afyonkarahisar Health Sciences University Faculty of Medicine is examined by collecting the data of the families who applied to our Medical Genetics Department and found to have triple repeats, and to provide a prevalence map of the triple repeat diseases in Afyonkarahisar.

In our study, first of all, the families who came to our clinic were identified and their pedigrees were drawn. One patient with fragile-X disease was first diagnosed with the molecular analysis made by PCR and Southern Blot method for detect to CGG repeat numbers in the *FMR-1* gene. In 11 patients with Myotonic Dystrophy disease, the exact number of repeats of the CTG trinucleotide for both alleles of the *DMPK1* gene was detect by molecular analysis. The 22 cases of 5 families with Huntington's disease were first diagnosed with CAG repeat numbers molecular analysis in the *IT15* gene. Afterwards, the age of the disease, the clinical severity of the disease, radiological and laboratory findings were compared with these patients. In addition, detailed pedigree analysis of the patients was performed and thus anticipation and variable expressivity of the disease was determined.

Families with Fragile-X, Myotonic Dystrophy and Huntington's diseases from different regions of Afyonkarahisar were examined. We was found to be that our patient with Fragile-X carried a full mutation in terms of increased CGG repeat count. The number of CAG repeats in the *IT15* gene of 5 different patients with Huntington's disease was 45,37,37,40,47, respectively. The age of onset of the disease was 41.52.54.46 and 68, respectively. While some of the patients' brain MRIs were found to be specific for the disease, some had no pathology. Pedigree analysis of all patients were performed and anticipation was detected in some patients, and variable expressivity in some patients. All patients with EMG (+) in our patients diagnosed with myotonic dystrophy were also examined in terms of their number of repetitions. Our patient, which we find most important in terms of myotonic dystrophy; It was clinically myotonic discharges and diagnosed as myotonic dystrophy, but when examined in terms of the number of repeats, the *DMKP1* gene was a normal number of repeats in terms of 8/17 for both alleles. Although there is an inverse proportion between the increase in CAG in Huntington's disease and the age of onset of the disease, there is no relationship between clinical findings and the number of CAG repeats. Korean movements, cognitive disorders up to dementia, psychiatric findings are the main features of the clinical picture. Since anticipation and variable expressivity are frequently observed, patients should be evaluated genetically, clinically, radiologically and laboratories in general and in detail.

Keywords: Trinucleotide Repeats Diseases, Expressivity, Anticipation

PP-003

A case report of rare mutation in *PIK3CA*

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Somatic mutations of *PIK3CA* gene (postzygotic mosaicism) are among the most common mutations in various types of cancer. Besides that, somatic and rare germline mutations in *PIK3CA* gene are associated with a series of syndromes, which are now called PIK3CA-related overgrowth spectrum (PROS). In this case report, we present a germline heterozygous c.1A>G (p.M1?) mutation in the *PIK3CA* gene detected by Whole Exom Sequencing in a 7.5 year old boy who applied to our clinic with epilepsy, mental retardation, macrocephaly and brain malformation. The detected variant was analyzed from different tissues of the case and segregation analyses were planned from first degree relatives. Although germline mutations in the *PIK3CA* gene are rarely seen, it should be considered in patients presenting with clinical findings such as epilepsy and brain anomalies.

Keywords: Brain Malformation, Epilepsy, Germline Mutation, *PIK3CA*

PP-004

Homozygous frameshift mutation in *DDB2* gene induced squamous cell and basal cell carcinomas in a child with xeroderma pigmentosum

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Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder of DNA repair characterized by increased sensitivity to ultraviolet radiation (UVR), dry skin, early development of pigmentary changes, UVR-induced ocular involvement, UVR-induced skin and mucous membrane cancers, and, in some patients, progressive neurodegeneration. In the current case report, we aimed to present a rare mutation in basal cell carcinoma(BCC) and squamous cell carcinoma (SCC) in a case of clinically diagnosed XP.

An 11-year-old male patient was admitted to our outpatient clinical diagnosis of xeroderma pigmentosum.because of the presence of squamous cell carcinoma and basal cell carcinoma. In the family history, it was learned that the parents were first degree cousins and there was no similar history of illness in the family. Physical examination revealed diffuse tumoral lesions in the body, pigmentation changes and actinic keratosis on the face. Neurological examination was normal.

In the current study, whole-exome sequencing (WES) and Sanger sequencing validation was used for genotyping of XP child with SCC and BCC by using total genomic DNA that isolated from peripheral blood sample. Homozygous c.726-729delAAAG (p.K244fs *0) frameshift mutation was detected in damage-specific DNA binding protein 2 (*DDB2*) gene in the current case after WES analysis. This mutation has been reported pathogenically in databases and has been associated with xeroderma pigmentosum group E. Reported mutation was also detected in the asymptomatic mother in heterozygous condition. The proband's father could not be analysed because he could not be reached. All results were confirmed by Sanger sequencing.

Our results identify the homozygous frameshift mutation in *DDB2* gene as an important role in developing basal and squamous cell tumours in XP. Same mutation was published by Işık E at all; our patient tested first time in our lab, and not known family member tested in Ege University so DDB2 c.726-729delAAAG (p.K244fs *0) mutation could be an ancestral mutation or a hot spot region. Our case is the second case in the literature where this mutation is reported in the *DDB2* gene, and we think that it will contribute to the literature, especially because it is one of the rare diseases with autosomal recessive inheritance in countries such as ours, where consanguineous marriages are intense.

Keywords: *DDB2* gene, c.726_729delAAAG (p.K244fs *0) Mutation, SCC, WES, XP

PP-005

Distribution of fetal chromosomal polymorphisms in high-risk pregnancies

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Chromosomal variations can be detected frequently during routine cytogenetic analysis. The term “primary constriction” is used to define the centromere, while “secondary constriction” is used to define other constricted regions on the chromosome. Chromosomes 1, 9, and 16 contain highly variable secondary constriction regions (qh) consisting of heterochromatic DNA. Our aim in this study is to determine the frequency of polymorphisms in karyotypes obtained in high-risk pregnancies in the prenatal period.

Keywords: Aneuploidy, Cytogenetics, Karyotype

PP-006

Distribution of cytogenetic findings in 4857 prenatal cases

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Chromosome disorders are reported between 1.9% and 5.8% in the prenatal period. Depending on the test result, different processes such as additional genetic tests, planning of pregnancy follow-up, and birth plans are waiting for the family. In this study, we aimed to evaluate the chromosome disorders and their frequencies in 4857 prenatal cases studied with the conventional cytogenetic method.

Keywords: Aneuploidy, Cytogenetics, Karyotype

PP-007

A rare chromosomal aneuploidy that diagnosed with array CGH and MLPA validation: Trisomy 4 in a fetus

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Aneuploidy is the most common and clinically the most important chromosomal abnormality and is seen in first trimester abortions most frequently. Although it was reported that first-trimester spontaneous abortions have a high frequency of chromosomal abnormalities, trisomy 4 is very rare. Here we aimed to present a missed abortion fetus at 8 weeks gestational age with trisomy 4.

Genomic DNA was isolated from fetal sample. The quantitative fluorescent polymerase chain reaction (QF-. PCR) analyse of the fetal DNA for chromosomes 13, 18, 21, X and Y was performed. Then SALSA MLPA Probemix P245 Microdeletion Syndromes-1A kit and Agilent Sure Print G3 Human CGH Microarray 8x60K was performed for the potential microdeletion/microduplications. The GTG banding karyotype analysis from couple's peripheral blood sample was performed.

A 31 years-old female and 30 years-old male couple with recurrent miscarriages were referred to our medical genetics department after a missed abortion at 8 weeks gestational age. This was their third miscarriage and they had no child alive. The couple were both healthy and nonconsanguineous. In the family history the mother of the female patient had three abortions too. The fetus was terminated because of the lack of fetal heart activity at 8 weeks gestational age that's why we could not perform the GTG banding karyotype analysis from fetal cell culture that was estimated to have no living cells. The QF-PCR analyse of the fetal DNA was normal. Then microdeletion MLPA resulted with a duplication at 4p16.3 region (including LETM1 and WHSC1 genes). aCGH method was used to determine the size of this duplication and total Trisomy 4 was detected in the fetal tissue DNA. The GTG banding karyotype analysis of the parents exhibited normal chromosomal constitutions.

Trisomies have a high frequency in first trimester miscarriages yet trisomy 4 is very rare. In a comprehensive study it was reported that in 165 of 233 fetuses with malformations had abnormal karyotype, of which 101 (61%) were trisomic and 37 (22%) monosomic X, however trisomy 4 was reported only in one case. In another study trisomies found approximately %50 in early spontaneous abortions, none of them had trisomy 4. In the literature severe microcephaly, facial dysplasia, absence of cervical exion, retarded limb development, bilateral cleft lip were reported in a macerated embryo with trisomy 4 by embryoscope at 8 weeks gestational age. Hyperploidy in germ cells was reported in a patient with recurrent trisomic fetus abortions. In our case our patient had recurrent miscarriages in the first trimester and the last one that we analyzed had no fetal malformation on ultrasound exams. The presence of recurrent trisomies in patients with recurrent miscarriages can be explained by germline mosaicism, balanced translocations in germline cells, polymorphic chromosomal aberrations that affect meiosis such as 9qh+.

Keywords: Aneuploidy, Array CGH, MLPA, Recurrent Miscarriage, Trisomy 4

PP-008

Frequency of chromosome disorders in patients with sperm number anomaly

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Numerical and structural chromosome anomalies play an important role in male infertility. Chromosome anomaly rate is higher in infertile men (5.8%) when compared to the normal population (0.5%). In our study, it was aimed to determine the frequency of chromosomal anomaly of patients with abnormal sperm count in the last 12 years.

Keywords: Infertility, Klinefelter, Chromosomal Anomalies

PP-009

A novel frameshift mutation of the *EXT1* gene in patient with hereditary multiple exostoses

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Hereditary multiple exostoses (HME), also termed hereditary multiple osteochondroma, is an autosomal dominant inherited disease characterized by the development of multiple exostoses, predominantly located on the limbs, shoulder blades, ribs, and pelvis. The exostoses can result in numerous health problems, including skeletal bowing and deformities, growth restriction, nerve and blood vessel compression. HME progresses into chondrosarcomas or osteosarcomas in ~2% of patients.

A 12 years old boy referred our clinic with multiple exostoses and short stature. Physical, radiological and laboratory investigation were performed. DNA isolated from peripheral blood lymphocytes and all exons and exon-intron boundaries of exostosin-1 (*EXT1*) gene were sequenced. Physical examination showed shortened legs and forearms and the patients has a mild walking impairment. There was no family history. An X-ray image of the bilateral hand shows an exostosis of the proximal and distal radius and a shortened ulna. The X-ray of the pelvis exhibits multiple exostoses on the pelvis and on the proximal / distal femurs and tibia. After *EXT1* gene sequencing, a novel heterozygous pathogenic frameshift c.1660dupG (p.Asp554GlysfsTer12) mutation in exon 8 of *EXT1* gene was detected.

HME is caused by heterozygous inactivating mutations of the genes for *EXT1* or exostosin-2 (*EXT2*). The majority of these mutations are nonsense, frameshift and splice-site mutations, but there are also missense mutations and deletions. About 65 % of the HME mutations occur in *EXT1* and 25 % in *EXT2*. We aimed to present a case with novel mutation which cause early termination in the *EXT1* gene and has enlarged the causal mutation spectrum of HME.

Keywords: Hereditary Multiple Exostoses, *EXT1*, Osteosarcomas,

PP-010

A recurrent *HPS1* gene mutation in a Hermansky Pudlak patient with uncommon clinical presentation

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Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by albinism with hemorrhagic diathesis. Additional findings like renal failure, granulomatous colitis and interstitial lung disease can also be part of this syndrome. HPS has ten known subtypes. Lung fibrosis can accompany HPS-1, 2 and 4. Granulomatous colitis had been described in patients with HPS-1, 4 and 6. Recurrent infections are associated with HPS-2. The most severe phenotypes were seen in HPS 1 and 4. *HPS* gene products form biogenesis of lysosome-related organelle complexes (BLOCs) and involved in biogenesis of melanosome and platelet dense granules.

Keywords: Hermansky-Pudlak, HPS1, Albinism, Autism

PP-011

Evaluation of the patient with recurrent fever

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Human autoinflammatory diseases are a group of disorders characterized by non-provoked inflammatory attacks in the absence of autoimmune or infectious causes. Most of these diseases occur with recurrent fever attacks, serosal inflammation, muscle, joint and skin involvement. These disorders are caused by mutations in gene associated with innate immune system. İnflammasomes are part of the regulatory process for innate immune system and dysregulation of inflammasomes causes production of pro-inflammatory cytokine such as IL-1. Patients' symptoms appear with increased interleukin levels. The aim of our study is to search the etiology of those patients with recurrent fever other than FMF (Familial Mediterranean Fever) as a result of clinical examination and genetic testing.

Six patients with recurrent fever, joint, muscle, and skin involvement were admitted to our outpatient clinic. After peripheral blood DNA isolation, all exon and exon-intron connection regions of 10 genes associated with recurrent fever were sequenced using the next generation sequencing (NGS) method.

At patient 1, heterozygous c.362 G>C (p.Arg121Pro) mutation was detected in the *TNFRSF1A* gene. This mutation was previously associated with TNF alpha-associated periodic fever syndrome.

At patient 2, heterozygous c.448 C>T (p.Arg150 Cys) mutation was detected in the *NLRP12* gene. Mutations in this gene are associated with familial cold autoinflammatory syndrome type 2.

At patient 3, heterozygous c.718 A>G (p.Lys240Glu) mutation in the *TNFRSF1A* genes. Mutations in these gene are associated with autoflammatory fever syndromes.

At patient 4, heterozygous c.2779 G>C (p.Gly927Arg) mutation was detected in the *NLPR12* gene, and the mutation was associated with familial cold autoinflammatory syndrome type 1.

At patient 5, no significant mutations were detected among the regions analyzed.

At patient 6, although the clinical and laboratory results were not compatible with FMF, there were heterozygous c.1223 G>A (p.Arg408Gln) and c.1105 C>T (p.Pro369Ser) mutations in the *MEFV* gene identified at the analysis.

As clinical approach, autoinflammatory diseases are considered for symptoms such as recurrent fever, serosal inflammation and arthritis. Since inflammatory process is the interplay of complex proteins and pathways, such patients should have careful clinical evaluation and be analyzed with a wide gene panel.

Keywords: Recurrent Fever, Autoinflammatory, Arthritis

PP-012

A male phenotype due to the occurrence of *SRY* gene product in a mosaic case of an idicY and XX male karyotype

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Isodicentric Y chromosome [idic(Y)] is a mosaic structural alteration of the chromosome Y. This common aberration is related with pubertal development, fertility status, and constitution of gonadoblastoma in the mosaic carriers. Phenotype depends on the genomic content of the derivative segments as well as on the proportion of each cell line in various tissue, especially in gonads. The gender vary from male to abnormal female or individual with ambiguous genitalia. The occurrence of idic(Y) and normal 46, XX cell lines is less clearly defined. In this article, we present the complex mosaic karyotype with idic(Y) chromosome by the usage of conventional and molecular cytogenetic analyses, detected in a 41-year-old azoospermic male phenotype patient. Fluorescence in situ hybridization (FISH) technique with Y chromosome-specific probes namely sex determining region of Y chromosome (SRY), short stature homeobox gene (*SHOX*), short arm (DXYS129) and long arm (DXYS61) of telomeric region of X/Y chromosomes, and centromeric (DYZ3) and Yq12 heterochromatic region (DYZ1) of chromosome Y were used to determine the structure and genetic content of the mosaic cell lines with idicY. The final karyotype was:

mos 46,XX[57]/47,XX,idic(Y)(q11)[10]/45,X[6]/46,X,idic(Y)(q11)[27].ish idic(Y)(DXYS129++,SRY++,SHOX++,DYZ3++,DYZ1-,DXYS61-).

Absence of the azoospermia factor regions was also indicated via real time polymerase chain reaction method. The presence of the 46,XX cell line in addition to the idic(Y), is most likely occurred as a result of nondisjunction of parenteral meiosis. The sexual differentiation of patients probably depends on the distribution of cell line in various tissues, including the gonads. The male phenotype in our case is probably related with the function of the *SRY* gene product in the cells of the early phase of the gonadal ridge. Extra attention should be given to the risk of developing gonadoblastoma, as the risk of this tumour is 15% in 45,X/46,XY mosaic individuals, while the ratio is 24% in patients with idic(Yp).

Keywords: Mosaic IdicY, XX male, SRY gene

PP-013

Investigation of *ARHGEF12* single nucleotide polymorphism in hypercholesterolemic primary open angle glaucoma

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Primary open angle glaucoma (POAG) is one of the most prevalent type of optic neuropathy leading to irreversible visual loss. Current studies concerning POAG have focused on the additive effects of intraocular pressure (IOP) related genes in aqueous outflow mechanisms. The *ARHGEF12* gene, a member of the Rho guanine nucleotide exchange factors (RhoGEFs), is involved in regulation of tissue remodeling and plasticity of trabecular meshwork (TM). The SNP rs58073046 A>G within the *ARHGEF12* gene has been reported to be significantly correlated with IOP homeostasis. Also, *ARHGEF12* gene have a functional role in lipid metabolism by stabilizing of ABCA1 protein. In view of this, we aimed to investigate the clinical influence of the SNP rs58073046 A>G on individuals with hyperlipidemic POAG. In this study, the subjects were divided into 2 groups: Group 1, consisting of 20 patients with hyperlipidemic POAG, and Group 2, consisting of 20 age and sex- matched healthy controls living in the same region. 40 subjects were sequenced for the polymorphism rs58073046 A>G within the *ARHGEF12* gene. The data were assessed by descriptive statics and Fisher exact x2 test. There were no significant differences between the groups in terms of age and gender (p=0.65, p=0.75, respectively). The homozygous mutant genotype (GG) was only found in one patient (5%) of Group 1, whereas homozygous genotype (AA) was present in 20 subjects (100%) of Group 2. There was no significant association between homozygous mutant genotype (GG) and the occurrence of hyperlipidemic POAG (p=0.5). In conclusion, we found no association between the SNP rs58073046 A>G and the disease profile.

Keywords: ARHGEF12, Hyperlipidemia, Primary Open Angle Glaucoma

PP-014

Novel compound heterozygote mutations in the *ATP7B* gene in a Turkish family with Wilson disease

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Wilson disease is an autosomal recessive disease in which copper metabolism is affected. This disease is caused by mutations in the *ATP7B* gene. The *ATP7B* gene encodes the protein called ATPase 2, which carries copper, which plays a role in transporting copper from the liver to other parts of the body. In this case, it was aimed to present the genetic diagnosis process of a 6-year-old girl with a diagnosis of Wilson disease in her two brothers.

The patient, who has no active complaints, applied to the pediatric gastroenterology outpatient clinic of our center for the purpose of screening, as there were 2 siblings who were clinically and pathologically diagnosed in the family. The general medical examination was made for the patient. The amount of copper in 24-hour urine was determined as 186.6 (increased), AST: 87, ALT: 136, GGT: 44, ALP: 302, free copper level: 44 (increased), ceruloplasmin 0.21 (decreased). The patient's liver biopsy was reported as chronic hepatitis, fibrosis (grade 2), macrovesicular steatosis. No pathological findings were detected in the echo, brain MRI and eye examination. Her parents were healthy and have no consanguinity. *ATP7B* gene sequence analysis was performed from the patient who was referred to the medical genetic outpatient clinic with a preliminary diagnosis of Wilson disease. ATP7B:c.1847G> A and ATP7B:c.3207 C> A heterozygous mutation was detected. These variants were classified as pathogenic according to the ACMG guidelines. C.3207 C> A; The most frequent mutations in Turkey and the European community have been reported in the literature. As we know to date the coexistence of these two heterozygous mutations was not found in the literature review. In this case, we indicated that even in a population like Turkey with a high rate of inbreeding it is still possible to find recessive disorders like Wilson Disease as a result of compound heterozygote mutations in a family with no recent consanguinity. Therefore, heterozygote mutations should also be considered both in affected and carrier members of high-risk families.

Keywords: *ATP7B* Gene, Compound Heterozygous, Wilson Disease

PP-015

A rare disease: Alpha thalassemia X-linked intellectual disability syndrome

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Alpha thalassemia X-linked intellectual disability (ATR-X) syndrome is a rare genetic disorder characterized by distinctive craniofacial features (microcephaly, hypertelorism, epicanthal folds, mid-face hypoplasia), genital anomalies (hypospadias, undescended testicles, hypospadias and ambiguous genitalia), severe developmental delays, hypotonia, intellectual disability and mild-to-moderate anemia secondary to alpha-thalassemia. ATR-X syndrome prevalence is unknown. More than 200 affected individuals have been reported. ATR-X syndrome is caused by mutations in the *ATRX* gene that are located on chromosome Xq21.1. The specific function of the ATRX protein is unknown, studies suggest that it helps regulate the activity (expression) of other genes *HBA1,HBA2* through a process known as chromatin remodeling.Here we present a patient with a novel mutation in the *ATRX*gene. One year old male patient was referred to our clinics with abnormal facial features, hypotonia and developmental delay. He was the third live birth of the consanguineous parents. His birth weight was 3800 g, length was 52 cm. His facial features were hypertelorism, epicanthal folds, low nasal bridge, small triangular nose, 'carp-like' mouth, widely-spaced upper incisors. The karyotype of the case was 46, XY. Molecular analysis revealed a novel hemizygous mutation; c.797A>G(p.Tyr266Cys). His mother result was normal. As a result, we have found both de novo and novel mutation in a rare disease.

Keywords: *ATRX* Gene, Novel Mutation, Alpha Thalassemia X-linked Intellectual Disability Syndrome

PP-016

A fetus with ınherited 22q11.2 deletion and importance of genetic counseling

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22q11.2 Deletion syndrome is a microdeletion syndrome characterized by congenital heart anomalies, palatal abnormalities, learning disability, and immunodeficiency. This syndrome can be suspected in the prenatal period with thymus aplasia / hypoplasia, conotruncal malformations and palatal abnormalities. About 93% of probands have a de novo deletion of 22q11.2 and 7% have inherited the 22q11.2 deletion from a parent.

Bifid uvula, thymus aplasia, interrupted aortic arch, perimembranous VSD were detected in fetal USG performed on 20 weeks and 3 days pregnant. While chromosome analysis made from amniotic fluid was found to be normal, deletion was detected in 22q11.2 FISH test. In detailed clinical evaluation of the mother and father, short stature and tubular nose structure was detected in the mother. No significant finding was found in the clinical evaluation of the father. In the karyotype and 22q11.2 FISH test performed from peripheral blood of the mother and father, 22q11.2 deletion was detected in the mother.

In fetuses or individuals with 22q11.2 deletion, pregnant and her spouse should be evaluated clinically. Chromosome analysis and 22q11.2 FISH / MLPA should be planned from the mother and father for this clinically variable syndrome.

Keywords: 22q11.2 Deletion, FISH, Inherited,

PP-017

A double dose effect of assisted reproductive technologies and surrogacy in the epigenome of art children: A metanalysis

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More than 7 million children have been born by Assisted Reproductive Technologies (ART) in last thirty years. No doubt, ART is associated with a range of adverse early life outcomes, including rare imprinting disorders. On the other hand, Surrogacy is an assisted reproduction-based approach in which the intended parents assign the gestation and birth to another woman called the "surrogate mother". The drivers of surrogacy refer largely to infertility, medical conditions, same-sex couples' parenting, and cases of diversity regarding sexual identity and orientation. Sperm and egg donation as well as surrogacy are legal in North Cyprus. Therefore, many people around the world travel to North Cyprus for ART treatment. Therefore, ART clinicals have a great contribution to the country's economy.

Children designed by Assisted Reproductive Technologies (ART) are at moderately increased risk for a range of undesirable consequences, including low birth weight. The potential impact of ART clinical and laboratory procedures on gamete and embryo epigenomes is one of the mechanical candidates who can explain the relationship between ART and undesired clinical outcomes. Thus, the periconception period and early embryogenesis are associated with widespread epigenetic remodeling, which can be influenced by ART and Surrogacy. The aim of this metanalysis is to coincide with the periods when large-scale rearrangement of the epigenome takes place during development, during ART clinical and laboratory procedures. Therefore, we evaluated the potential of ART clinical and laboratory procedures to alter epigenomes. There is an evidence from several meta-analyses that ART outcomes might increase risk of preeclampsia, preterm delivery, placenta previa, placental abruption, intrauterine growth restriction. Recent studies have been indicated changes in chromatin structure, DNA methylation and miRNA expression during trophoblast migration and invasion. These results have suggested that epigenetic regulation during early pregnancy. A meta-analysis of 23 studies reported positive associations between ART and four imprinting disorders: Beckwith-Wiedemann, Angelman, Prader-Willi and Silver-Russell syndromes. Studies have shown differential methylation in *H29, IGF2, SNRPN, GNAS, PEG10, PRCP2 and RUX3* genes between ART-conceived fetuses and control group. Furthermore, significant methylation differences between placentas from pregnancies using donor egg and naturally conceived controls were observed. Controversy, the latest study showed evidence for specific ART-associated variation in methylation around birth which largely resolves by adulthood with no direct evidence that it rise an abnormality on development and health. In human, anchoring the link between aberrant epigenetic marks and adverse perinatal outcomes is difficult. Thus, to validate the current studies, it is significant to conduct animal studies. Especially, they might be helpful in examining potential long-term effects of epigenetic changes. To conclude, probably in the future, animal studies will give the answer to this contraversion in the literature.

Keywords: Epigenetics, IVF, Surrogacy

PP-018

Case report: Hereditary form of methemoglobinemia

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Autosomal recessive hereditary methemoglobinemia (ARHM) is characterized by disruption of blood oxygen transport due to abnormally higher methemoglobin levels. *CYB5R3* gene is involved in the production of cytochrome b5 reductase 3 enzyme. The deficiency of the enzyme can occur as a result of mutations in the *CYB5R3* gene and has two clinical phenotypes based on defects in either the soluble or the membrane-bound isoforms. Soluble *CYB5R3* is specifically expressed in erythrocytes for methemoglobin (MetHb) reduction and its deficiency is responsible for ARHM. Enzyme activity and stability decreases in ARHM type 1, however in ARHM type 2, the enzyme loses its activity completely and other somatic cells affected severely and can cause neurological disorders. By reporting our case, it was aimed to emphasize the significance of hereditary causes of methemoglobinemia. An 18-year-old woman accepted to our chest clinic with complaints of shortness of breath and cough. She had mild cyanosis and her arterial oxygen saturation was 85%. The other examinations, including thorax CT, CT angiography of abdominal aortic branches, pulmonary perfusion scintigraphy, and echocardiography, revealed no abnormalities. The patient has no other known disease. There was no history of drug use. The methemoglobin level in the arterial blood gas was 13%. There was 3rd-degree consanguinity between the patient's parents and there wasn't another individual with a similar condition in the family. Whole gene sequence analysis showed homozygous c.136 C>T mutation in the *CYB5R3* gene. The mutation had evaluated with in silico genetic tools like Mutation taster and Varsome and predicted as a pathological variant. Genetic counseling had given to the family and the patient forwarded to the relevant departments. The incidence of hereditary methemoglobinemia is unknown. As in our case, ARHM type 1 progresses less severely in previous patients and their complaints begin at elder ages. In addition to the acquired form in cases of methemoglobinemia, the rare hereditary type should be kept in mind in the differential diagnosis. In this way, carrier individuals can be detected and also ARHM type 2, which has severe neurological findings, can be prevented.

Keywords: *CYB5R3* Gene, Hereditary Methemoglobinemia

PP-019

Trifunctional protein deficiency due to a de novo *HADHB* mutation in three siblings

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Mitochondrial trifunctional protein (MTP) deficiency is a rare autosomal recessive disorder of mitochondrial fatty acid beta-oxidation caused by homozygous or compound heterozygous mutation in the genes encoding either the alpha (HADHA) or beta (HADHB) subunits of the mitochondrial trifunctional protein. The disease can be a life-threatening with early onset, but it can also present with peripheral neuropathy in adults. Clinically, the disease can be classified into three main clinical phenotypes; neonatal onset of a severe, lethal condition resulting in sudden unexplained infant death, infantile onset of a hepatic Reye-like syndrome and late-adolescent onset of primarily a skeletal myopathy. A 29-year-old woman applied to our clinic with slowly progressive muscle weakness and sensory disturbances especially in her lower and upper limbs since her 10's. Her parents were third-degree consanguineous, and she had 3 siblings, both of her brothers were suffering from the same complaints. A nerve conduction studies showed sensorimotor axonopathy, echocardiography revealed left ventricular diastolic dysfunction. Genetic analyses showed a novel homozygous mutation in *HADHB* gene and it was found that the mutation has not been reported before then we performed mutation based studies to the other siblings. Analyses showed that both of her brothers also have the same mutation. By searching the literature, it was found that the mutation has not been reported before. It is important to identify new mutations to clarify their clinical importance and to assess the prognosis of the disease.

Keywords: Mitochondrial Trifunctional Protein, Sensorimotor Axonopathy, HADHB

PP-020

A rare copy number variation of Xp22.33 region: A case report

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Copy number variation (CNV) is exist in the whole genome. Some of them have no pathological effects, while others may have pathological consequences. Here, we present a case who was referred to our polyclinic because of dysmorphic findings and the copy number changes in PAR region of X chromosome were determined. It was learned that the patient was born preterm from a healthy parent as a first cousin marriage. The male baby borned from a 36 years old mother via C/S at the end of 35+1 weeks gestation period as being the first live birth among four pregnancies was referred to our polyclinics with the indications of bilateral pes planus, anterior and posterior fontanel width and story of recurrent abortus in mother. Physical examination did not reveal any additional findings. In the karyotype analysis, chromosome construction was found as 46,XY. Mother and father's karyotype analysis was also normal. The microarray analysis revealed a gain of 384 kb in the Xp22.33 region. In this region, there were 2 OMIM genes (GTPBP6 and PPP2R3B) localized in the X chromosome PAR region and the changes were pathogenic. Mother's microarray result was normal. The gain in the *GTPBP6* and *PPP2R3B* genes localized in the Xp22.33 PAR region was evaluated as pathogenic in the literature. DECIPHER has been described in a patient with extensive growth retardation and macrocephaly in the database. Other phenotypic features did not correlate with genotypes.

Keywords: Copy Number Variation, PAR Region, *GTPBP6* Gene, *PPP2R3B* Gene

PP-021

***SNORD116* deletions cause all features of Prader-Willi syndrome**

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Prader-Willi syndrome (PWS) is characterized by hypotonia, feeding difficulties in infantile period, excessive eating in early childhood, intellectual disability, behavioral problems and growth hormone deficiency. Approximately 65-75 % of patients with PWS have a deletion 15q11.2-q13, which can be detected using fluorescence in situ hybridization (FISH) or arrayCGH. This ratio increases up to 99% with Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). MS-MLPA not only provides a high rate of diagnosis, but also gives the clinician a better genotype phenotype correlation, giving the deletion site information more specific. With current report, we aimed to compare the clinical findings of our case with PWS syndrome in whom *SNORD116* gene deletion was detected by MS-MLPA method with the clinical findings of very few cases reported in the literature.

Keywords: Deletion, Prader Willi Syndrome, SNORD116

PP-022

Determination of the frequency of the *STAT3* polymorphisms (c.-1915C>G, c.1671C>T, c.-1- 13666T>C, c.273+314A>G/T) in patients with kidney and urinary system congenital anomaly (CAKUT)

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Congenital anomalies of the kidney and urinary tract (CAKUT), collectively refers to various structural malformations characterized by renal developmental disorders in the embryonic period and this malformation accounts for approximately 20-30% of all congenital malformations. Currently, 36 genes found to be related to CAKUT phenotype. However, only 20% of CAKUT patients have mutations in these 36 genes. These data indicate the presence of high genetic heterogeneity in CAKUT. STAT3 is a member of the STAT protein family. The members of this protein family have roles in different cellular mechanisms such as cancer, inflammation, immune response, apoptosis, and early stage of embryonic development. It has been shown that STAT3 plays a role in kidney development and is associated with renal diseases. In this study, four different single nucleotide polymorphisms (SNP) localized in the *STAT3* gene was investigated in patients diagnosed with CAKUT. rs1053004 is located in the 3' untranslated region (UTR) of the gene and rs4796793 is located in the 5 'UTR. rs744166 is located in the intronic region between exon 1 and exon 2, and rs3816769 is in the intronic region between exon 3 and exon 4. We used PCR-RFLP method for the analyses of rs744166 ve rs4796793, and melting curve analyses for rs1053004 and rs3816769. The selection of the patient and control groups was made in collaboration with Başkent University Faculty of Medicine Department of Pediatric Nephrology. Total of 145 CAKUT patients between 0-18 years old, and 128 control individuals enrolled in this study. As a result of statistical analysis, no polymorphism was found to be related to CAKUT.

Keywords: Congenital Anomalies of The Kidney and Urinary Tract, CAKUT, STAT3, Medical Genetic, Single Nucleotide Polymorphism, SNP

PP-023

Pitt-Hopkins syndrome: A rare genetic cause of global developmental delay.

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Up to 40% of developmental disability cases have an underlying genetic cause and with the aid of developing genetic testing techniques the importance of genetic factors in global developmental delay is on the increase day by day. Pitt-Hopkins syndrome, characterized by severe intellectual disability, delayed motor development, typical facial features, hyperventilation and epilepsy has an autosomal dominant inheritance pattern and was first described by Pitt and Hopkins in 1978. Later in 2007 Zweir et al. discovered the *TCF4* gene (MIM:602272), located on 18q21.2, that was responsible for this syndrome. In this case, we present a 3 year 10 months old girl with distinctive facial features, microcephaly, poor speech development, limited walking abilities, who was referred to our department from pediatric neurology clinic. Peripheral blood karyotyping was unremarkable (46,XX).Clinical exome sequencing was performed and a heterozygous frameshift variant in TCF4 gene (c.1365del, p.(Glu456Lysfs*6)), that had not been previously reported, was detected. Sanger sequencing was used for the confirmation and family segregation analysis. Both of the parents were normal for this truncating variant, so the mutation was shown to occur de-novo and it was classified as " pathogenic" according to ACMG Guidelines.

Keywords: Clinical Exome Sequencing, Developmental Delay, Pitt-Hopkins Syndrome

PP-025

A child with double trisomy (48,XXX,+21) Down syndrome: Case report

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Trisomies generally arises by non-disjunction at either the first or second meiotic division. Down syndrome that is known as Trisomy 21 is the most common chromosomal aneuploidy and also the genetic reason of mental retardation. Double trisomy is the presence of two numerical chromosome anomalies together and is rarely observed. Here we describe a postnatally detected case of double trisomy involving chromosome 21 and the X. The case was sent to our medical genetics laboratory because of the clinical features of Down's syndrome. Conventional cytogenetic technique was used for evaluation. Case karyotype was found as 48, XXX,+ 21. The case represents the characteristic multiple dysmorphic features of Down syndrome and is compatible with literature data.

Keywords: Down's syndrome, Double Trisomy, Human Karyotyping, Triple-X

PP-026

Investigation of whether HSP70-hom and with endoplazmic reticulum stress gene can be therapeutic marker

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Endometrial cancer (EC) is the most common malignancy of the female genital system in developed countries. EC is the fourth most common cancer in women after breast, bowel and lung cancer. In general, EC will develop in 2-3% of women throughout their lives. Until today, Although EC is very common, there is little information about its molecular mechanism. HSP70 gene family have three members and these are; HSP70-1, HSP70-hom and HSP70-2. HSP70-1 and HSP70-2 similar protein. Heat Shock Proteins (HSP's) are expressed at high levels in wide range of tumors. They are determining factors for tumor cell survival as they promote autonomous cell proliferation, inhibit cell death pathways, delay senescence as well as influence the immune response to tumor cells. Polymorphic Pst1 site at location1267 A>G[=1249A>G,(GI=5123454)] of the Hsp70-2. Other polymorphic Nco1 site at location [=1630 C>G,(GI=27436929)] of the Hsp70-hom. The aim of the present case-control study was to determine the association between the heat shock protein 70 (HSP70) and risk of Endometrial Cancer (EC) patients by genotyping gene polymorphism. Genomic DNA was extracted from peripheral blood using commercial DNA isolation kit (QIAamp DNA blood kit). The Quality of DNA (ng/µl) samples were assigned using agarose gel-electrophoresis and exact quantities assessed by spectrophotometry (Nano Drop 1000, Thermo Scientific, Wilmington, NC). Polymorphism was performed using (PCR-RFLP) technique. Pst-1 site within the HSP70-2 gene and NcoI site within the HSP70-hom gene. As a result; a direct sequencing approach (Company of Sequetech,CA) was performed to confirm the genotypes obtained by PCR-RFLP for some of the different groups. All statistical analyses were examined in SPSS (SPSS Inc., Chicago, IL, USA).We used fisher exact test, And we found non-significant association between genotype and presence of EC patients and controls. The allele and genotype frequencies for HSP70-hom p=0.05 and HSP70-2 p=0.440. These observations need upward investigations in a bigger controls and relevant patients.

Keywords: Endometrial Cancer, HSPs, RFLP-PCR