1st Bursa International Genetics Days: Dermatogenetics Symposium

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Invited Speaker Abstracts

What is Artificial Intelligence and Its History

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Abstract
Artificial intelligence is the science of making intelligent machines that model human intelligence using computer programs, and was formally born in 1956. Researchers working on artificial intelligence may not observe human and animal behavior, so the methods used are not necessarily biologically observable. Using fuzzy logic, artificial neural networks, expert systems, and genetic algorithms, researchers can make machines that are capable of logical thinking and reasoning, such as the ability to benefit from historical knowledge, plan, learn, communicate, perceive, play objects, and even may develop software that does much more than people can (Kurzweil, 1985). Artificial intelligence is actually considered to have begun with the invention of robotic techology. The term originates from the Czech word robota, which refers to biosynthetic machines used as work force. Artificial intelligence has a wide range of applications in the field of medicine; such as robotics, medical diagnosis, medical statistics and human biology. Firstly, it has shown itself in the field of robotic assisted surgery (Hamet and Tremblay, 2017). Artificial intelligence differs from standard statistics and databases, but it overlaps with extracting useful information from large data sets and data mining, and there is data processing and machine learning in its center. With the rapid developments in computer science, it has become easier to perceive patterns that cannot be come to light by processing large data sets and using biostatistics. Before, artificial intelligence was then used for image analysis in radiology, pathology and dermatology. The development of intelligent machines does not eliminate the need for physicians, but combining machines and physicians can dependably improve system performance. Artificial intelligence can optimize the care course of chronic disease patients, offer sensitive treatments for complex diseases, and lower medical errors (Miller and Brown, 2018). Fuzzy logic has recently become popular to diagnose diseases based on different parameters and methodologies, while traditional algorithm approaches are not seen appropriate for the diagnosis of diseases (Thukral and Bal, 2019). Artificial intelligence can make an enormous contribution to our lives in the future. Because today, there are still problems in the diagnosis of some diseases such as infectious diseases and cancer. For early diagnosis, artificial intelligence is becoming increasingly important in the field of health, and innovative artificial intelligence architectures that are able to work with a small amount of data are evolving, rather than traditional artificial intelligence that requires rich data and is weak in practice. In this way, it will be possible to prevent unnecessary or expensive medical tests and to increase the survival rates of patients with early diagnosis.

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Artificial Intelligence and Genetic Engineering: Bio-Singularity

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From self-driving cars to cancer screening; from the algorithm-driven monitoring program to the racial profiling, the computers that make up their own encryption, the new developments about artificial intelligence (AI) technologies show us that the world is changing rapidly and unpredictably. With artificial intelligence systems, researchers can analyze DNA faster, cheaper and more accurately. Thus, they can draw a perspective on the specific genetic plan that regulates all the activities of that organism. With this insight, AI and machine learning can help us make high-precision decisions about breeding of animals, what a creature can tolerate in the future, which mutations can cause different diseases and how to prepare for the future.
Behind the interest in genome regulation is CRISPR, a newly discovered tool that makes genetic regulation cheaper, easier and more accurate. CRISPR / Cas genome regulation technology has a deep potential to solve the secrets of basic cell biology and to model the underlying causes of hereditary diseases. This genetic engineering approach has been developed since 2012 as a genome-wide efficient and scalable biotechnological tool through sequence-specific guide RNAs to be targeted to achieve double-stranded DNA breaks or to achieve gene expression. Many studies are published on how CRISPR and AI can work together to solve untreatable health problems. In this symposium, it is aimed to explain how bio-singularity is formed instead of AI and genetic engineering and technological singularity; It will be talked about as exciting and high added value, as it will be an eerie development. In addition, although CRISPR / Cas technologies have opened the door to a golden age in the treatment of hereditary diseases with gene therapies, the latest CRISPR dolls and the development of super-animals and plants will also be described as a concern for genetic chaos.

Machine Learning in Bioinformatics, A Historical Perspective

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The term bioinformatics was coined in the 1970s, meaning computational analysis of biological data. The first significant impact of bioinformatics on biological sciences was the identification of viral integration to the human genome, by using computational alignment methods. With the completion of the human genome project, we started to produce sequence data more and more from all possible sources. The data and associated statistics methods first enabled the molecular classification of human disease. Regression, classification and deep learning have been further used for personalized medicine, preventive medicine, drug development, gene identification, sequence analysis, and medical data integration. We have developed a technique to regress out the effect of proliferation from cancer which significantly alters the interpretation of cancer-normal comparisons.

AI Algoritm for Symptom Based Variant Prioritization and Its Application to Rare Diseases

Uğur SEZERMAN
Acibadem Mehmet Ali Aydınlar University

Advancements in Omics technologies enabled access to crucial information that can be used to study disease aetiology at molecular level.
Especially sequencing data facilitated to investigate genetic mechanisms that are at play in rare diseases. In this talk a brief survey of omics technologies and type of information it provides are summarized. Variant prioritization approaches are described and Molecular dynamics based approaches that can be used to determine the impact on mutation to protein function and stability are described. Several application examples in rare diseases are described.

Fuzzy Logic Approaches in Precise and Protective Medicine

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Abstract
Integration of artificial intelligence (AI) approaches such as machine learning and fuzzy logic transforms big data into clinically actionable knowledge and becoming the foundation of precision medicine. Since uncertainty is the inseparable nature of medicine, fuzzy logic methods have been used as one of the best methods to decrease this ambiguity. 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. 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. To date, thousands of different disease-associated variations of BRCA1/2 genes have been detected. Several studies have estimated the penetrance associated with BRCA1/2 mutations. Thus, identification of genetics variations within the BRCA gene family is crucial for early diagnoses. The aim our study to develop a variant selection method based on a fuzzy logic algorithm, and to validate the variant signatures obtained on BRCA1/2 positive breast cancer patient cohorts. 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 software 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: Fuzzy Logic, Artifical Inteligence, precise medicine, breast cancer, BRCA1, BRCA2

In Silico Modelling and Analyzing of Protein Structure

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Proteins are the building blocks of cells and executors of majority of processes in the cell. Catalyzing biochemical reactions, generating cell membrane channels, carrying intercellular signals and acting as hormones are some of their critical roles. Three-dimensional shape of proteins is vital to carry out these crucial tasks. Genetic factors causing missense or nonsense mutations change amino acid(s) or lead to an attenuated protein product, respectively, may disrupt protein-protein interactions which may lead to accumulation of an unwanted intermediate or inhibition/overactivation of a critical pathway. As a result, genetic disorders changing the coding sequence of a gene (modifying the protein) may be pathogenic. It is, therefore, essential to obtain structural information of proteins and associate mutation with the proteins' structure to elucidate the effect of pathogenic mutations at the molecular level. Although NMR and X-ray crystallography techniques are two principle methods to resolve protein structures, they are very expensive and time consuming. Thanks to various in silico protein structure prediction methods we may conveniently model a protein.
Among different approaches homology modelling which utilizes experimentally determined structure having high primary sequence similarity to the protein of interest as a template can precisely and successfully predict the three-dimensional structure of a protein. In this talk I will discuss the fundamental principles of protein homology modelling technique and how to utilize this method to understand the molecular mechanism in genetic diseases mutating the coding region of a gene.

Modeling Human Birth Defects Using Xenopus Model System

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Birth defects are the most common cause of infant mortality. Among them, congenital heart disease and congenital hydrocephalus constitute a significant burden. Unfortunately, genetic mechanisms remain mostly uncharacterized. Currently, human genomics studies are identifying sequence variations in patients with congenital heart defects and hydrocephalus at a rapid rate, but only a small percentage have second unrelated alleles to validate them as disease-causing. Strikingly, many of these candidate genes have no known role in development, reflecting the considerable gap in our understanding. There is a critical need to develop a rapid model system for testing these candidates to provide evidence supporting the candidate gene as a disease-causing. Here we show that the frog Xenopus model system can be effectively used to phenotype congenital heart disease and congenital hydrocephalus. Xenopus is an ideal model that has an optimal balance between human modeling and cost/efficiency. Importantly, Optical Coherence Tomography (OCT) imaging can be easily applied to tadpoles for cardiac and brain phenotyping. OCT is a high-speed, cross-sectional, label-free imaging modality, which can outline dynamic in vivo morphology at micrometer resolution. OCT utilizes infrared light and the image forms due to the echo time delay of the reflected to analyze cardiac and brain phenotypes seen in our patients in tadpoles. Pairing rapid animal model Xenopus with microscale imaging allows detailed phenotyping of the developing heart and brain, which in turn enables identifying specific gene-phenotype relationships over a short time.

Caenorhabditis Elegans as a Model to Understand The Molecular Basis of Rare Diseases

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In the world, substantial efforts have been made to identify the molecular basis of rare diseases and to find treatment methods for them, although the world is still far from the optimal level of treatment for over 10,000 rare diseases. The poor understanding of the molecular mechanism for rare disease complicates to seek the treatment of these conditions. Model organisms such as Drosophila melanogaster, Caenorhabditis elegans and zebrafish (Danio rerio) have been employed to figure out the molecular mechanism of rare diseases. In this talk, so we will discuss how ciliopathies (disorders involving a cilia) can be modeled using C. elegans in our rare disease laboratory, and give a number of examples from our latest laboratory studies.

Drosphilia Melanogaster as a Model to Understand The Molecular Basis Of Diseases

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Drosophila melanogaster has been used as a model organism for basic research for more than 100 years and has been instrumental in the elucidation of many molecular mechanisms. More recently, it has also become a valuable model for the study of human genetic disorders. In my talk I will explain the advantages of using Drosophila melanogaster to model a human disorder. I will particularly focus on our recent studies trying to model intellectual disability in human.
Intellectual Disability is defined as significant deficit in intellectual functioning and adaptive behavior affecting 1-3% of people worldwide. In recent years, with the help of next generation sequencing, large scale systematic studies are being performed to identify genes involved in the pathology of ID. We use Drosophila to validate these candidate ID genes and determine the biological pathways in which the candidate gene is involved.
The Drosophila brain has about 100,000 neurons which control its complex behaviors. In particular, the mushroom body (MB) is a noticeable pair of neuropil structure that is associated with olfactory learning and memory. The study of candidate genes involves the generation of mutants for the fly homolog and transgenic lines that carry the human variant. Fly brains are then analyzed for immunohistochemical analysis of brain structures and the use of different behavioral tests such as olfactory learning and courtship conditioning, spatial learning and habituation assays to evaluate the ability of flies carrying disease-causing mutations to learn and memorize.

Use of Induced Pluripotent Stem Cells and Crispr/Cas9 Genome Editing in Dermatology: In Vitro and In Vivo Approaches
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Stem cells are basically divided into two: embryonic and adult stem cells. Embryonic stem cells are usually obtained from unused and discarded embryos in vitro. The stage at which they are obtained corresponds to the fifth day after fertilization. At this stage, the embryo consists of 2 main layers. From these layers, the cell population, called the inner cell mass, is separated from the embryo by mechanical methods and propagated in cell culture media in its own culture medium. These cells are capable of being transformed into all cell types that make up the body except the placenta. For this reason, they show promise in the treatment of diseases that cannot be treated with medication and that can only be cured by replacing the cells. It also offers the possibility of testing various drug tests that cannot be performed on human cells on embryonic stem cells and transformed body cells. In this way, they allow to determine the side effects of various drugs and their success in treating the disease. However, the use of these cells has been prevented by laws in various countries for purely ethical reasons. In 2006, scientists named Takahashi and Yamanaka first identified skin cells from mice, and in 2007 four transcription factors to human skin cells; Oct4, Sox2, Klf4 and c-myc were transformed into embryonic cells by external delivery. The cells thus obtained were called induced pluripotent stem cells (iPSC), while these factors became known as Yamanaka factors.
iPSCs have been obtained from various body cells, and the introduction of these factors to the cells with different combinations of factors or safer ways has been started to be investigated by the groups working in the field of stem cells in the world. While these cells have all the features of embryonic stem cells, they have been confirmed by many studies that can be obtained from any body cell in various ways. In addition to having no ethical problems, iPSCs have another feature that embryonic stem cells cannot provide; personal treatment. If a piece of tissue or blood can be obtained from a person, then iPS cell of that person can be generated. Thus, iPSCs of the person's own genetic structure can be converted to the cells that the person needs, the drug that can best treat this person, can be screened in these cells, and even organs can be formed from these cells in the future and will be easily accepted by the body since it is the person's own cells. In fact, if the disease in which the person needs treatment is caused by a defect in the genetic background, this can be corrected in the laboratory and gene therapy can be provided and genetically corrected cells can be offered to the person as a treatment. Regarding that, iPSCs are involved in research studies to reveal the molecular mechanisms of many diseases or for regenerative uses, including dermatological disorders. In addition, as the applications of genome regulation techniques (TALEN, ZFN, CRISPR / Cas9) became easier and faster, research on correcting the patient genotype in many diseases including dermatological disorders. This talk will focus on the latest research topics that involve the use of iPSCs and CRISPR/Cas9 genome editing tool in skin disorders.

Palmoplantar Keratodermas: Syndromes and Disease Mechanisms
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The ability of cells and tissues to withstand and respond to a variety of stressors is fundamental to life. In mammals, the skin plays a unique role in the defence against external damage, pathogens and allergens, and therefore displays many specialised adaptations to environmental stress. In order to maintain homeostasis, respond to stress and mediate tissue repair, the skin requires a network of systems to co-ordinate this activity including regulated intercellular communication (for example, via gap junctions) and various intra-and inter-cellular signaling pathways. In particular, the epidermis of palmoplantar (palm and sole) regions is uniquely adapted to withstand remarkable physical stress and insights into the key molecules to maintain cutaneous homeostasis have come from the study of inherited disorders of this skin site, the palmoplantar keratodermas (PPK). This lecture will provide a brief overview of some of these genetic findings and disease mechanisms. A particular focus will be on some of our recent work on iRhom2 in which dominantly-inherited point mutations are associated with a syndrome in which affected individuals develop PPK and have a very high risk of oesophageal squamous cell carcinoma. Based on multiple lines of evidence generated by our laboratory, we show that iRhom2 functions as a major regulator of the response to cellular stress and disease. We have shown iRhom2 to have diverse roles in context-dependent cellular signalling within the keratinocyte, including regulation of the sheddase enzyme ADAM17, coordination of the keratin-associated cytoskeletal stress response plus orchestrating palmoplantar epidermal thickening and its barrier activity.

Melanoma, From the Oncologist's Perspective
Türkkan EVRENSEL
Bursa Uludag University School of Medicine

In some countries such as Australia has one of the world's highest incidences of melanoma; it represents over 10% of new cancer diagnoses, and it is estimated that 1774 deaths will be attributed to metastatic melanoma in 2016.
Before 2010, there was less effective therapy for advanced melanoma. The diagnosis carried a dismal prognosis, with a median overall survival of 6–9 months and less than 20% chance of surviving for 2 years. Chemotherapy with dacarbazine was the standard of care for decades; however, a meta-analysis in 2007 found that a patient's chance of responding to this chemotherapy was only 15% without improving survival.
Recently, there has been a paradigm change in the management of advanced melanoma with the development of highly effective, targeted immunotherapies, which has revolutionised the management of patients.
The years 2012 and 2013 saw the opening of two phase III dabrafenib and trametinib combination therapy trials and a vemurafenib and cobimetinib (MEK inhibitor) combination trial. The progression-free survival results of all these trials were reported, demonstrating a significant improvement in progression-free results, with overall survival reported in 2015
While the current data potentially suggest that PD-L1 may be useful in helping to select who would benefit most from a CTLA-4 antibody, we await the overall survival results from Checkmate 067 and confirmatory trials. The currently available data would suggest that we cannot use PD-L1 negativity as a biomarker to deny a patient's access to PD-1-based monotherapy as there is still a survival benefit for patients when given PD-1 antibodies. When administered as monotherapy in clinical studies, CTLA-4 and PD-1 blockers demonstrated impressive durable response rates, increased the survival time of responding patients significantly and had a manageable safety profile . However, benefits of monotherapy were limited by low response rates and only a fraction of patients were found to respond to the therapy
Combination of CTLA-4 and PD-1 blockers was then evaluated to increase the response rates in patients, and ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) combination was shown to significantly enhance efficacy in metastatic melanoma patients. Subsequently, ipilimumab plus nivolumab was approved for treatment of metastatic melanoma,
The current treatment landscape for advanced melanoma has changed rapidly in the last few years, and there are now several different classes of therapy that can be offered to patients depending on their mutational status and disease burden However, there is still a need for improvement, and as such, ongoing patient enrolment and participation in clinical trials is vitally important for us to be able to offer our patients improved response rates and long-term disease control either to ‘cure’ patients or turn advanced melanoma into a ‘chronic’ disease.

Genetic Alterations and Personalized Medicine in Melanoma

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The field of cancer genetics and precision medicine are continuously on the move. Individualizing therapeutic selection for patients is a major goal in cancer treatment today. This goal is best facilitated by understanding both an individual's inherited genetic variation and the somatic genetic changes arising during cancer development. In my talk, I will highlight mainly two topics that are of growing interest.

The first topic is the melanoma genetics. An estimated 5%–10% of all cutaneous melanoma cases occur in families. Germline mutations in mainly two genes that play a pivotal role in controlling cell cycle and division CDKN2A and CDK4 are the most frequent genes found to be mutated in melanoma predisposed cases. These genes are known to be high penetrance familial melanoma genes. Although rare, melanoma predisposed pedigrees with BAP1, TERT and POT1 mutations have been found. There are also low penetrance genes have been reported in familial melanoma cases: melanocortin-1 receptor, epidermal growth factor, glutathione s-transferase M1, cytochrome p450 debrisoquine hydroxylase locus (CYP2D6) and vitamin D receptor.

Dermatologists and other health professionals should incorporate family history and risk assessment into clinical practice to identify patients who may be at increased risk for melanoma. Individuals with 3 or more primary melanomas and/or families with at least one melanoma and two or more other diagnoses of melanoma and/or pancreatic cancer in aggregate among first- or second-degree relatives on the same side of the family should be referred to a geneticist for constitutional analysis and specific counselling. Appropriate screening for patients who are genetically predisposed to melanoma by a dermatologist is recommended.

The second topic that I'd like to focus on is current knowledge of melanoma development and personalized medicine in melanoma treatment.

Although melanomagenesis is still not fully understood, recent studies have identified several genetic alterations that provide insight into molecular mechanism of melanoma development and potential implications for prognosis and therapy. It is well known that melanomas are associated with mutations in BRAF, TP53, NF1, CDKN2A, PTEN and RAS family of genes, primarily NRAS. BRAF and MEK inhibitors are now used to treat melanoma patient with BRAF or RAS mutations.

Involvement of mutations of these well defined oncogenes and tumour suppressor genes were confirmed with high-throughput genomic analysis and new mutations, amplifications, deletions and translocations in other genes have been identified. The Cancer Genome Atlas (TCGA) study, in addition to identification of new melanoma genes and pathways, has allowed the researchers to classify melanomas into four distinct subtypes: mutant BRAF, mutant RAS, Mutant NF1 and triple wild type. There was no significant outcome correlation with genomic classification, but samples assigned a transcriptomic subclass enriched for immune gene expression associated with lymphocyte infiltrate on pathology review and high LCK protein expression, a T cell marker, were associated with improved patient survival. No significant association was found between a specific subtype and a targeted therapy, but the triple-wild-type subtype was associated with KIT mutations, focal amplifications and complex structural rearrangements. Although KIT mutated melanomas are successfully treated with Imatinib, triple-wild-type subtype melanoma response to imatinib need to be evaluated with clinical trials.

Personalized therapy targeting melanoma patients are not limited to BRAF, KIT and MEK inhibitors. Comprehensive genomic profiling studies might reveal other potentially actionable genetic alterations include IDH1, EZH2 mutations and PDGFRA and KDR amplifications. In addition to targets, comprehensive genomic profiling might provide resistance profile, facilitating prognosis and monitoring.

In my talk, I will discuss novel melanoma diagnostic, prognostic and therapeutic markers and its near future.

Tumor Microenvironment in Primary Cutaneous T-Cell Lymphoma

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Primary Cutaneous T-Cell Lymphoma

Primary cutaneous T-cell lymphomas are a heterogenous group of non-Hodgkin lymphomas which do not exhibit extracutaneous involvement at time of diagnosis and which originate from T-lymphocytes localizing to the skin. They comprise 70% of all primary cutaneous lymphomas and are classified according to clinical presentation, etiopathogenesis, histopathology, immune phenotype and prognosis. The most common types in this group are mycosis fungoides (MF) and Sézary syndrome (SS) which are considered as prototypes of primary cutaneous T-cell lymphomas. Unfortunately, there is no treatment option that provides complete recovery and these disorders tend to relapse in most cases. Better understanding of MF tumor microenvironment and underlying molecular mechanisms in MF thus holds great importance for the development of novel therapeutic approaches in these entities.

MF has different clinical and histopathological characteristics in various stages of the disease. In early MF, lesions present as desquamating lightly erythematous patches. As disease-specific histopathological characteristics are not established at this stage, it may be difficult to diagnose early MF through skin biopsies. Detecting epidermotropism histologically may help diagnosis. With the increase in the lymphocytic infiltrate, plaque lesions begin to be seen clinically. Histologically, epidermotropism becomes more prominent, and Pautrier microabcesses which are formed through gatherings of malignant lymphocytes around epidermal Langerhans cells appear. At tumor stage there is a heavy lymphocytic infiltration malignant lymphocytes start losing their epidermotropism and invading dermis. In erythrodermic MF and SS, malignant lymphocytes almost entirely leave the skin and go into the systemic circulation. Lymph node and visceral metastases can be seen at this stage. There is erythema and desquamation almost on the entire skin surface. As the lymphocyte infiltration is sparse at this stage, it may be challenging to make a histopathologic diagnosis through skin biopsies. These patients usually die due to immunosuppression leading to infections.

Pathogenesis, Immune Dysregulation and Tumor Microenvironment in MF

While pathogenesis of MF is not entirely understood, it is considered as a condition caused by skin homing T-cells exposed to chronic antigenic stimulation getting the clonal proliferation ability with the help of genetic predisposition, chemokine and cytokine profile of the individual.

Malignant lymphocytes in MF interact with many other cells in the tumor microenvironment. CD8+ cytotoxic T-cells and Th1 cells are responsible for anti-tumor immune response which holds tumor cells under control, especially during the early stage. Regulatory T-cells (Tregs), Th2 cells and Th17/Th22 cells facilitate proliferation and survival of malignant lymphocytes by establishing a pro-tumor microenvironment. Other cells in the skin such as dendritic cells, macrophages, mast cells, keratinocytes and fibroblasts also support this pro-tumor microenvironment through cytokines and chemokines they secrete and co-stimulatory molecules they express.

MF cells have a CD4+ CD45RO+ mature memory T-cell phenotype. Cutaneous lymphocyte antigen (CLA) and chemokine receptor CCR4 are important markers of these cells. Expressions of various Treg, Th2 and Th17 cell-specific markers have also been reported in MF cells. As the disease progresses, MF microenvironment turns from a tumor suppressing anti-tumor state to a pro-tumor state where anti-tumor immune response is suppressed. CD4/CD8 ratio increases, the number of Tregs augments and macrophages in the microenvironment gain an M2 phenotype supporting tumor cells as the disease stage advances. The cytokine profile shifts from Th1 type to Th2 type, this Th2 response becomes systemically prominent with time and the patient becomes deeply immunosuppressed. As Th2 cytokines increase, eosinophils are attracted to the tumor microenvironment and pruritus appears clinically. Itching is a finding that points to an unfavorable prognosis.

At the early stage of the disease, neoplastic T-cells exhibit skin homing through interactions of E-selectin they express with dermal postcapillary venules and of CXCR3 they express with CXCL9 and CXCL10 secreted by dermal fibroblasts and epidermal keratinocytes. At plaque stage, CXCR3 expression leaves its place to CCR4 and CCR10. The ligands of CCR4 are CCL17 and CCL22 secreted by Langerhans cells, dermal fibroblasts and macrophages. This chemokine receptor and its ligands, which are responsible for Pautrier microabcess formation, play a crucial role in disease pathogenesis. CCR10, whose ligand is CCL27 originating from keratinocytes, is responsible for epidermotropism. In advanced stage, neoplastic cells downregulate CCR4 and CCR10 expression and start expressing CCR7. This chemokine receptor which is responsible of lymphocyte recirculation between skin and lymph nodes in normal physiology, provide the malignant lymphocytes the ability to leave the skin and enter the systemic circulation.

Anti-tumor immune response during MF disease progression sequentially exhibits the 3Es (elimination, equilibrium, escape) of the tumor immunology concept. While neoplastic cells are under immune surveillance at the beginning, they accomplish immune escape through the chromosomal and phenotypic changes they gain, the cytokines they secrete and cause other cells in the microenvironment to secrete, suppression of CD8+ cytotoxic T-cells by expressing co-inhibitory molecules such as PD-1 and CTLA-4 and downregulation of Fas expression to evade cytotoxic T-cell induced apoptosis; thus getting the ability to rapidly proliferate and enter the systemic circulation.

The Role of Fibroblasts in MF Tumor Microenvironment

While the effects of many cells in MF tumor microenvironment on disease etiopathogenesis and progression have been investigated, the role of fibroblasts, which are one of the most numerous cells in the skin, on the pathogenesis of MF, which is a malignancy originating from skin-homing lymphocytes, has not been elucidated. Fibroblasts are known to increase proliferation and survival of tumor cells, support angiogenesis and metastasis and suppress anti-tumor immune response in many solid tumors and lymphomas. These fibroblasts located in tumor microenvironment, having a pro-tumor effect and resembling activated fibroblasts morphologically and phenotypically, are called “cancer associated fibroblasts”.

In our studies with the objective to investigate the effects of fibroblasts on proliferation and survival of MF cells, we found that fibroblasts increase MF skin derived lymphocytes while suppressing healthy skin derived lymphocytes and peripheral blood CD4+ T-cells. We did not see a prominent difference between the effects of fibroblasts derived from healthy skin or MF skin. In cytokine assessment from co-culture supernatants, we showed that IL-13 and interferon-gamma levels are parallel with lymphocyte proliferation rates. However, we showed that fibroblasts decreased MF cell survival in the absence or presence of doxorubicin, a chemotherapeutic drug. We thought this issue arised due to competition of fibroblasts for space and nutrients within culture wells.

While these investigations we performed in MF tumor microenvironment throw light on certain issues of disease pathogenesis, they also lead to many new questions which are yet to be answered. To treat the disease effectively, pre-clinical research on MF tumor microenvironment should be supported to gain speed.

Immunotherapy in Dermato-genetic Malignancies

Ercüment OVALI

The importance of the immunotherapy on cancer control was known for very long time but it was not thought as a treatment option. When the first cellular immunotherapy trials were started, the results were disappointing due to an unexpected rapid disease progression. However, in the patient follow-ups, the tumors of the patients increased initially, but the tumor growth rate slowed down and created a survival advantage. Many studies have shown that after immunotherapy, progression (psoudo) is a positive response, unlike RECİST. There are four types of cellular immunotherapy products which are lymphokine activated killer cells, adoptive immunotherapy cells (CIK, TIL, NK and VST), dendritic cell vaccines, genetically modified T and NK cells. Most significant cellular immunotherapy product in melanoma patients are Tumor İnfiltrated Lymphoctes (TIL).

According to 2019 meta-analysis among heavily treated 410 malignant melanoma patients in 13 different clinics, the overall all remission rate estimate was %41, complete remission rate was %14 [1]. The duration of response within 1 year was %59, 8 and median duration of response was 21 months. The 4-year survival rate of the patients undergoing complete remission was 80%. This actually means that the disease was cured[1]. Cutaneous T cell lymphomas are another group of dermatological malignancy, consists of heterogeneous monoclonal T cell proliferation involving the skin [2]. MF and Sezary syndrome are most common forms and there is no curable treatment option available today. The future target antigens for CAR based therapies in cutaneous T cell lymphomas are CD30, CCR4, CD37, TCR1 and 2[2]. Since the disease is a T cell lymphoma, patients are thought to benefit from CAR- NK cell therapies rather than CAR-T cell therapies.

Keywords: İmmunotherapy, Malign Melanoma, Cutaneous T cell lymphoma, Tumor İnfiltrated Lymphocyte, CAR- based Therapy

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In Vivo and In Vitro Crispr-Cas9 Applications for Genetic Studies

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Almost all cells of any living organism contain DNA, a hereditary molecule that passes from generation to generation during reproduction. The term "genome" generally refers to the total DNA sequences in an organism. Genome consists of DNA sequences called “gene”, which plays a role in the basic biological processes involved in many phenotypic and genotypic characteristics, such as performing cellular functions, controlling numbers and species, regulating energy production, metabolism, and combating diseases.

Gene editing is the process of pre-designing and modifying a particular DNA sequence in a targeted gene. Genetic repair technologies such as Zinc finger nucleases (ZFN, Zinc-finger nuclease), TALEN and CRISPR-Cas have been developed to repair damaged DNA regions called mutations that cause genetic diseases. These nuclear-based technologies introduce double-strand breaks (DSBs) in the targeted region of the human genome. The worldwide popular CRISPR/Cas gene-editing technology provides the widest potential to solve the underlying causes of genetic diseases. For this purpose, the DNA helix is cut at a certain point, to form a double strand brake (DSB), and naturally existing cellular repair mechanisms repair the DSB. Modes of the repair mechanisms may affect the gene function. When DSB is formed, gene editing techniques can be applied to remove, insert or replace a newly modified sequence using a synthetic donor template DNA.

In developed and developing countries, CRISPR-Cas studies in addition to research and development studies are rapidly increasing. In addition to increasing population, changing weather conditions, declining farmland, increasing biotic and abiotic stresses are other important barriers to agricultural production, food and feed supply.

Here, I will present how CRISPR toolbox provides the means to decode human T cell function and has important implications for the identification and validation of novel therapeutic targets. CRISPR-Cas applications will be introduced in detail from the studies that carried out gene modifications in the fields of health, animals, plants, microorganisms, and food supply. In addition, these technologies and applications have been examined in terms of world biosafety legislation and the scientific risk assessment of the products developed using CRISPR-Cas technique.

Retinoids in Dermatology: Rational Use of Drugs

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Retinoids have been used in dermatology since the 1940s when vitamin A was first used to treat acne vulgaris. After that increasingly used for topical and systemic treatment of hyperkeratotic skin disorders, genodermatoses, severe acne, and also for therapy and/or chemoprevention of epithelial skin cancer and cutaneous T cell lymphoma. Oxidative metabolites of vitamin A are natural retinoids in the peripheral blood. Synthetic retinoids are classified into 3 generations that non-aromatic, mono-aromatic and poly-aromatic compounds. Retinoids exhibit anti-proliferative, anti-inflammatory, immunomodulatory, and anti-cancer effects by binding to nuclear retinoic acid receptors and retinoid-X-receptors. This eventually leads to the activation of specific regulatory regions of DNA involved in regulating cell growth, differentiation and apoptosis. The major concerning side effect of retinoids is teratogenicity(FDA Category X), all other side effects (mucocutaneous xerosis, conjunctivitis, etc.), are dose-dependent and controllable with dose modification. Effective contraception and blood donation prohibition to women of child-bearing potential, even after the end of therapy is essential. Transient elevation of laboratory values including, transaminases and triglyceride levels may be seen. Hence, periodic monitoring of laboratory values is necessary during systemic retinoid treatment. Simultaneous use of tetracyclines should be avoided since both show synergistic effects in the development of pseudotumor cerebri. Although the previous corcerning reports, data on suicidal behavior during retinoid treatment are insufficient to establish a meaningful causative association.

The use of retinoids in therapeutic field seems effective and safe, patients should be informed about possible side effects, and close follow up of the patients is required.

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Genodermatosis From Patology Eye

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Congenital skin diseases are rare diseases that occur after a number of genetic disorders, most of them show themselves with nonspecific histopathological pictures that do not contain specific diagnostic features.
Generally speaking;
1- Ichthyoses
2- keratodermas
3- Acantholysis / bulla formation disorders
4- Connective tissue diseases
5- mastocytosis
6- Incontinantia pigmenti
the main emerging disease groups. There are also syndromic skin diseases.

Ichthyosis
There are four major and three minor disease tables and some related syndromes under this heading.
Ichthyosis vulgaris
Ichthyosis due to X
Epidermolytic hyperkeratosis
Lamellar Ichthyosis
In the pathological evaluation, it is possible to diagnose epidermolytic hyperkeratosis only with the appearance of special vacuolic degeneration and keratohyalen granules in the epidermis. Diseases in this group have varying degrees of hyperkeratosis. However, the diagnosis can be made by clinicopathological correlation, and the diagnosis is confirmed by the detection of genetic disorder.

Keratodermas
Keratoderma Palmoplantaris
It is a group of diseases characterized by localized or diffuse compact thickening of the keratin layer in the palms and soles. It can occur without any other symptoms, or it can develop as part of a common disorder. Most of them are hereditary. Diseases with autosomal dominant or recessive transition are diagnosed by clinicopathological correlation.

Porokeratosis
It is a rare keratinization disorder with various lesions. It has an autosomal dominant transition and is more common in men. The five major types are described.
a) Plaque type
b) Disseminated superficial actinic porokeratosis
c) Lineer porokeratosis
d) Porokeratosis plantaris palmaris et disseminatus
e) Punktate porokeratosis
Nonspecific findings such as hyperkeratosis, irregular acanthosis, the presence of keratotic plugs, the presence of parakeratotic cuff (cornoid lamella) in the middle of the keratotic plugs, loss of granular layer under the cornoid lamella, lymphocytic infiltration in the dermis. Together with the clinical findings, the diagnosis is made.

Xeroderma Pigmentosum

It is a rare disease with an autosomal recessive trait that occurs at an early age and is characterized by skin cancers. In the individual who is normal at birth, the disease begins after the first exposure to the sun. Pathological findings are evaluated in 3 periods.
1. period; characterized by nonspecific histopathological findings. Hyperkeratosis, thinning in the malpigia layer, thinning in some retreats, elongation in others, chronic inflammatory infiltration in the upper dermis, irregular distribution of melanin in the basal layer
2. Period; hyperkeratosis and irregular hyperpigmentation becomes evident, the epidermis is irregular atrophic or acantotic. There are solar keratosis areas.
3. Period; tumor stage.

BULLOUS OR ACANTOLITHIC DISORDERS
Epidermolysis Bullosa
Family Benign Pemphigus (Hailey-Hailey Disease)
Keratosis follicularis (Darier's Disease)
Acrokeratosis Verrusiformis of Hopf
Epidermolysis is a group of diseases that go to the bullosa by decomposition under the basement membrane or above. Light microscopic findings are similar. Electron microscopy is helpful in determining the dissociation area. Dermal findings are nonspecific and immunofluorescence tests are negative.
In Hailey hailey disease, suprabasal cleft occurs in the epidermis initially. Then, full-layer acantholysis and intraepidermal bulla occur. Acantholytic cells or groups of cells, some of which show premature keratinization, are seen in the bull cavity.
Darier disease has hyperkeratosis and papillomatosis, the presence of dyskeratotic cells in the form of corps ronds and grains, suprabasal acantholysis, dermal nonspecific chronic inflammation.
Acrokeratosis Verrusiformis of Hopf: mostly seen as verrucous papules on the dorsal faces of the hands. In its pathology, regular papillomatous and hyperkeratosis resembling church towers are observed.

TISSUE TISSUE DISEASES
While Connective Tissue Nevus and Ehler Danlos syndrome pathological findings are nonspecific, the presence of degenerate and calcified elastic fibers observed in the dermis in Pseudoxanthoma Elasticum is very characteristic.

URTICERIA PIGMENTOSA
While four different tables are clinically observed, pathological CD117 immunohistochemical stain, mast cell proliferation, which becomes apparent with Toluidine blue and Giemsa, are definitive.

INCONTINANTIA PIGMENTI
In the first weeks after birth, girls appear as urticarial, vesicular or verrucous inflammatory lesions, then return to pigmentation. Histopathologically, intraepidermal vesicles and spongiosis and a large number of eosinophils are seen in the first period. In the second period, acanthosis, hyperkeratosis and papillomatosis occur. Recently, there are plenty of melanin-laden macrophages in the dermis.

AS A RESULT;
In most genetically transmitted skin diseases, their pathological findings are nonspecific and difficult to diagnose. However, the diagnosis is approached or made with a clinicopathological approach. Genetic tests are essential for confirmation. For this reason, it is very important to give detailed information about the patient in the pathology request reports.

Ichthyosis: Dermatological Approach and Treatment
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Ichthyosis is a group of inherited keratinisation disorder characterised by dry skin, scaling and hyperkeratosis. In all forms, epidermal barier is disrupted. In 2009, classification of ichthyosis was revised. Based on this new classification, icthyosis is grouped as non-syndromic and syndromic ichthyosis. Non-syndromic ichthyosis was subdivided into common ichthyosis, autosomal recessive congenital ichthyosis, keratinopathic ichthyosis and other forms. Depending on the type of ichthyosis, varying severities of hyperkeratosis, and scaling are accompanied by erythema, fissures and erosions.
Syndromic forms include genetic disorders that ichthyosis is one of the symptoms besides involvement of other organs. Syndromic ichthyosis is divided into X-linked ichthyosis syndromes (Syndromic X-linked ichthyosis, ichthyosis follicularis, atrichia and photophobia syndrome and Conradi-Hünerman syndrome), autosomal ichthyosis syndromes with prominent hair abnormalities (Netherton syndrome, ichthyosis –hypotrichosis syndrome, ichthyosis –hypotrichosis-sclerosing cholangitis syndrome, trichothiodystrophy), with prominent neurological signs (Sjögren-Larsson syndrome, Refsum syndrome, MEDNIK syndrome), with fatal disease course (Gaucher type 2, multiple sulphatase deficiency, CEDNIK syndrome, arthrogryposis-renal dysfunction-cholestasis syndrome) and with other associated signs (Chanarin-Dorfman syndrome, KID syndrome, ichthyosis prematurity syndrome). Accurate diagnosis of ichthyosis, which is necessary for adequate patient approach, is now possible by advanced genetic analysis methods .

Ichthyoses: Genetics and Genetic Counseling

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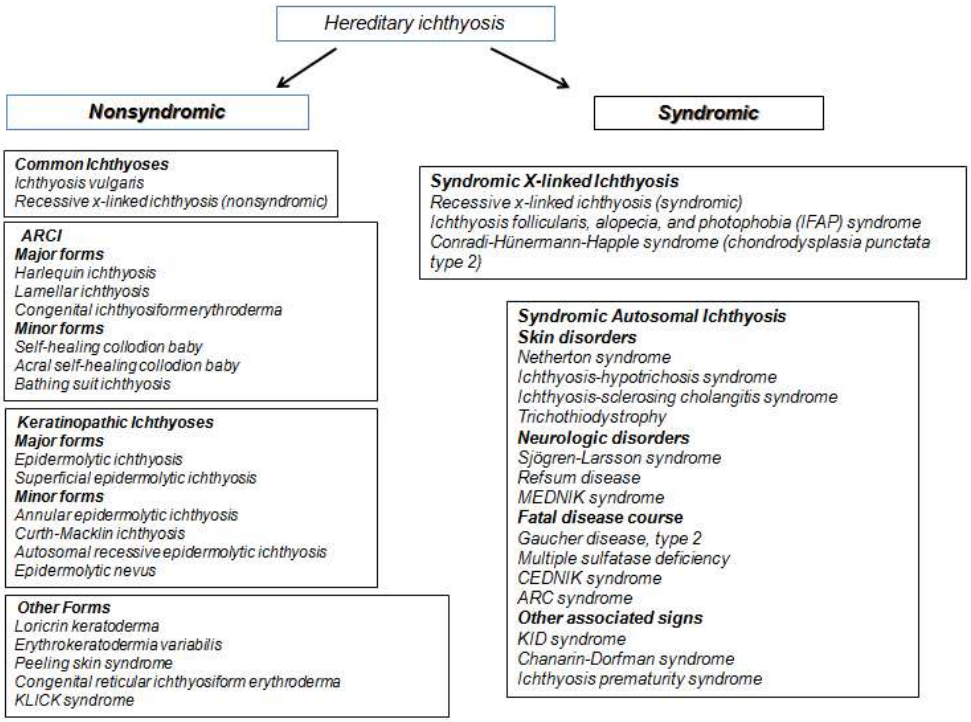
Ichthyosis is one of the most common hereditary dermatologic disorders characterized by localized or generalized scaling. Other associated manifestations include palmoplantar keratoderma, erythroderma, recurrent infections, and hypohidrosis. Hereditary ichthyosis are classified into two groups: nonsyndromic and syndromic forms (Table1) (1). Mutations in more than 50 genes affecting structural proteins which plays roles in the skin barrier functions cause syndromic and non-syndromic ichthyoses (2). Molecular diagnosis of hereditary ichthyosis is essential not only for patient information about prognosis and therapeutic options but also for genetic counseling .

Table I: Classification of Hereditary Ichthyosis (1)



Abbreviations: ARC, arthrogryposis---renal dysfunction---cholestasis; ARCI, autosomal recessive congenital ichthyosis; CEDNIK, cerebraldysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma; KID, keratitis ichthyosis deafness; KLICK, keratosis linearis withichthyosis congenital and sclerosing keratoderma; MEDNIK, mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis,keratoderma.

NONSYNDROMİC ICHTYOSIS

Common Ichthyoses

Ichthyosis vulgaris

Ichthyosis vulgaris is the most common monogenic hereditary skin disorder with a frequency of 1/250 (3). It is caused by Loss-of-function mutations in the filaggrin (FLG) gene. Hetrozygous FLG mutations is associated with susceptibility to allergic- atopic skin phenotypes and these mutations are carried by up to 10% of most human populations. Homozygus mutations cause typical skin manifestations with dark, scaly skin. FLG gene encodes a protein called profilaggrin and is composed of three exons. Profilaggrin protein is encoded almost entirely by large third exon which contains near identical 10 to 12 repeats of the 37-kD filaggrin monomer. Its repetitive nature makes the molecular analysis (PCR and sequencing) diffucult. Profilaggrin is an unfunctional protein that is cleaved into individual functional filaggrin monomers. Filaggrin contribute to skin-barrier formation, hydration, pH, and protection against ultraviolet radiation. Filaggrin deficiency allows allergens cross the epidermis and trigger Th-2 allergic immunity(3-4).

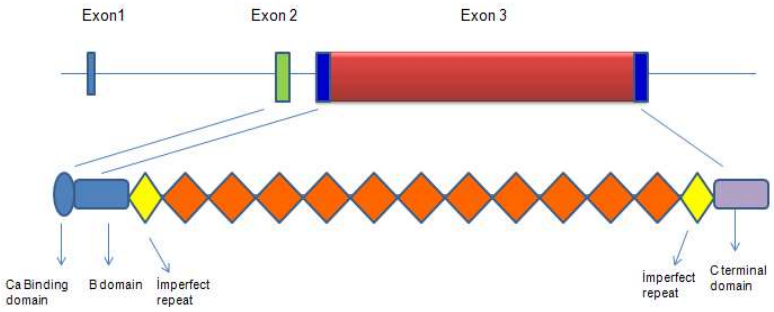


Fig 1: FLG gene and encoded protein

Recessive X-linked ichthyosis

X-linked ichthyosis (XLI) is the second most common form of hereditary ichthyosis with a prevalence of 1 in 2,000 -6000 males. It is caused by molecular defects in the STS gene which codes steroid sulfatase, located at Xp22.3 and contains 10 exons. In most XLI cases (80-90%) have complet deletion of STS gene. Symtoms usually begin between 2-6 weeks of age as mild, light coloured scaling skin. In later ages scaling progresses adherent dark scales and involves mostly extensor regions of the extremities, preauricular areas, neck and upper trunk (5). A number of XLI cases shows extracutaneous manifestations, such as corneal opacities, cryptorchidism, increased risk of testicular germ cell cancer, CNS functional disorders. Those cases are classified into syndromic XLI (Table1).

Autosomal Recessive Congenital Ichthyosis

Autosomal Recessive Congenital Ichthyosis (ARCI) is a very heterogeneous disorder. Combined prevalence for major forms (lamellar ichthyosis and Congenital ichthyosiform erythroderma) is around 1 per 200 000 to 300 000 population (6). These disorders are limited to the skin, and most of patients present severe symptoms. Common features of different ARCI forms are a generalized scaling of the skin and varying degrees of erythema. Newborns usually are born with a collodion membrane that is lost during the first weeks of life. According to First Ichthyosis Consensus Conference in Sorèze 2009 ARCIs are classified into two main groups: Major forms and minor forms. Major forms are harlequin ichthyosis, lamellar ichthyosis , and congenital ichthyosiform erythroderma (Table 1). Other less common minor forms are self-healing collodion baby, acral self-healing collodion baby, and bathing suit ichthyosis (6-7).

To date, 12 genes have been described to be associated with ARCI: TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4, LIPN, CERS3, PNPLA1, CASP14, SDR9C7, and SULT2B1, and at least 10%–15% of affected individuals do not have mutations in any of the known genes.

Major forms

Harlequin ichthyosis

Harlequin ichthyosis (HI) is one of the most severe inherited ichthyosis forms. The children are usually premature and It can be fatal. The clinical findings include shiny hyperkeratotic plaques, separated by deep fissures, severe ectropion, eclabium, and flattening of the ears (8). The hands and feet are swollen and edematous, and often covered by a glove-like layer. They may have finger contractures (9).

ABCA12 gene mutations underlie HI. ABCA12 have 53 exons, and encodes aprotein belongs to a family of ABC transporters. It binds adenosine triphosphate and plays a role in the transport of a number of molecules across the cell membrane. Unfunctional ABCA12 causes lipid transport disorders in lamellar bodies leading to a decrease in intercellular lipid levels in the stratum corneum. As a compensatory response to a deficient lipid barrier, massive hyperkeratosis occurs in these patients (10). in vitro studies suggest that ABCA12 mutations also have an effect on epidermal differentiation (11). To date, more than 50 mutations have been defined in the ABCA12 gene. Complete loss of function mutations in the ABCA12 gene leads to the HI phenotype whereas less severe missense mutations cause Congenital ichthyosiform erythroderma or Lamellar ichthyosis (12). To date, the rate of detection of mutations in the ABCA12 gene in patients with HI is close to 100%, showing it is a genetically homogeneous condition. Because of its characteristic phenotype, diagnosis of HI is usually not difficult. Molecular diagnostic confirmation is important for an accurate prenatal diagnosis.

Lamellar Ichthyosis and Congenital Ichthyosiform Erythroderma

Lamellar Ichthyosis (LI) and Congenital Ichthyosiform Erythroderma (CIE) are caused by the same gene mutations. LI and CIE have not been associated with a clear genotype/phenotype correlation. In the same family, patients with the same mutations can develop different phenotypes (13). Most patients show clinical manifestations of both entities and are born as collodion baby. Collodion membrane

disappears within one or two weeksks of life and is replaced by the definitive phenotype. Hypohidrosis, severe heat intolerance, and nail dystrophy are frequently observed in both LI and CIE. Patients with LI usually have more severe clinical manifestations than those with CIE They usually present large, thick scales over the entire body and palmoplantar keratoderma is frequently seen. Erythroderma is either absent or minimal. Patients with LI generally have ectropion, alopecia, especially at the edge of the scalp, eclabium, hypoplasia of joint and nasal cartilage. Patients with CIE normally present fine, whitish scales as well as generalized erythroderma. Some patients have marked erythema and generalized scaling. In less severe cases, erythema is mild and the scaling is fine (8). Eight genes have been defined to be associated with LI and CIE : transglutaminase 1 (TGM1), NIPA-like domain containing 4 (NIPAL4/ICHTHYIN); ABCA12; lipoxygenase-3 (ALOXE3); 12R-lipoxygenase (ALOX12B), ceramide synthase 3 (CERS3); cytochrome P450, family 4, subfamily F, polypeptide 22 (CYP4F22); and patatin-like phospholipase domain-containing protein 1 (PNPLA1) (14). Most patiens with LI (more than 50%) carry TGM1 mutations, however, TGM1 mutations have also been defined in CIE (15,16).

The TGM1 gene located on chromosome 14q11.2 has 15 exons and encodes the transglutaminase 1 enzyme. This enzyme play roles in the formation of the cornified envelope and also catalyzes binding

of omega-hydroxyceramides in the outer layer of the cornified envelope with proteins in the inner layer(17).To date more than 130 mutations have been reported in patients with ARCI . Mutations in TGM1 are the most common cause of ARCI.

The NIPAL4 gene located on chromosome 5q33 and encodes a protein which Its function is not clear. It has been hypothesized that it plays roles in lipid transportation to the outer layers of the skin and lamellar bodies formation (18). To date less than 20 mutations have been defined in NIPAL4 gene. Our group molecularly analyzed 23 LI patients from two small village and found two different NIPAL4 mutations in the patients (unpublished data). This observation and previous study shows that NIPAL4 mutation are common in Turkish ARCI patients (18).

The ALOXE3 and ALOX12B genes located on chromosome 17p13.1 both have similar structures and encodes enzymes having similar functions.These enzymes plays roles in epidermal differentiation and lamellar boy formation (8). To date 19 and 39 mutations have been defined in ALOXE3 and ALOX12B respectively. Their mutations usually cause minor forms of ARCI. However LI and CIE patients having mutations in those genes have been reported (19).

The CYP4F22 gene, which encodes a fatty acid hydroxylase cytochrome P450 member is loceted on chromosome 19p13.12 and contains 12 exons. Defects in this gene usually cause LI. To date 13 pathogenic mutations have been reported in this gene. Our group investigated CYP4F22 gene mutations in 22 LI Patients with no mutations in TGM1 and NIPAL4 genes and 5 patients were found to have 5 different CYP4F22 mutations. Mutations in CERS3, PNPLA1, SDR9C7, and SULT2B1, have been identified in few families with ARCI presenting mainly LI phenotypes

Minor forms

Self-healing collodion baby

At birth, collodion babys is covered by a shiny taught transparent membrane and usually have ectropion, eclabium, and hypoplasia of the nasal and joint cartilage. Collodion baby is the usual presentation for severe forms of ARCI. However a number of syndromic ichtyosis such as Sjögren-Larsson syndrome, trichothyodystrophy, juvenile Gaucher disease, neutral lipid storage disease, Conradi-Hünermann-Happle syndrome present as collodion baby at birth. Self-healing collodion baby (SHCB) is a minor variant of ARCI and is defined as a collodion baby with nearly complete resolution of scaling within the first 3 months of life. Most of these patients show a variable degree of anhidrosis, heat intolerance and mild signs of ichthyosis later in their life. Because of this, 'self-improving collodion ichthyosis ' term has been suggested for this disorder. Mutations in the TGM1, ALOXE3, and ALOX12B genes have been reported in patients with SHCB (8,14).

Acral self-healing collodion baby

In some neonates collodion membrane confined to the acral regions, hands and feet, and disappears after neonatal period. In most of the acral SHCBs, TGM1 mutations, causing decreased enzymatic activity, have been detected.

Bathing Suit Ichthyosis

Bathing suit ichthyosis (BSI), another minor variant of ARCI, is characterized by a typical distribution of scaling on the trunk, proximal parts of the upper limbs including axillae, the scalp and the neck. Central face distal part of extremities is usually covered normal skin. The palms of the hands and soles of the feet may have mild diffuse hyperkeratosis. But the backs of the hands and feet are not involved. Most patients reported to have BSI have South African origin (20). Almost in all BSI patients have missense TGM1 gene mutations. There is no genotype/ phenotype correlation. The same mutation of TGM1 can cause in either generalized ARCI or BSI (21)

Keratinopathic Ichthyoses
Major forms

Epidermolytic ichthyosis
Epidermolytic ichthyosis (EI) usually presents congenital ichthyosiform erythroderma with marked blistering at birth. EI, also previously known as bullous congenital ichthyosiform erythroderma (BCIE) or Epidermolytic hyperkeratosis (EHK). It requires differential diagnosis from epidrmolysis bullosa. Blistering improves in the first month of life and hyperkeratosis develops. Because of the epithelial barrier defect, neonates with EI are at risk of developing severe infection, electrolyte imbalances, and sepsis. In the later period of life recurrent blistering on the background of erythroderma, spiny scales, especially in flexural regions and axillae, palmoplantar hyperkeratosis are seen (14,22). EI is caused by heterozygous or homozygous (rare) mutations in the KRT1 and KRT10 genes. These two keratins stabilize intermediate filaments in the suprabasal keratinocytes. Mutations in these genes cause increased proliferation, leading to trichoichthyosiform lesions. Most of KRT1 and KRT10 mutations are missense mutations and usually involve highly conserved regions of the alpha-helical rod domains and the non-helical HI domain. (23) Palmoplantar keratoderma is a more common in EI patients with with KRT1 mutations than in those with KRT10 mutations. However, ther are rare exceptions with KRT10 mutations, and severe EI and PPK (24)

Superficial epidermolytic ichthyosis
Superficial epidermolytic ichthyosis (SEI) is milder and more localized form of EI. It is caused by mutations in KRT2, rather than in KRT1 or KRT10. Regional keratosis involving dorsal aspects of hands and feet, arms, axillary region and navel is seen. To date around 20 mutations causing SEI have been defined in KRT2 gene (14,22).

Minor forms
Annular epidermolytic ichthyosis
Annular epidermolytic ichthyosis, also termed cyclic ichthyosis, is characterized by the intermittent development of annular, polycyclic, erythematous, scaly plaques involving the proximal extremities and the trunk. Lesions persist for several weeks to several months. A unique mutation in KRT10 gene responsible for this disorder is identified (23).

Curth-Macklin ichthyosis
Ichthyosis Curth-Macklin is another rare autosomal dominant severe keratinopathic ichthyosis characterized by verrucous Lesions involve the large joints and the trunk. Palmoplantar Keratoderma can be seen. Histologically, vacuolated or binucleated keratinocytes in the granular and suprabasal layers are observed. cells in the granular and suprabasal layers. Dominant mutations in KRT1 cause the disease (23,24).

Autosomal recessive epidermolytic ichthyosis
A number of homozygous KRT1 and KRT 10 mutations cause epidermolytic ichthyosis as is mentioned above.

Epidermolytic nevus
Epidermolytic nevus is caused by mosaic mutations in one of the keratin genes. Cases with gonadal mosaicism resulting in recurrent affected child have been reported (25). Therefore it may be of significance in the context of genetic counseling.

Other Forms
Loricrin keratoderma (LK) is characterized by honeycomb palmoplantar keratoderma with pseudoainhum and mild ichthyosis. Ocasionally patients with LK are born as a collodion baby (26). Heterozygous mutations in the LOR gene are responsible for LK. The LOR gene encodes a protein which is a major component of the cornified cell envelope found in terminally differentiated epidermal keratinocytes. It contributes to the protective barrier function of the stratum corneum (14)

Erythrokeratodermia variabilis (EKV) is a group of inherited disorders characterized by hyperkeratotic plaques and well-demarcated erythematous lesions. Usually heterozygous dominant mutations in the genes GJB3, GJB4 and GJA1 cause EKV. These proteins are gap junction proteins classified in transmembrane proteins that form intercellular channels. All EKV mutations defined so far are amino acid substitution mutations, resulting in impaired epidermal differentiation (27)

Peeling skin syndrome (PSS) is a rare form of ichthyosis and classified into two groups: a non-inflammatory type (type A), and an inflammatory type (type B). PSS is caused by homozygous mutations in te CDSN gene which codes corneodesmosin, an extracellular adhesion glycoprotein located in desmosomes and corneodesmosomes. In patients with PSS have superficial, painless, continual, or seasonal cutaneous exfoliation. Disruption in epidermal barrier function causes pruritus and a susceptibility to skin infections (14,28)

Congenital reticular ichthyosiform erythroderma (CRIE) which is also known as 'Ichthyosis with confetti' and 'ichthyosis variegata' is an autosomal dominant congenital ichthyosis. It is caused by dominant negative mutations in the KRT10 and KRT1 genes. CRIE present severe congenital ichthyosiform erythroderma or collodion baby at birth. It is a very rare skin disorder, with a prevalence of <1/1,000,000. To date around 50 cases have been reported. Patients develop confetti-like spots of healthy skin which is the characteristic feature of the disease. Spots start appearing during childhood and gradually increase in number.
The underlying mechanism of those spots is the somatik recombination resulting in genetic correction of pathologic molecular defect. Patients with CRIE can also have dysmorphological findings such as ear deformities, mammillae hypoplasia, palmoplantar keratoderma, hypertrichosis and ectropion (22, 29).

Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK) syndrome is a rare autosomal recessive skin disorder characterized by palmoplantar keratoderma with sclerodactyly, linear hyperkeratotic plaques located in flexural areas, circular constrictions around fingers and congenital ichthyosis (22). Patients have no developmental or growth delay and no other anomalies. It is resulted from a single nucleotide deletion of the 5' untranslated region of the POMP gene (22.30). No other reported mutation in the POMP gene has been reported. It has been reported that reduced levels of proteasome maturation protein results in proteasome insufficiency in keratinocytes in KLICK syndrome (22)

SYNDROMIC ICHTYOSIS
Syndromic X-linked Ichthyosis
Recessive X-linked ichthyosis (syndromic)
Common form of XLI is somtimes associated with extracutaneous abnormalities such as corneal opacities, cryptorchidism, testicular germ cell cancer and psychiatric disorders. This clinical features result from contagious gen deletioss associated with STS gene deletions (5).

Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome
This very rare **X-linked disorder is caused by** the MBTPS **gene defects. The MBTPS gene encodes a** membrane-bound transcription factor protease,site 2 protein. Main features of the syndrome are Ichthyosis follicularis, alopecia, and photophobia. Additionally patients may have seizures, mental retardation, short stature, skeletal abnormalities and susceptibility toinfections (31)
Conradi-Hünermann-Happle syndrome(chondrodysplasia punctata type 2)
It is result from mutations in the EBP gene which encodes is an enzyme involved in the process of cholesterol synthesis. Cardinal findings of patients are ichthyosis, punctuate cartilage aplasia, cataract and a short stature (31,32)).

Syndromic Autosomal Ichthyosis

This gropu of disorders are classified according to the main clinical feature.

Skin disorders

Netherton syndrome

Netherton syndrome is a rare, autosomal recessive disorder and characterized by : erythroderma at birth, ichthyosi, bamboo hair and predisposition to atopy and infections. SPİNK5 gene mutations are responsible for Neterton syndrome. SPINK5 encodes a serine protease inhibitor,lympho-epithelial Kazal-type-related inhibitor (LEKTI) which is involved in dermal cornification and hair development. Netherton patients also have T cell immune deficiency and hyper IgE levels (31)

Ichthyosis-hypotrichosis syndrome

One of the very rare syndromic ichtiyosis. Patients show severe hypotrichosis, lacking eyebrows and eyelashes at birth onset. It is transmitted autosomal recessively and caused by missense mutations in the ST14 gene encoding the recently identified protease, matriptase. It has been reported that this enzyme plays a role in epidermal desquamation (31).

Ichthyosis-sclerosing cholangitis syndrome

Neonatal ichthyosis-sclerosing cholangitis (NISCH syndrome) is extremely rare ichthyosis syndrome caused by mutations in the CLDN1 gene encoding the claudin-1 protein, which is located at tight junctions. It is characterized by scalp hypotrichosis, scarring alopecia, ichthyosis and sclerosing cholangitis (33)

Trichothiodystrophy

This syndrome result from defect in a number of DNA repair genes: ERCC2 (XPD), ERCC3 (XPB) and GTF2H5 (TTDA). These genes are involved in nucleotide excision repair and transcription. Phenotypic features of patients are collodion membrane at birth, chthyosis,
microcephaly, fragile hair, short nose, big ears, teeth anomalies, naildysplasia, osseous abnormalities, hypogonadism, photosensitivity and mental retardation (34)

Neurologic disorders

Sjögren-Larsson syndrome

Sjögren-Larsson syndrome (SLS) is an autosomal recessive disorder characterized by congenital ichthyosis, spastic paralysis of the lower exremities and severe mental retardation. Ichthyosis is more prominent in the neck, abdomen and on the flexion side of the limbs. Mutations in the ALDH3A2 gene which encode the fatty aldehyde dehydrogenase responsible for the metabolism of long-chain aliphatic aldehydes and alcohols cause SLS. Accumulation of aldehydes in various organs results in characteristic feature (32,35)

Refsum syndrome

Refsum syndrome (RS) is an autosomal recessively inherited congenital metabolic disease. In RS, symptoms usually begin childhood to adolescence and show progression, but remission and exacerbation can be seen. Typical features of RS in adults are retinitis pigmentosa, sensory-motor polyneuropathy, sensorineural hearing loss, ataxia, anosmia, ichthyosis and cardiomyopathy. Homozygous mutations in the PHYH gene and PEX7 gene cause RS. The PHYH gene encodes phytanoyl-CoA hydroxylase (PHYH), which degrades phytanic acid in the peroxisomes. the PEX7 geneencodes the receptor (PTS2), which mediates PHYH trafficking to peroxisomes. In RS patients PHYH mutations are more common than PEX7 mutations (32,36).

MEDNIK syndrome

MEDNIK syndrome-acronym for mental retardation, enteropathy, deafness, neuropathy, ichthyosis, keratodermia-is caused by AP1S1 gene homozygous mutations. The AP1S1 gene encodes a protein that plays an important role in clathrin coat assembly and mediates trafficking between trans-Golgi network, endosomes and the plasma membrane. Patients with MEDNİK syndrome shows hypocupremia, hypoceruloplasminemia and liver copper accumulation, along with intrahepatic cholestasis (37)

Fatal disease course

Gaucher disease, type 2

Gaucher disease (GD) is the most common lysosomal storage disease resulting from a deficiency of the lysosomal enzyme glucocerebrosidase. It has been classified into 3 type: 1,2,3. Type 2, is arare and the most severe type of GD. Symptoms begin pre- or perinatally or in the first few months of life and characterized by rapidly progressing neurological degeneration, visceral signs. At birth, skin is erythematous and shiny, and involves all over the body. Prenatally Hydrops fetalis may develop due to type 2 GD. It is generally associated with severe mutations in the GBA gene encoding glucocerebrosidase enzyme. Tpe 2 GD is often results from homozygosity for a recombinant allele or severe mutations in the both alleles (38)

Multiple sulfatase deficiency

Multiple sulfatase deficiency (MSD) is a rare autosomal recessive disorder resulted from homozygous or compound heterozygous mutation in the sulfatase-modifying factor-1 (SUMF1) gene. In patients with MSD, at least seven sulfatases are simultaneously affected. The symptoms are progressive and similar to three different disorder groups: metachromatic leukodystrophy, mucopolysaccharidosis and ichthyosis. Patients become unable to sit at the age of 2-3, speech is delayed.Cardinal features include coarse facies, deafness, ichthyosis, skeletal abnormalities and neurological damage. The disease is fatal. Most patients die at 10–15 years of age

CEDNIK syndrome

CEDNIK is acronym of CErebral Dysgenesis, Neuropathy, Ichthyosis, and palmoplantar Keratoderma. Clinical features includes severe developmental retardation, microcephaly, facial dysmorphism and ichthyosis. It results from mutations in the SNAP29 gene which encodes a SNARE protein involved in vesicle fusion. The syndrome has been reported to be fatal between the ages of 5 and 12 years (39)

ARC syndrome

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive multisystem disorder. The syndrome is fatal and caused by mutations in the VPS33B or VIPAR gene. Cardinal features of ARC includes joint contractures, renal tubular dysfunction, and cholestasis. Additionally ARC syndrome patients show ichthyosis, central nervous system involvement, failure to thrive, and platelet anomalies (40)

Other associated signs

KID syndrome

Keratitis–ichthyosis–deafness (KID) syndrome is inherited autosomal dominant fashion and characterized by keratitis with corneal neovascularization, cutaneous manifestations including palmoplantar hyperkeratosis, nail dystrophy, ichthyosiform scaling, and bilateral sensorineural hearing loss. Progressive alopecia of the scalp is noted. These features appear until adolescent period. KID syndrome is caused by heterozygous mutation in the connexin-26 gene, GJB2.

Chanarin-Dorfman syndrome

Chanarin- Dorfman syndrome is a very rare autosomal recessive syndrome characterized by lipid droplet in leukocytes, congenital ichthyosiform erythroderma, cataract, deafness, liver dysfunction, muscular weakness, renal dysfunction, mental retardation and a short stature. Patients have high triglyceride levels. There is severe pruritus. Chanarin- Dorfman syndrome is caused by homozygous mutation in the comparative gene identification-58 (CGI58) gene (32)

Ichthyosis prematurity syndrome

Ichthyosis prematurity syndrome (IPS) is a rare form of autosomal recessive syndromic congenital ichthyosis. Its features are prematurity, neonatal respiratory asphyxia, eosinophilia and a thick, caseous and desquamating epidermis. Perinatal mortality is increased. It is caused by mutations in SLC27A4 which encodes a fatty acid transport protein 4 (FATP4) that affect keratinocyte differentiation and skin barrier formation (42). Affected patients show a spontaneous improvement in the health with time. Skin findings continue as mild follicular hyperkeratosis with atopy (42).

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Epidermolizis Bülloza
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Summary
Epidermolysis Bullosa (EB) refers to a group of genodermatosis characterized by bullous lesions that occur as a result of varying friction or trauma of the skin or spontaneously. EB are divided into four major forms based on the level of skin cleavage. These are EB simplex, Junctional EB, Dystrophic EB and Kindler syndrome. EB simplex is most common and more benign form in this group. It is characterized by bullous lesions that develop in traumatic area. Localized EBS, as a most common form, is frequently seen on hands and feets. Bullous lesions in EBS heal in a short time without scarring due to intraepidermal cleavage. In Junctional EB, the skin cleavage locate in lamina lucida of the dermo-epidermal junction and bullous lesions leads to atrophic scars on the skin and mutilation on the knuckles. In dystrophic EB, cleavage occurs below the basement membrane Atrophic scars and milia can observed on the patient's skin. Diagnosis could be made by immunofluorescence mapping and electron microscopic analysis from skin biopsy samples.
The treatment of EB consist of many options but there is no cure. Palliative treatment such as protection from friction or overheating, avoidance of trauma, control of secondary infections are main concerns. Nutritional supplemantation, itching and pain control are essential preventive points for EB patients. Treatment of common complications such as anemia, esophageal strictures, osteoporosis, cardiomyopathy, delayed puberty and cutaneous squamous cell carcinomas are required special care by special care team. The best appropriate care needs well-educated medical team. This team should consists of EB trained dermatologist, plastic surgeon, pediatrician, pediatric surgeon, psychiatrist, nephrologist, endocrinologist, gastroenterologist, genetic specialist, pain specialist, dietician, EB trained nurses and social workers. Clinicians need to know that different types of EB show different features of associated co-morbidities. Recently, for most severe subtypes are RDEB and JEB, some experimental approaches such as allogeneic cellular therapy (allogeneic fibroblasts, mesenchymal stromal cells and gene-corrected autologous epidermal stem cells), gene therapy, and protein therapy (using collagen VII protein therapy in preclinical models) could be use.

Genetics of Epidermolysis Bullosa and Genetic Counselling
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Epidermolysis bullosa (EB) encompasses genodermatoses caused by pathogenic variants in genes encoding proteins expressed at the derma-epidermal junction zone, most of them having structural functions (e.g. integrins, laminins, collagens). Four main types – simplex, junctional, dystrophic and Kindler EB – and more than 30 EB subtypes are defined by clinical and molecular features. In addition to the affected genes, the allelic variants determine the spectrum of clinical phenotypes. Generally, variants leading to premature termination codons (PTC) and loss of protein expression or function associate with severe phenotypes while different levels of protein expression and function result in intermediate or mild phenotypes. Modifiers such as genetic variations in the same gene or in other genes, epigenetics or the environment play rather minor roles that have been demonstrated in single cases or families. EB simplex is the most heterogeneous type of EB. Mutations in seven different genes cause both non-syndromic and syndromic EB subtypes, yet mutations in the genes for keratin 5 and 14 account for 85-90% of the EB simplex cases. Since the discovery in 2016, more than 40 cases of EB simplex with KLHL24 mutation have been published. All are caused by mutations in the translation initiation codon of the gene. The phenotype is very characteristic comprising congenital skin defects, burn-like scars, hypopigmentations, nail dystrophies and hair loss. Patients may develop dilated cardiomyopathy in young adulthood. Besides these classical types of EB, other disorders with skin fragility comprise peeling skin, erosive disorders, hyperkeratotic disorders and connective tissue disorders with skin fragility. Because of the common manifestation of skin fragility, these "EB-related" disorders should be considered in the differential diagnosis.

Recent Advances in Managing Epidermolysis Bullosa: Cukurova University Experience
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Epidermolysis bullosa (EB) is a group of hereditary skin blistering diseases which is clinically and genetically heterogeneous, but all EB forms are associated with mechanically induced skin blistering and fragility. The most EB types are caused of well-known gene mutations and classified into four main types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (KS). Whether the etio-pathogenesis is well-known the differences in their genetic, biological or clinical characteristics make it difficult to cure. Traditionally, EB treatment strategies have been symptomatic, but increasing understanding of disease is facilitating development of novel evidence-based therapy approaches. Thus, in this case-series, we present our experience of different treatment modalities of genetically and clinically diagnosed EB patients in our genetic diseases diagnosis and treatment center.
While there are several therapies being tested at preclinical level and in clinical trials, considerable progress has been made.

1- Six children who had recessive dystrophic epidermolysis bullosa were treated with immunomyeloablative chemotherapy and allogeneic stem-cell transplantation. We assessed C7 expression by immunofluorescence staining and we measured chimerism by means of competitive polymerase-chain-reaction assay, and documented blister formation and wound healing with the use of digital photography.
2- One patient with recessive dystrophic EB had been grafted genetically modified skin tissue whom the research team took skin biopsies and applied gene therapy. During the process a harmless retrovirus had been used to deliver a corrected form of the type VII collagen gene into the keratinocytes. The modified tissue was then grafted onto the patient to help speed the healing of wounds.
3- Eight patients that were diagnosed recessive dystrophic EB had topical treatment within several clinical trials including an anti-inflammatory compound and an mTOR inhibitor.

Here, we review current treatment modalities available together within our patient group. Future research investigations will provide better understanding of all EB types and identify the most suitable therapeutic targets. However it is unlikely that there will be a one kind of treatment strategy for each major EB type. Rather, the treatments will be based on patients mutations, disease mechanisms, and phenotypic characteristics.

Aging From a Dermatologist's Perspective
Berna ŞANLI
Dermatology, İzmir

Skin, fat, muscle and bone are structural components of facial aging. With aging, the bones show changes due to atrophy, expansion and resorption. Due to hypertrophy in superficial fat compartments and atrophy in deep fat compartments, the shape, contour and projections of the skin change. Convexities disappear as a result of changes in the muscles, and the tone of the muscles increases. Mature collagen loss, increased matrix metalloproteinase (MMP) expression, impaired TGF-□ signal and changes in glycosaminoglycans. Type III / Type I collagen ratio increases. In photoaging, hyperplasia occurs in elastic tissue. As a result, there is an increase in dryness, roughness, wrinkles, paleness, hypo-hyperpigmentation, looseness and sagging, fragility, easy bruising, benign neoplasms and UV-related cancer clinically.

Genetics of Aging
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Genetics of aging is a complex process involving genetic and environmental factors that affect most physiological pathways. Many aging theories have been proposed, and important aging pathways have been discovered. These theories, which fall into two main categories: programmed and error theories, have been proposed to explain the process of aging. The programmed theory has three sub-categories: Programmed Longevity, Endocrine Theory and Immunological Theory. The damage or error theory includes; Wear and tear theory, Rate of living theory, Cross-linking theory, Free radicals theory and Somatic DNA damage theory.
These theories may interact with each other in a complex way. Model organisms have had a crucial role in this process because of their short lifespan, cheap maintenance, and manipulation possibilities. These studies identified many genes and pathways that regulate aging, several of which are conserved in other species, including mammals. Longevity-regulatory pathways including insulin/IGF-1 (insulin-like growth factor 1) signaling, TOR (target of rapamycin) signaling, autophagy, mitochondrial respiration, and AMPK (AMP-activated protein kinase) pathways may influence human longevity.
Also Centenarians are the extreme phenotype of human longevity and their genomes undoubtedly contain clues about genes and pathways that are involved in longevity. Candidate gene studies have identified variants at APOE and FOXO3A associated with longevity.
Furthermore, genetic and epigenetic mechanisms are being identified that have a positive effect on longevity. The gerontogenes are classified as lifespan regulators, mediators, effectors, housekeeping genes, genes involved in mitochondrial function, and genes regulating cellular senescence and apoptosis.

Stem Cells in Dermatology
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Recent insights into stem cell (SC) biology promise the regeneration of damaged organs. Stem cells (SCs) have the capability of self-renewal and differentiation into a wide range of cell types with various potential clinical and therapeutic applications. SCs are providing hope for many diseases that are currently in need of effective therapeutic methods, including neurodegenerative disorders like; stroke, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and as well as muscular dystrophy disorders like Duchene Muscular Dystrophy and Facio-scapulo-humeral Muscular Dystrophy. For this aim, numerous pre-clinical studies have been achieved and\or in progress on different types of stem cells including, induced pluripotent stem cell (IPS), embryonic stem cell (ESC) and neural stem cells. But there are some complications on the clinical utilization of these cells, due to the reason of ethical issues and especially because of the potential of formation of teratomas via IPSs and ESCs. For this reason, as we glance to the clinical trials ongoing nowadays, we see that mesenchymal stem cells (MSCs) are studied intensely on clinical applications. MSCs attracted particular interest because of their ease of isolation, characterization, apparent multipotency and pleiotropic effects. MSCs are capable of self-renewal and differentiation into specialized cell types and thus have the potential to promote organogenesis, tissue regeneration, maintenance and repair. With the main goal of regeneration or sustained genetic correction of damaged tissue, advanced tissue-engineering techniques are especially applicable for many dermatological diseases including wound healing, genodermatoses (like the severe blistering disorder epidermolysis bullosa) and chronic (auto-)inflammatory diseases. The current and future perspectives of stem cell therapy in dermatology will be introduced in this presentation.

Photosensitivity Syndromes
Demet KARTAL
Erciyes University Medical School

Photosensitivity in humans can result from defects in repair of light-induced DNA lesions, from photoactivation of chemicals (including certain medications) with sunlight to produce toxic mediators, and by immune reactions to sunlight exposures. Deficiencies in DNA repair and the processing of damaged DNA during replication and transcription may result in mutations and genomic instability.
Hereditary photosensitivity syndromes are characterized by an increased sensitivity to sunlight caused by a genetic defect. Most are autosomal recessive and manifest during infancy. Deficiencies in DNA repair and the processing of damaged DNA during replication and transcription may result in mutations and genomic instability. These disorders are linked in some cases like Xeroderma pigmentosum, Bloom syndrome, and Rothmund Thomson with early development of internal and cutaneous malignancies. The other group of these syndromes like cockayne syndrome, cerebro- oculo-facial-skeletal syndrome, ultraviolet-sensitive syndrome, and trichothiodystrophy may also have other extracutaneous involvement affecting the neurologic system and growth and development. Early determination and diagnosis is crucial to prevent actinic injuries that can lead to cutaneous malignancies. In this presentation, clinical findings and current treatments of hereditary photosensitive syndromes will be discussed.

V-Sensitivity Syndromes From a Clinical Genetic Point of View
Altunoglu U, Theil AF, Kalaycı T, Uyguner ZO, Kayserili H
Abstract

The UV-sensitivity syndromes are rare, inherited diseases with marked clinical and genetic heterogeneity, causing pigmentary, inflammatory and neoplastic skin changes. Extradermal findings may include growth deficiency, neurological defects, benign or malignant hematological changes, immunological problems, and premature aging. Most of these diseases can be attributed to impaired DNA repair, with defects in DNA helicases, DNA damage repair and nucleotide excision repair mechanisms. Defective DNA repair may greatly increase risk of sun-induced skin cancers, as in the example of Xeroderma pigmentosum. The risk of non-skin malignancies ranges from very high in individuals with Rothmund-Thomson and Bloom syndromes, to none in Cockayne syndrome and Trichotiodystrophy patients.
The photosensitive changes on the face are usually the first to be recognized, but may be initially subtle. This may complicate the clinical diagnosis, and delay the screening and detection of associated medical problems. While clinical evaluation of phenotypic features are usually enough for diagnosis, identification of the causative mutations is needed for prenatal testing and thorough counseling. Molecular and functional research on this rare group of syndromes has lead to identification of novel genes, paving the road for genetic-based classification and targeted therapeutic options.
A genetic overview on photosensitivity syndromes and counseling issues will be presented along with clinical examples.

Photosensitivity Beyond the Skin

Sabatella M, Theil AF, Ribeiro-Silva C, Slyskova J, Thijssen K, Voskamp C, Brandt RMC, Barnhoorn S, Vermeij WP, Hoeijmakers JHJ, Lans H, Vermeulen W

The severe clinical consequences associated with inborn defects in NER clearly emphasises the vital importance of this DNA repair system. Persistent DNA damage will severely hinder essential DNA processes replication and gene-transcription, causing cell malfunction or even cell death. Xeroderma pigmentosum (XP) is a very rare inherited disease that is characterized by extreme sensitivity to sunlight (sunburn), abnormal skin pigmentation (pigment freckles or lentigines) and increased risk for skin cancer, especially in sun-exposed areas. XP patients have an inborn defect in one of the seven XP genes (XPA to XPG), all encoding for proteins involved in the Nucleotide Excision Repair (NER) pathway. Skin cells from XP patients have a reduced NER capacity and are therefore unable to repair UV-light induced DNA damage. Some patients from complementation groups XP-B, XP-D, XP-G and XP-F combine dermatological features of XP with other severe symptoms commonly associated with Cockayne syndrome (CS), including developmental problems, progressive loss of neuronal function (hearing, vision and gait) and extreme fast ageing, representing the rare Xeroderma pigmentosum-Cockayne syndrome (XPCS) complex. Strikingly, most of these serious clinical problems arise from complications in tissues (mainly neuronal) that are not exposed to sunlight and – importantly – are mainly composed of post-mitotic or non-dividing cells.

We analysed the functional impact on NER capacity of individual pathogenic XPF (officially called ERCC4) alleles, causative for either XP or XPCS-complex. We found that XP-causing XPF has reduced interaction with DNA damage, whereas XPCS-XPF show persistence of XPF and other NER factors at DNA damage, suggesting that this could be a determining factor contributing to the development of additional developmental and/or neurodegenerative features in XP patients.

Premature Aging Syndromes: Clinical Features and Current Treatment Options

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Early aging syndromes are rare (incidence 1: 50000), clinically and genetically heterogeneous, complex, overlapping group of monogenic diseases, with more than 100 different syndromes so far described in the literature. Premature signs of aging are detected in more than one organ or tissue and some organs are relatively preserved; therefore, they are defined as Segmental Progeroid Syndromes (SPS). Clinical findings and molecular changes overlap (progerin deposition, changes in the nucleus membrane, genomic instability) with the «normal aging» process.

The genetic basis of Hutchinson-Gilford Progeria Syndrome (HGPS) was described in 2003. Since then, many studies have been conducted to understand the pathophysiology of SPSs, targeted therapies have been developed and a better understanding of physiological aging is provided.

SPSs can be classified as congenital, infantile, juvenile-adult forms, depending on the age of onset of manifestations. Since they are clinically and genetically heterogeneous, after clinical suspicion, the first diagnostic step should be NGS techniques. With early diagnosis, patients would be able to access new treatment options at an early age and patient-specific follow-up and screening programs could be established.

I. Congenital SPS

- Wiedemann – Rautenstrauch Syndrome
- PYCR1 associated cutis laxa
- Restrictive Dermopathy
- Bloom syndrome, Rothmund – Thomson syndrome, Dyskeratosis congenita,….

II. Infantile SPS

- Hutchinson-Gilford Progeria Syndrome
- Mandibular hypoplasia, deafness, progeria, lipodystrophy syndrome (MDPL)
- Néstor-Guillermo Progeria Syndrome
- Mandibuloacral dysplasia
- Fanconi anemia, Xeroderma pigmentosum, Cockayne syndrome, Ataxia telangiectasia, Trichotiodystrophy,…

III. Juvenile-adult SPS

- Werner Syndrome
- Atypical Werner Syndrome
- Myotonic dystrophy type 1

Common clinical findings of SPS in the neonatal period can be summarized as growth retardation, sparse hair, wrinkled-thin skin, prominent scalp veins. Over the time, scleroderma-like changes, lipodystrophy/lipoatrophy, osteoporosis/osteopenia, graying of hair, alopecia, hypo and hyperpigmentation, hearing loss, cataracts, atherosclerosis and coronary artery disease, type 2 diabetes and malignancy may develop. These changes are similar to changes with physiological aging, but differently, mandibular hypoplasia and growth retardation are found in SPSs. In congenital and infantile forms, micrognathia, prominent eyes, beaked nose, and typical triangular facial appearance are observed.

Hutchinson-Gilford Progeria Syndrome (HGPS) is the prototype of infantile-onset SPSs and whereas Werner Syndrome (WS) is the prototype of juvenile/adult-onset SPSs:

Hutchinson-Gilford Progeria Syndrome (HGPS)

Following normal gestation and birth, the first clinical findings manifest around the 6th month of life. The genetic cause is a de novo heterozygous silent point mutation in the LMNA (c.1824C> T; G608 G) gene.The accumulation of progerin, a toxic, mutant form of lamin A, which encodes nuclear membrane proteins, is responsible for the pathophysiology of the disease.

The earliest and the most common clinical finding is the scleroderma like skin changes. It causes a dimpled appearance due to subcutaneous adipose tissue herniation from the fibrotic areas. It is commonly observed on the abdomen and lower extremities, starting from the 2nd month of life. The veins become prominent as a result of lipoatrophy/lipodystrophy. Hypo and hyperpigmentation develop around the sclerodermoid changes. Clinical findings, including growth retardation and typical triangular face, are diagnostic around 12-18 months of life. Alopecia starts from the temporal region in 2nd-3rd months of life. Then it affects the occipital area, while the vertex hair is preserved for a longer period. At the 3rd year of life, total alopecia is observed in the scalp, eyebrows and eyelashes. Over time, bone defects, decreased joint movements, severe atherosclerosis develop. Patients die around 15 years of age due to atherosclerosis and complications of the cardiovascular system.

Many HGPS-like syndromes caused by different mutations develop as a result of the toxic effects of the progerin.

Werner Syndrome (WS)

The disease, also known as Adult Progeria, occurs due to the WRN gene mutation encoding the DNA helicase RecQ family, a DNA repair protein. The normal growth spurt seen early in puberty is not observed (relative short stature, micrognathia). Progressive progeroid findings start to manifest from the second decade of life. Hair whitening, sclerodermoid skin changes, regional atrophy in subcutaneous tissue, high pitched voice, hyperkeratosis and ulcers (around the malleols) on bony areas, osteoporosis (long bones), calcification in the Achilles tendon, bilateral cataracts, type 2 diabetes, hypogonadism, atherosclerosis of the coronary arteries develop. There is a high risk of myocardial infarction and malignancy (meningioma, sarcoma, melanoma, thyroid). Patients die at an average age of 54, due to cardiovascular diseases or malignancy.

SPS Treatment:
The aim of the treatment of SPSs is to prevent the development of symptoms, signs and complications, to improve the quality of life and to prolong the life. Patients should be evaluated with an interdisciplinary approach; cardiological, dermatological, orthopedic, ophthalmological, endocrinological, oncological follow-up should be performed. Routine vaccination should be done, routine diet and multivitamins in normal doses should be given. Low-dose aspirin (risk of MI) and if necessary nitroglycerin is recommended for the cardiovascular system. Physiotherapy should be started early for bone and joint dystrophies.

In HGPS and other HGPS-like syndromes, progerin has a dose-dependent toxic effect, so the treatment approach should be aimed at reducing progerin levels starting from an early age. Progerin is responsible for nuclear deformity (diameter increase, intussusception), thickening of nuclear lamina, DNA damage, genomic instability, telomere shortening, loss of heterochromatin, impaired nucleocytoplasmic transport, premature aging and inflammatory response.

Vitamin D provides improvement in HGPS cell phenotypes with an increase in Vit D receptor signaling. In the presence of all-trans retinoic acid (ATRA), LMNA gene expression is reduced; With ATRA therapy, the expression of progerin is reduced in HGPS fibroblasts. N-acetyltransferase 10 (NAT10) small molecule inhibitor Remodelin, improves nuclear morphology and decreases the DNA damage. N-acetyl cysteine (decreases DNA damage due to increased ROS), methylene blue (mitochondria antioxidant), resveratrol (increase in SIRT1 deacetylase activity) are the other supportive agents used in treatment.

Lonafarnib (farnesyl transferase inhibitor), which was first developed as an anti-cancer agent, prevents the conversion of prelamine A to progerin. An increase of 1.6 years in life time and a decrease in mortality were observed in clinical studies for HGPS. Inhibition of mTOR pathway with rapamycin and everolimus, increases progerin turnover and autophagy in HGPS cells and improves progerin-associated nuclear shape anomalies and proliferation defects. Phase I and II studies of everolimus and lonafarnib, and rapamycin and lorafarnib are currently ongoing.

Sulforafan and MG132, similar to everilumus, increases the clearance of the progerin through autophagy. Statins (pravastatin) and aminobiphosphonates (zoledronate) are inhibitors of farsenylation and geranilgeranilation. They have improved the phenotype in invitro progeria mouse models, and a clinical study for HGPS is currently ongoing.
ASO (antisense oligonucleotide) reduces the production of lamin A / progerin. Smurf2 (E3 ubiquitin ligase) binds directly to lamin A/progerin, reducing its expression, also reduces nuclear deformities. Small molecule inhibitors of p38 MAPK pathway are found to be effective in WS fibroblasts.

Ectodermal Dysplasias and Treatment Approaches from a Dermatologist's Perspective

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Abstract
Ectodermal dysplasias (EDs) are an inherited group of diseases characterized by developmental defects of the four major ectodermal structures that includes hair, teeth, nails and sweat glands. Other ectodermal structures, such as breast tissue, thyroid, thymus, anterior pituitary, adrenal medulla, central and peripheral nervous system, outer ear, melanocytes, cornea, conjunctiva, lacrimal glands and lacrimal ductus may be involved. Various clinical features such as ankyloblepharon, cleft palate and/or lip, split hand and/or foot malformation, syndactyly, mammary gland and/or nipple hypoplasia or aplasia, conductive hearing loss are observed. Additionally, non-ectoderm-derived structural defects may be present. EDs are grouped according to the involvement of at least two of the four major ectodermal structures or at least one of the major and one of other ectoderm-derived structure involvement. Up to date, 200 disease forms are described with 80 having an established molecular genetic data. The most common form is hypohidrotic ED (HED). HED is typically charactirized by hypotrichosis and hypohidrosis with the involvement of teeth that is presented as delay of tooth development in infancy and as hypodontia and conical shaped teeth later in life. Dry skin is a common finding in patients with ED. Alopecia is variable and hair changes are permanent. Patients often complain of heat intolerance in varying degrees. In infancy, hypohidrosis or anhidrosis may lead to febrile convulsions during recurrent idiopatic fever spikes. Superficial erosions on the scalp is a typical feature of Ankiloblefaron filliforme adnatum-Ectodermal dysplasia-Cleft palate/lip syndrome. Follow-up and treatment of EDs require a multidisciplinary approach.
Key words: Ectodermal Dysplasia, Hypohidrosis, Hypotrichosis, **Nail** Abnormalities, Anodontia

Ectodermal dysplasias: Description, History and Classification
Ectodermal dysplasias (EDs) are an inherited group of diseases characterized by developmental defects of major ectodermal structures that includes hair, teeth, nails and sweat glands. Ectodermal dysplasia was first described by Danz in 1792 in two patients with hypotrichosis and hipodontia. Weech specified 3 essential features of EDs: developmental nature, ectodermal origin and hereditary characteristics. Other ectodermal structures, such as breast tissue, thyroid, thymus, anterior pituitary, adrenal medulla, central and peripheral nervous system, outer ear, melanocytes, cornea, conjunctiva, lacrimal glands and lacrimal ductus may be involved in varying degrees. Various clinical features such as ankyloblepharon, cleft palate and/or lip, split hand and/or foot malformation, syndactyly, mammary gland and/or nipple hypoplasia or aplasia, conductive hearing loss may be observed. Additionally, non-ectoderm-derived structural defects may also be present (1). EDs are grouped according to the involvement of at least two of the hair, tooth, nail and sweat gland structures, or at least one of the four major structures and one of other ectoderm-derived structure involvement. The classification of EDs began with the studies of Freire-Maia in early 1970s. In these studies, two groups, A and B, are described. In group A, there are 11 subgroups that present with the involvement of four major epidermal structures in diverse combinations. In group B, there are 4 subgroups that present with involvement of other ectodermal structure in addition to the four major structures (2). Priolo and Laganá, included molecular genetic data with corresponding clinical findings in 2001 (3). Lamartine proposed a classification system that was based on involved genes and pathophysiological processes: cell-cell communication and signaling, cell adhesion, transcription regulation and development (4). In 2004, Itin et al. overviewed this classification and other researches followed them as the molecular genetic data flourished (5-8). Up to date, 200 disease forms are described with 80 having an established molecular genetic data (9). Recently, EDs were organised based on EDA, WNT and TP63 molecular pathways and under an additional structure group with the studies of an international advisory working group (10). The chronological schema of classification studies for EDs is presented in figure 1.

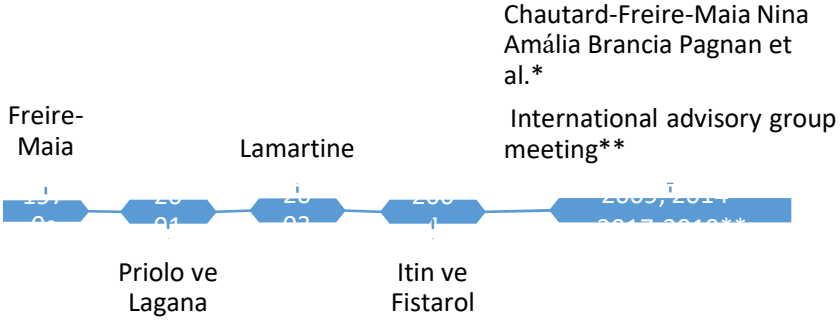


Figure 1: Chronological schema of classification studies for EDs

General Clinical Features and Treatment Approaches

Hairs are affected by 87.1%, teeth 78.5%, nails 73% and sweat glands 37.4% (8). Scalp hair is usually sparse, brittle, coarse, wiry and light-colored. Morphological alterations in the hair shaft are observed in some forms of EDs. Eyebrows and eyelashes may be sparse and body hair may also be affected. In these patients, alopecia is variable and hair changes are permanent. Besides the use of protein-coating shampoos and conditioners, the use of wigs can also be suggested to improve self-image,if needed. Hypodontia and anodontia are common dental features. Both permanent and primary teeth are affected. In childhood and adolescence, malformed anterior teeth usually have a cone and peg shape appearence. In some disease forms, early caries and tooth loss are observed due to developmental enamel defects. Patients should be referred to the dentist for dental examination in early childhood and for prostodontia in the following years. Nail findings such as dystrophy, hyponychia, anonychia, discoloration, hyperconvexity and micronychia of the nail plate are seen in variable degrees in EDs. Sweat glands may be normal or reduced in number, and occasionally, are not observed in histopathological sections. Patients often, complain of heat intolerance in varying degrees. Extremely hot environments and excessive physical activities should be avoided, as well as hot drinks and food. In hot and warm climates, cooling vests, wrist and neck wraps, hats or bandanas may be used. EDs should be investigated in the presence of unexplained high fever in an infant. In infancy, hypohidrosis or anhidrosis may lead to febrile convulsions during recurrent idiopatic fever spikes. Dry skin is a common finding in patients with ED. Skin desquamation may be present in neonatal period and skin erosions may be observed. Superficial erosions on the scalp is a typical feature of ankiloblefaron filliforme adnatum-Ectodermal dysplasia-Cleft palate/lip (AEC) syndrome in neonatal period. It is observed in almost all patients. It may cause cicatricial alopecia and hypotricosis. Erosions may also occur on the head and neck, palms, soles and skin folds. Erosions tend to be recurrent and resistant to treatment. Secondary infections may develop. Congenital erythroderma in the accompany of skin erosions is observed in 70-90% of infants with AEC syndrome. Collodion membrane may be present giving the red shiny appearance to the skin. Fluid-electrolyte balance should be monitored carefully and infection control should be provided. Freckling on sun-exposed skin is a typical feature of acro-dermo-ungual-lacrimal-tooth (ADULT) syndrome. It progresses with age and sun exposure. Patients are advised to avoid excessive sunlight and use of sunscreens are recommended. Follow-up and treatment of EDs require a multidisciplinary approach (1,5,11).

Hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)

The most common form of EDs. Hypohidrotic ED (HED) is typically charactirized by hypotrichosis and hypohidrosis with the involvement of teeth that is presented as delay of dentition in infancy and as hypodontia and conical shaped teeth later in life. HED usually shows X-linked recessive inheritance pattern caused by mutations in the EDA gene. X-linked recessive HED presents with dry and peeling skin and unexplained high fevers in infancy. Periorbital darkening and absent epidermal ridges are noted (1,2,12). Absent epidermal ridges may also be seen in dry or atrophic skin and in many other conditions (13). Other secretory glands may be affected in HED and complications such as rhinoconjunctivitis, asthma, pneumonia, otitis media and sinusitis may ocur (14). Autosomal recessive and dominant forms of HEDs and female carriers of X-linked HED have milder disease with sparse hair, patchy hypohidrosis and few, small or missing teeth. EDAR, EDARADD and WNT10A gene mutations are detected in autosomal recessive and dominant forms of HED and IKBKG gene mutations are reported in HED with immune deficiency (1,2,10,12).

Hidrotic ectodermal dysplasia (Clouston syndrome)

Hypotrichosis, nail abnormalities and palmoplantar hyperkeratosis are the hallmarks of the disease. Sweating is normal. Dental caries may develop. Connexin gene mutations are detected (1,2,12).

Ectodermal dysplasia-skin fragility syndrome

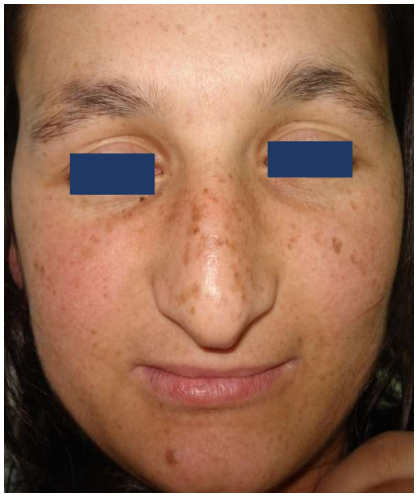
Hypotrichosis, nail abnormalities, skin fragility, chronic chelitis and palmoplantar hyperkeratosis are typical features of ectodermal dysplasia-skin fragility syndrome. Plakophilin 1 gene mutations are reported (15).

Ankiloblefaron filliforme adnatum-Ectodermal dysplasia-Cleft palate/lip (AEC) syndrome

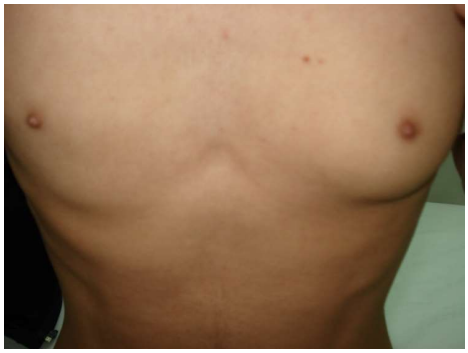
Ankiloblefaron filliforme adnatum and cleft palate and/or lip are typically present at birth. Ankiloblefaron filliforme adnatum is characterized by strands of tissue that completely or partially fuses the upper and lower eyelids. It may not be noticed when there is minimal fusion and spontaneous lysis occurs. Lacrimal puncta is often absent. Skin erosions are observed especially on the scalp. Other areas such as head and neck, skin folds and palmoplantar regions may be affected. Congenital erythroderma is usually present. New borns may have collodion membrane at birth. Postinflammatory pigmentary changes may develop later in life. Hypotrichosis, nail abnormalities and dental findings are the usual clinical findings. Patients report heat intolerance. Hypohidrosis does not lead to hypertermia and fever spikes are not observed in infancy. Syndactyly, camptodactyly and rarely split hand and/or foot malformation are noted. Conductive hearing loss is often present. TP63 gene mutations are detected. The disease is inherited in an autosomal dominant manner (11) .

Acro-dermo-ungual-lacrimal-tooth (ADULT) syndrome

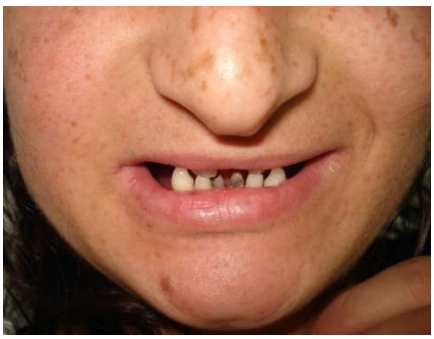
Feckling on sun exposed areas is a distinctive clinical feature. Increases with age and excessive sun exposure. Mammary gland and/or nipple hypoplasia or aplasia are typically seen in 90% of patients. Patients report heat intolerance. Hypohidrosis does not lead to hypertermia. Skin is dry and erosions are absent. Hypotrichosis, nail abnormalities, hipodontia and teeth malformations are observed. Syndactyly and split hand and/or foot malformation may be present. TP63 gene mutations are detected and the disease is inherited in an autosomal dominant manner (11). (Pictures 1-3 are obtained from personal archive)



Picture 1: Excessive freckling in a young girl with ADULT syndrome (personal archive)



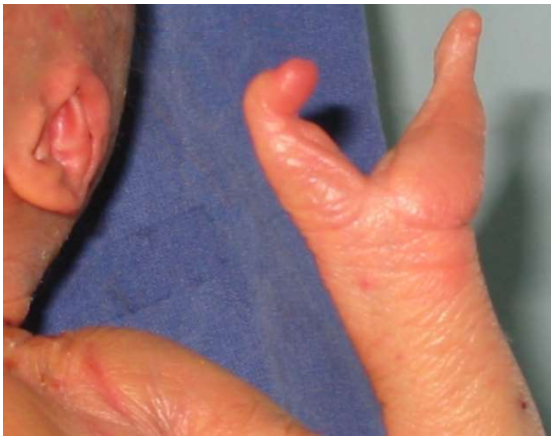
Picture2: Mammary gland hypopasia in a young girl with ADULT syndrome (personal archive)



Picture 3: Dental malformation (personal archive)

Ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3 (EEC3)

Limb abnormalities are observed in 68-90% patients with 60% tetramelic involvement. Syndactyly, oligodactyly, split hand and/or foot malformation (Picture 4), cleft lip and/or palate and digital duplication may be present. Lacrimal punçta is absent. Hypotrichosis, nail abnormalities, hipodontia and teeth malformations are typical clinical features. Patients report heat intolerance. Hypohidrosis does not lead to hypertermia. Skin is dry and erosions are absent. Genitourinary malformations are reported. TP63 gene mutations are detected and the disease is inherited in an autosomal dominant manner (11,16). (Picture 4 is obtained from personal archive)



Picture 4: Split hand deformity in an infant with EEC 3 syndrome (personal archive)

Limb-Mammary Syndrome

Limb anomalies include split hand and/or foot malformation and syndactyly. Mammary gland and/or nipple hypoplasia or aplasia are characteristic features and present in almost all patients. Lacrimal duct atresia is reported in half of the patients. Cleft lip and/or palate may be seen. Nail and dental abnomalites may be observed. Skin and hair involvement are not reported. TP63 gene mutations are detected and the disease is inherited in an autosomal dominant manner (11).

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Ectodermal Dysplasias and Treatment Approaches: A Dentist's Perspective

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Oral manifestations of ectodermal dysplasia (ED) are mainly include anomalies in tooth number (hypodontia/anadontia), shape (conical/tapered front teeth, malformed teeth), and structure (enamel hypoplasia). Other orocraniofacial concerns are reduced alveolar ridge height due to absence of teeth, maxillary retrusion, high palatal arch, abnormal pattern of tooth eruption, widely spaced teeth, and low salivary secretion. Congenital absence of teeth may also cause chewing and speech problems, nutritional deficiencies, and compromised facial appearance. Therefore, it is important to identify associated problems in dentoalveolar complex and to establish a proper treatment plan to rehabilitate the patient at optimum level. Many factors including the age of the patient, number of teeth present and their position and shape, alveolar bone volume, jaw growth and development, and cost of treatment need to be addressed in planning dental treatment. Dental management of ED patients should be implemented using a multidisciplinary team approach involving a pediatric dentist, an orthodontist, a prosthodontist, an oral surgeon, and a speech therapist in order to improve the aesthetics, phonetics, masticatory function, and overall quality of life. Dental rehabilitation should start in early childhood. Treatment options range from removable dentures at an early age to implant-supported removable or fixed prostheses in adolescence or adulthood after eventual orthodontic alignment of existing teeth or after orthognathic surgery. Early prosthodontic management in ED patients helps to restore and normalize function of chewing muscles and the skeletal growth pattern. Moreover, it helps to reduce the unwanted side effects caused by absence of teeth, such as alveolar ridge resorption and loss of vertical dimension.

Genetics of Ectodermal Dysplasia and Genetic Counseling
Assoc. Prof. Dr. Hakan GURKAN

Ectodermal dysplasias include a large group of congenital developmental disorders in at least two ectoderm-derived structures: eccrine sweat glands, teeth, hair, skin and / or nails. The most common of more than 170 types of dysplasia is ectodermal dysplasia 1 (OMIM # 305100), an X-linked hypohydrotic form (HED) that occurs frequently in the general population at 17,000 live births. HED encompasses a genetically heterogeneous group of diseases and is caused by pathogenic / possible pathogenic variations of several genes that encode components of the signal pathway related to tumor necrosis factor α (TNFa). Pathogenic / likely pathogenic variations of these genes disrupt the interaction that occurs during embryonic development between the epithelial cells located on the surface and the underlying mesenchyme.
As a result, the process of initiation, formation and differentiation of skin extensions is disrupted.
HED has been shown to result from pathogenic / possible pathogenic variations of different genes: EDA (EDA1), a ligand-ectodisplasinA-A1, EDAR, ectodisplasinA-A1 receptor, EDARADD, which program the structure of NEMO, the EDAR-related death site protein and protein product NFκB basic modulator (NEMO), is required for indirect activation of the nuclear factor κB (NFκB). Except for EDA and NEMO, both of which are localized on the X chromosome, all other genes encoding the components of the TNFa-related signal pathway that play a role in the differentiation of skin extensions are localized on the autosomes.

Mosaic Skin Disorders
Cristina Has
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Mosaic skin disorders comprise various non-syndromic and syndromic conditions resulting from postzygotic mutations. Postzygotic pathogenic variants may occur either in “lethal” genes, or in genes for dominant disorders (type 1). In individuals with a monoallelic germline mutation, a second post-zygotic mutation may account for a segmental aggravation or manifestation of the condition (type 2). The clinical manifestations of mosaic skin disorders depend on the time-point of the mutational event, on the stem cell in which it occurs, on the affected gene and on the type of mutation. The mosaic disorders seen in our genodermatoses clinic most commonly are mosaic neurofibromatosis 1, incontinentia pigmenti and pigmentary mosaicism. Pigmentary mosaicism is mostly associated with neurologic, musculoskeletal and ocular anomalies, and is caused by chromosomal mutations, or by postzygotic MTOR or RHOA mutations. Epidermal nevi also have a heterogeneous genetic background with complex correlations between the histological and molecular features. Clinical diagnosis is sufficient for limited skin mosaic lesions, but molecular genetic diagnosis is required in cases with complex phenotypes. Genetic testing by next generation sequencing of affected versus not affected skin/tissue is mandatory. Finally, therapeutic options emerge by targeting the dysregulated pathways.

Neurocutaneous Syndromes
Prof. Dr. Rebiay KIRAN
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Neurocutaneous syndromes, also known as phakomatoses, are a heterogeneous group of inherited disorders with germline mutation in a tumor suppressor gene. Many tissues derived from neuroectodermal crest are affected in these syndromes. Disorders classified as neurocutaneous syndrome include neurofibromatosis type 1 (NF-1), neurofibromatosis type 2, schwannomatosis, tuberous sclerosis complex, von Hippel Lindau syndrome, ataxia telangiectasia, and Sturge Weber syndrome. NF-1, also known as von Recklinghausen disease, is the most common phakomatosis, encountered in clinical practice,
Neurocutaneous syndromes are characterized by cutaneous, ocular, neurological and other distinct lesions in multiple organs. The affected patients have also risk for development of malignant tumors. The recognition of the clinical findings associated with these rarely seen disorders is important for the early diagnosis. Neurocutaneous syndromes are mainly diagnosed clinically, but genetic testing is available to clarify an uncertain diagnosis. Many lesions could only be treated symptomatically or in some cases surgically. Recently, increasing knowledge about specific genetic defects and protein functions in these disorders provide the development of new therapeutically options known as disease modified therapies. It is suggested that the quantity of biological-based drugs in practical use may increase in upcoming years.

Genetics of Neurofibromatosis and Tuberous Sclerosis Complex
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Neurofibromatosis type 1 (NF1) and 2 (NF2), and Tuberous sclerosis complex (TSC) are the most common neurologic disorders with skin manifestations amongst the spectrum of Neurocutaneous syndromes. The genetics of these disorders mainly involve the disturbance of the ectoderm during embryogenesis. The genes associated with NF and TSC phenotype are NF1, NF2, TSC1 and TSC2, respectively. Although, their function still remains to be elucidated in its entirety, they are known to play an important role in RAS/MAPK and mTOR signaling pathways, tumor suppression and apoptosis.
The diseases have an autosomal dominant inheritance pattern, caused by de novo or familial pathogenic variants with a penetrance close to 100% and a high probability of somatic mosaicism (i.e.25-33% for NF2). Although the major clinical findings lead to a suggestive diagnosis, molecular genetic testing is considered to be a more reliable diagnostic tool, especially for TSC and NF2. Most of the pathogenic variants on the corresponding gene are SNVs detectable by sequencing and CNVs to a lesser extent. Standardized diagnostic techniques, such as next generation sequencing, targeted-gene CNV analysis by MLPA and microarray analysis increased the detection rate considerably. The pathogenic or likely pathogenic variants are a tool for straightforward diagnosis. Yet the frustrating challenge of interpretation of variants of unknown significance (VUS) seem to be vital for a better understanding of gene mechanism, disease ethiopathogenesis and develop effective treatment strategies.
The content of this talk will include the molecular diagnostic algorythms and the challenges encountered for related diseases, upon a brief introduction to the underlying mechanisms known to date.

The Tale of Two Inherited Self-Healing Skin Cancers

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ABSTRACT
John Ferguson-Smith reported in 1934 a family of Scottish coal miners with an autosomal dominant self-healing skin cancer known as multiple self-healing squamous epithelioma (MSSE). In 2011, we identified a dozen loss-of-function alleles in the TGFβ Receptor 1 gene as being responsible for MSSE.
Here, I will introduce another inherited self-healing skin cancer which we named multiple self-healing palmoplantar carcinoma (MSPC). We have mapped and identified germline mutations in the inflammasome sensor protein NLRP1 as the cause for MSPC. We find that NLRP1 is the most prominent inflammasome sensor in human keratinocytes, and all pathogenic NLRP1 mutations are gain-of-function alleles that trigger pyroptotic release of IL1/IL18.
Our search for novel NLRP1-interacting proteins and their associated diseases have begun to establish a group of genodermatosis which provide valuable therapeutic intervention point for the treatment of common inflammatory skin conditions.

SHORT BIOGRAPHY

Bruno was trained as a developmental biologist with Prof. De Robertis at UCLA. After his PhD in 2008, he was awarded the inaugural A*STAR investigatorship and set up his team at the Institute of Medical Biology in Singapore. There, he switched to human genetics, placing emphasis on monogenic, fully penetrant and unique genetic traits as a means to understand complex and common diseases.
Combining the power of Mendelian genetics, patient-derived organoids and animal modeling in zebrafish, Xenopus and mice, his team has resolved various human disorders affecting embryogenesis, metabolism, ageing, cognition and familial cancers. Some of these discoveries have been licensed and are being developed for therapeutic purposes.
Bruno is a Research Director at A*STAR in Singapore, a fellow of the Branco Weiss (Switzerland) and National Research Foundations (Singapore), the first EMBO Young Investigator based outside Europe, and a distinguished Professor of Genetics at KOÇ University (Turkey) and Amsterdam UMC (Netherlands).

Approach to Cutaneous Vascular Anomalies as a Dermatologist and Principles in Their Diagnosis and Treatment

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Vascular anomalies can be classified as vascular malformations and vascular tumors. Vascular malformations which represent vascular ectasia can be divided as fast flow-slow flow and also as capillary,venous, lymphatic, arterio-venous or various combinations of these. Vascular malformations can be solitary or can also be a part of a complex syndrome involving anomalies in some other organs. Laser can be used in the treatment of capillary malformations while in other malformations obliteration of the ectatic vascular channels via sclerotherapy or embolization, surgery, or their combination may be necessary and may necessitate incorporation of many different medical professionals such as dermatologist, plastic surgeon, radiologist, ortopedic surgeon and should be maintained as a team work experienced in the treatment of such vascular malformations. Sirolimus is another medical option and is still under survey in the treatment of some complicated venous- lymphatic malformations. Vascular tumors on the other hand show real endothelial cell proliferation and the most common form is infantile hemangioma which is marked by proliferation in the early infantile period so correct timely diagnosis is of utmost importance to prevent proliferation in the early phase and so to prevent aesthetic and functional complications. Propranolol is very effective and the gold standard in the treatment of infantile hemangiomas and its effect is maximum in early proliferation phase so correct early diagnosis is very important to be able to start early treatment before any complications due to proliferation ensue and the patients should be referred to experienced centers for treatment. While propranolol is very effective in the treatment of most IH, some complicated forms may necessitate other treatment options such as systemic corticosteroids, surgery, laser or their combinations for optimal results. Topical beta-blockers can also be used in the treatment of small flat lesions.

Genetics of Cutaneous Vascular Malformations and Genetic Counseling

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Abstract
Cutaneous vascular malformations are developmental defects of the vasculare. Majority of the lesions occurs sporadically. The identification of genes mutated in different types of vascular malformations indicate that intracellular signaling pathways in endothelial cells have been identified to play a critical role in development of vascular malformations. Here in this report, the authors present a brief review about cutaneos vascular malformations and their genetic etiology.
Keywords: Vascular malformations, RAS/MAPK, PI3K/AKT/mTOR, VEGF, RASA1, PIK3CA
Cutaneous vascular malformations are one of the most common congenital abnormalities. Especially vascular anomalies in the head and neck area make up about 60% of the lesions and ocur in about 5% of children. Vascular malformations are classified into two groups: vascular tumors and vascular malformations.
Vascular Tumors:
a. Congenital hemangioma:
Congenital hemangiomas (CH) are in full shape and size at birth. The expression of the glucose transporter-1 protein (GLUT1) is not detected in the lesions (1, 2). According to their clinical behaviour, they are seperated into three types (3):

1. Rapidly involuting (RICH)
2. Partially involuting, and
3. Noninvoluting (NICH).

Mosaic missense mutations of the lesion in GNAQ/11 gene at codon 209 (Gln209) have been identified in the literatüre. This gene plays an important role for the control of MAPK and/or YAP signaling pathway. The Gln209 missense mutations lead to constitutive activation of these pathways (4).
b. Pyogenic granuloma:
This common benign vascular tumor can be either primary lesion or secondary within a capillary malformation (CM). Similar to CHs, upregulated RAS/MAPK signaling seems to be key mechanism. Somatic mutations in GNAQ (p.Arg183Gln), BRAF (p.Val600Glu) and NRAS (p.Gln61Arg) have been identified (5, 6).
c. Infantile hemangioma:
Infantile hemangioma (IH) originates from endotelial cell (EC) hyperplasia. Changing in vascular endotelial growth factor (VEGF)-A signaling pathway seems to be a key in the formation of IH. Jinnin et al. conducted a study to identify germ-line risk factor variants and sequenced 24 genes involved in EC proliferation, migration, adhesion and/or regulation of VEGF-A expression. The authors identified variants in TEM8 and in VEGFR2 (7).

Vascular Malformations:

a. Capillary malformations:

Capillary malformations (CMs) are also known as “port-wine stains (PWS)”. Somatic Arg183 GNAQ mutations are associated with CMs (8).

Sometimes CMs can be together with arteriovenous malformations (AVMs) and this situation is called CM-AVM. CM-AVM is an autosomal dominant condition and it is caused by RASA1 mutations. In approximately 50% of patients with CM-AVM, RASA1 mutation is caused by RASA1 mutations. To date, more than 40 different mutations have been reported in about 100 CM-AVM families. In these abnormalities, there is phenotypic heterogeneity and reduced penetrance, so it might be a somatic second mutation on the other allele of RASA1 gene in the lesion. This gene encodes p120RasGAP which is inactivates RAS. p120RasGAP plays an essential role in cellular growth, differentiation and proliferation. It is also bound to AKT and this leads to protection of cells from apoptosis (9, 10, 11).

A second causative gene which is identified in a different clinical type of CM-AVM is EPHB4. This gene also has a role in RAS-MAPK-ERK1/2 pathway and its direct effector is p120RasGAP (12).

b. Venous malformations:

Venous malformations (VMs), hereditary cutaneomucosal venous malformations (VMCMs), and blue rubber bleb nevus syndrome (BRBN) are caused by mutations in the endothelial receptor tyrosine kinase TIE2 encoding TEK gene. The somatic activating mutations in VMs are found and interestingly, there could be double mutations on the same allele. This gene is an essential for the PI3K/AKT/mTOR signaling pathway (9, 13).

c. Lymphatic malformations:

Lymphatic malformations (LMs) are caused by somatic activating mutations in PIK3CA. These mutations can enhance the activation of the AKT/mTOR cascade which regulates cell growth, proliferation, and migration (14, 15).

In conclusion, several mutations in key proteins of EC intracellular signaling pathways have been identified to play a critical role in development of vascular malformations.

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Genodermatosis with Hyperpigmentation

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Skin diseases that progress with congenital hyperpigmentation are divided into two, circumscribed and diffuse. Dermal melanocytosis, lentigines, cafe au lait spots, nevus spilus and segmental pigmentation diseases are circumscribed pigmentation diseases.

Skin diseases with diffuse pigmentation are divided into two as patterned and non-patterned. Patterned group is also divided into two; linear and reticulate groups. While the pigmentary demarcation lines, incontinentia pigmenti, linear and whorled nevoid hypermelanosis are in the group displaying a linear pattern; Dowling-Degos disease, dyskeratosis congenita, dyschromatosis hererditeria universalis, Naegeli-Franceschetti- Jadassohn syndrome, Kitamura's reticular acropigmentation, X-linked reticulate pigmentary disorder and dermatopathia pigmentosa reticularis are in the group displaying reticular pattern.

Factors such as congenital or acquired, localized or widespread lesion pattern, presence of additional systemic involvement and family history should be questioned in patients with pigmentation disorders.

Patients should be followed up for possible comorbidities. In necessary cases, families should be given genetic counseling.

Current Approaches to Hypopigmentation Diseases

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SUMMARY
Hypopigmentations of the skin is a frequently encountered problem in childhood, being totally innocent or representing the first sign of a multisystem disorder. Cutaneous hypopigmentions encompass a wide range of disorders, which can be mainly differentiated based on the age of onset (congenital or acquired), the extent of involvement (diffuse or localized) and the underlying aetiology. In early childhood, diffuse or generalized hypopigmentation usually have a genetic origin, in contrast to the acquired localized form at a later age. An adequate medical history and a thorough clinical evaluation are very useful tools to make a rational diagnosis, which can be followed by further diagnostic investigations. In routine clinical practice, the clinician can ask several key questions concerning age of onset (congenital or acquired), evolution of the lesions (stable or progressive), family history and associated disorders (e.g., autoimmune disorders, loss of sight or hearing, developmental disorders, neurological disorders, skeletal anomalies). In addition, other clinical features have been proven to be crucial in the differentiation of hypomelanoses: Subtype of pigment disorder (hypopigmentation, depigmentation or hyperpigmentation), distribution pattern and shape of the lesions (body location, unilateral or bilateral, solitary or multiple lesions, linear pattern, Blaschkoid distribution or ash leaf-like pattern) or other distinct clinical findings (anomalies of hair, eyes, teeth, nervous system or skeleton). Medical history, clinical examination, Wood's light investigation, histological analysis of the skin and a multidisciplinary approach can contribute to a correct and early diagnosis of the different types of hypopigmentations.
KEYWORDS: Depigmentation, hypopigmentation, hypomelanosis

Genetics and Genetic Counseling of Pigmentation Diseases

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The skin color is controlled by the pigment system (melanocytes and melanin) and is mainly determined by the amount, type and distribution of melanin in the skin. Melanin is a crucial pigment that determines skin and hair color in humans and is synthesized in melanocytes. Following its synthesis, melanin is stored in the specialized melanosomes found in the hair follicles, the iris uveal tract and the inner ear, as well as the retinal pigmented epithelium (RPE). Melanocyte development originates from the neural crystal and is regulated by various signaling pathways and transcription factors. Paired Box 3 (PAX3) and Microphthalmia Transcription Factor (MITF) genes in this developmental pathway are important for hypopigmentation. Melanocyte precursor melanoblasts differentiate and migrate to their final places (basal epithelium of the epidermis in the skin, hair follicles, uveal tract of the eye and inner ear). In mature form, melanocytes synthesize and pack melanin in lysosome-like organelles called melanosomes. Melanosomes are transferred or secreted to the keratinocytes around the epidermis through melanocytic dendrites. Melanin biosynthesis begins with the conversion of L-phenylalanine to L-tyrosine with the phenylalanine hydroxylase (PAH) enzyme. L-Tyrosine is converted to 3,4-dihydroxyphenylalanine (L-DOPA) with tyrosinase enzyme, which is the type I membrane protein and catalyzes the first and rate-limiting reaction in melanin synthesis. The final product of the catalysis process, which starts from tyrosine, is dopaquinone, which works as the precursor of melanin.

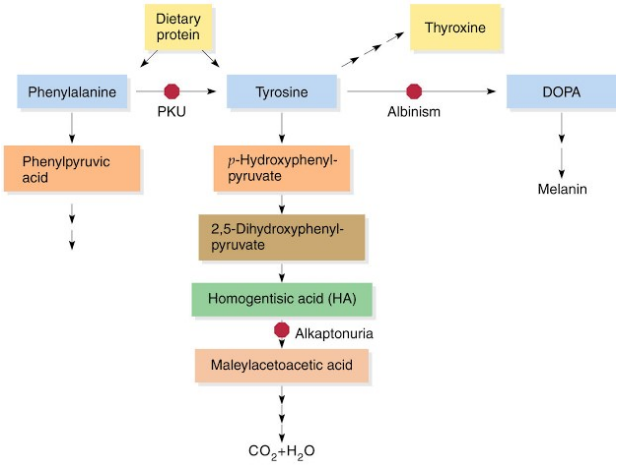

Figure 1: Tyrosinase Pathway

After dopaquinone synthesis, the pathways of eumelanin and pheomelanin are separated. There are three major enzymes involved in melanin synthesis in melanosomes; Tyrosinase (TYR), tyrosinase-associated protein-1, (TYRP1), dopachrome tautomerase (TYRP2). In addition, many factors such as BLOC1, OA1, SLC45A2 are responsible for enzyme traffic and function.

Albinism is the common name for a rare group of diseases, both clinically and genetically highly heterogeneous, often with an autosomal recessive transition. Although the prevalence varies among different races, but worldwide prevalence is 1/17000 (1/10000-1/20000). The characteristic eye findings of albinism can be described as nystagmus, iris translumination and photophobia, these findings are present in almost all patients. Albinism is studied in three main groups: oculocutaneous (OCA), ocular (OA) and syndromic type (HPS, CHS). Today, there are 23 genes in the literature that have been associated with albinism disease or have been shown to cause hypopigmentation. Among these genes, TYR, OCA2, TYRP1, SLC45A2 and SLAC45A5 play a role in melanin synthesis or melanogenesis and cause types of oculocutaneous albinism (OCA) 1, 2,3 4 and 6, respectively. In molecular epidemiological studies, the molecular basis of 70-75% of albinism patients can be explained by screening known genes (Table-1) and approximately 40% of mutations are observed in the TYR gene. Due to the wide heterogeneity observed in clinical and genetic findings, a common diagnostic criterion has not been established in the world and in our country. This situation also makes it difficult to establish genotype-phenotype correlation.

Gen Adı	Lokalizasyon	Albinizm Türü	Kalıtım Şekli
TYR	11q14.3	OCA1A and 1B	OR
OCA2	15q12-q13.1	OCA2	OR
TYRP1	9p23	OCA3	OR
SCL45A2	5p13.2	OCA4	OR
SLC4A5	15q21.1	OCA6	OR
LRMDA (C10ORF11)	10q22.2-q22.3	OCA7	OR
GPR143	Xp22.2	OA1	XL
SLC38A8	16q23.3	FHONDA	OR
HPS1	10q24.2	HSP1	OR
AP3B1	5q14.1	HSP2	OR
HPS3	3q24	HSP3	OR
HPS4	22q12.1	HSP4	OR
HPS5	11p15.1	HSP5	OR
HPS6	10q24.32	HSP6	OR
DTNBP1	6p22.3	HSP7	OR
BLOC1S3	19q13.32	HSP8	OR
BLOC1S6	15q21.1	HSP9	OR
AP3D1	19p13.3	HSP10	OR
LYST	1q42.3	CHS1	OR

Table 1: Genes associated with albinism disease of hypopigmentation

Approach to the patient with albinism

Phenotype can be clearly observed in oculocutaneous albinism. However, in non-generalized individuals, the diagnosis is delayed and eye examination by an experienced ophthalmologist is essential. Dermatology follow-up is important for possible different lesions. It is recommended to use high factor sun cream in summer and winter against skin burns that may occur after sun exposure. It is necessary to protect the skin and eyes with hats and sunglasses, especially when the sun is upright.

Molecular diagnosis in albinism

Molecular diagnosis is important for the definition of the heterogeneous phenotype. In syndromic forms, early diagnosis is of great importance. Cases of syndromic form that have not been identified at birth and have severe symptoms at advanced ages have been reported. In couples with affected children, the chance of preimplantation genetic diagnosis is important. In addition, a genetic examination was requested from an individual who wanted to obtain a disability report.

Albinism and immunodeficiency

Especially in cases of Chediak-Higashi Syndrome, there is immune deficiency. In addition, cases with severe neutropenia other than CHS have been reported. Therefore, patients with albinism should be directed for immunological evaluation as well.

Albinism and social life

Due to severe visual impairment, patients with albinism are affected by education, work and daily life. They should be encouraged to get psychological support. We must increase social awareness. Their eyes are not dazzled by the sun, they cannot see.

Acıbadem University Project

Association made with albinism result of cooperation projects reached a total of 117 patients from all over the turkey. These patients were primarily evaluated by an ophthalmologist who specializes in albinism. Genetic analyzes were started after dermatological evaluations were made. 66 OCA individuals were studied; TYR gene variant was detected in 43 of these patients.

Rare Case Abstracts

NVS3

A Rare Mutation in the ALOX12B Gene in a Newborn With Autosomal Recessive Congenital Ichthyosis

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Abstract
Ichthyosiform dermatoses are genetically inherited diseases characterized by crust deposition covering almost the entire surface of the skin. The clinical spectrum of the disease is quite wide. Patients may have extensive skin dryness, skin peeling and flaking, and erythroderma. The disease is divided into two groups as congenital and acquired. Congenital ichthyosis forms include classic lamellar ichthyosis, nonbullous congenital ichthyosiform erythroderma, harlequin ichthyosis (1).

Congenital ichthyosis is autosomal recessive and occurs at a frequency of 200,000 births. The cases are born surrounded by a collodion membrane. Diagnosis is based on clinical findings and skin biopsy and molecular analysis (2). In this case report, we aimed to discuss the phenotypic findings of a newborn with a rare mutation in the ALOX12B gene which was diagnosed as autosomal recessive congenital ichthyosis type 2.

NVS4

Rare Ehler Danlos Syndrome Samples: Vascular and Kyphoscoliotic Types

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Introduction: The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. According the classification made in 2017 there are 13 subtypes. Because of there are many subtypes, it is important to determine the EDS subtype in terms of genetic counseling and patient management. The incidence of EDS, including all subtypes is estimated to be between 1 in 2500 and 1 in 5000. EDS hypermobility type is the most common subtype. Kyphoscoliotic and Vasculer types are very rare. Vascular and organ rupture are the most important and fatal complications of EDS most commonly seen in Kyphoscoliotic and Vasculer types. In cases with suspected EDS, urgent medical evaluation should be performed at the onset of sudden pain. It is necessary to inform patients and their relatives about emergency symptoms and to explain the need for emergency intervention. Here, we report two rare cases of Vascular and Kyphoscoliotic EDS that may cause fatal complications.
Case 1: The 5 years old patient was the first child of non-consanguineous healthy parents, born at term with a birth weight of 2600gr. Easly bruising even with small traumas have been noticed from the infancy period. She also had difficulty in wound healing. Physical examination revealed wide forehead, deep-set eyes, thin translucent skin with multiple bruising and atrophic scars, joint laxity, and profound superficial veins. Next-generation sequencing (NGS) was performed on Illumina MiSeq (v1.9) platform using the virtual panel for collagenopathy. The heterozygous variant in COL3A1(c.3563G>A) was detected. EDS Vascular type was diagnosed.
Case 2: The 4 years old patient was the first child of 1th degree consanguineous healthy parents, born at term with a birth weight of 2800gr. She has neuromotor development delay. The patient had a history of easy bruising and difficulty wound healing. On physical examination, he had arched eyebrows, marked scoliosis, pes planus and joint laxity. Beighton score was 8. -5.00 D glasses needed. NGS was performed on Illumina MiSeq (v1.9) platform using the virtual panel for collagenopathy. The bioinformatics Copy Number Variation analysis of the NGS data in PLOD1 gene revealed a highly reliable homozygous deletion in exon 10. Gene-specific MLPA analysis could not be performed, but with the clinical history she was diagnosed with EDS Kyphoscoliotic type. Genetic counseling was given to the families , possible risks were explained and directed to related departments. An information form was prepared for them to carry with them at all times.
Discussion: Vascular and organ ruptures are the most important complications of EDS. Although it can be seen in all subtypes, it is most commonly seen in Vascular and Kyphoscoliotic type. Therefore, it is very important to make the diagnosis and inform the patient and family. These complications can be spontaneous or during surgical procedures. In such cases, early medical intervention and avoiding unnecessary surgical procedures are getting great importance. Conclusion: Describing rare types of EDS before complications develop is crucial to prevent life-threatening serious complications.

NVS5

Trıchohepatoenterıc Syndrome

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Introduction&aim: Trichohepatoenteric syndrome(THES) is an autosomal resesive, extremely rare syndrome, characterized by intractable diarrhea, wolly and easily break off hairs, intrauterine growth retardation(GR), recurrent infections, various skin lesions and hepatic failure. TTC37 and SKIVL2 are the two main genes that are identified in THES up to date. Four cases who admitted in different times with distinct complaints are presented in this report.
Material&methods: Clinical findings:
Cases 1&2; 7-year-old male patient was referred due to diarrhea and abnormal hair pattern. He had history of recurrent diarrhea since birth, frequent hospitalization for bronchiolitis and eczematous skin lesions up to this age. Her parents were consanguineous. On examination his weight, height and OFD were under 3th percentile. He had sparse, wooly hair; bilateral sparse eyebrows on laterals and conic-shaped mandibular lateral incisor teeth. The eyelashes and nails were noted normal. He had frequent fever attacks, but no hypo-or-anhydrosis. IgE levels were high. 2-year-old, case 2(brother of case 1) was also examined due to suffering from GR with neonatal-onset, recurrent diarrhea and frequent lung infections. He had sparse and wooly hair similar as his brother. Although the teeth eruption were started after the 18th month, the shape and color of his teeth were normal.
Case 3&4;Two male siblings were consulted for short stature. 10-year-old one (case 3) had a history of postnatal-onset GR, frequent fever attacks and hospitalization for recurrent lung infections. Diarrhea was not noted. He had been followed up in hospital through one month for hepatic failure 3 years ago. Her parents were first cousins. On examination he had brittle, wooly hair, and sparse eyebrows. There were not obvious nail abnormalities. 7-year-old, case 4 (brother of case 3) was suffering from GR since birth, frequent fever attacks, eczematous skin lesions and recurrent lung infections. His hair was similar as his brother. Multiple scars-due to severe varicella infection-on body and the sign of dermographism on skin were also noted. IgE level was found high in both siblings. The paternity of second family was questioned in detail due to having children with the similar phenotypic characteristics with family 1 and it was learned that the parents of four cases were cousins.
Genetic analysis: A nonsense homozygous mutation (c.4572G>A,p.W1524X) in TTC37 gene was detected in cases 1&2 by clinical exome analysis performed on Illumina Trusight One Sequence platform using NGS method. The same mutation was showed by TTC37 gene sequence analysis, which was performed afterwards.
Discussion&results: No significant genotype-phenotype correlation could be established neither in TTC37 nor SKIV2L related THES up to date. Nevertheless there are clinical heterogenity, the brittle and wooly hair which is predicting trichorexis nodosa has been reported in allmost all. While woolly hair, frequent infections, eczematous skin findings, GR and high IgE were the common findings in all four cases, intractable diarrhea was the chief complain in only case 1 and 2. Although all patients had a history of frequent fever, hypo-anhydrosis was not observed. There were no cases with conic shaped teeth except case 1. Hepatic failure was reported in only case 3. Even though a diagnostic algorithm for THES has not yet been established, this rare syndrome should be kept in mind in the differential diagnosis of patients with GR, diarrhea, frequent infections, eczematous skin findings and high IgE levels.

NVS6

Rothmund Thomson Syndrome

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Rothmund Thomson Syndrome (RTS) is rare inherited disorder presenting with poikiloderma, sparse scalp hair, sparse eyelashes and eyebrows, cataract, skeletal anomalies, toth abnormalities and increased risk of cancer, especially osteosarcoma. Around 300 cases have been reported so far, but the prevelance is unknown. RTS type 1 is caused by homozygous or compound heterozygous mutation in the ANAPC1 (608473) gene and RTS type 2 is caused by homozygous or compound heterozygous mutation in the RECQL4 (603780) gene. Here, we report that two siblings, carried novel homozygous mutation in the RECQL4. The patients presented with cutaneous manifestaions (cutaneous rash, erythema and hyperpigmentation on the face and extremities. In two sisters, we identified the previously unreported mutation c.2415_2419del (p.Gly806fs*1) homozygous in the RECQL4 gene with clinical exom analyses. The genomic variant was confirmed by sanger sequence analyses because of %84 variant fraction. Mother and father were found to be disease carriers. We aimed to diagnose rapidly this rare and cancer predisposing syndrome.

NVS9

Three Sublings With Mal De Meleda

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Introduction and purpose: Mal de Meleda (MDM) is a rare hereditary palmoplantar keratoderma. Here, it is presented three siblings with unreported mutations in Turkey. Patients A 58-year-old male patient presented with complaints of palmoplantar hiperkeratosis, diffuse erythema and itching. His two brothers also had similar complaints. Clubbing, subungal hyperkeratosis; sharp-edged, erythematous plaques were observed on the knee-elbows. There was thinning on the fingertips and flexion contracture on the hands. Biopsy was consistent with palmoplantar keratoderma. Acitretin was started. Fungal hyphae were observed in KOH examination. Itching regressed with systemic itraconazole. The 52-year-old brother had accompanying hearing impairment. c.211C>T(p.Arg71Cys) mutation was detected in SLURP1 gene in 50-year-old brother. Discussion The prevalence of MDM is 1 / 100,000. It shows OR transition. It has been shown to affect 19 ethnic populations, spread to 21 countries, and be associated with at least 20 mutations. It is characterized by sharp limited glove-sock style erythema and palmoplantar hyperkeratosis. Clinically worsens with age. (progredien structure) The lesions progress to the dorsum of the fingers in children and to the dorsum of the hands and feet in adulthood. (transgredien structure) Knee-elbow, nail involvement and perioral erythema are seen. There may be pseudoainhum and spontaneous autoamputations. Mutations in the SLURP1 gene on chromosome 8 cause disease. Topical keratolytic agent, systemic retinoid, 5-FU, bath PUVA can be used in treatment. The risk of bacterial and fungal infection is increased.
Result :Three siblings were presented because they have a rare disease and carry an unreported mutation from our country.

NVS10

Birt-Hogg-Dubé Syndrome: Diagnostıc Journey of Three Cases From Skin to Gene

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Birt-Hogg-Dubé syndrome (BHDS) is an unusual, rare disorder characterized by the triad of cutaneous lesions, renal tumors and lung cysts and characterized by inactivation of the gene Folliculin (FLCN). Herein, we present three female patients diagnosed with BHDS. First patient a 55-year-old female had flesh moles histopathology compatible with fibrous papules, multiple air cysts in the lung, renal multiple cysts, fibrous papules in the skin and FLCN gene mutations ('c.1285dupC (p.His429Profs *)' 11th exon and 'c.653G> A (p.Arg258His)' 7th exon). Second patient a 76-year-old female had tricodiscoma on her skin, multiple air cysts in the lung, spontaneous pneumothorax, FLCN gene mutation 'c.1285dupC (p.His429Profs*27)11th exon'and, her son had renal carcinoma history under 50 years of age. Our third patient, also the daughter of patient two, had dermal papules histopathology compatible with eccrine epithelial hyperplasia, spontaneous pneumothorax, FLCN gene mutation 'c.1285dupC (p.His429Profs*27)11th exon' and, parotid oncocytoma. This three cases highlight that the skin lesions can be the first clues for systemic diseases and syndromes. Facing papuler lesions BHDS should be kept in mind. Through our cases, we document the ninth known case of parotid oncocytoma associated with BHDS and the first case of two mutations ('c.1285dupC (p.His429Profs *)' 11th exon and 'c.653G> A (p.Arg258His)' 7th exon) in the same FLCN gene in the light of the literature. Keywords: Birt-Hogg-Dubé syndrome, FLCN, Pneumothorax, Renal neoplasms.

NVS11

Overview of H Syndrome With Case Presentations

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Introduction: H syndrome (OMIM 602782) is a rare, autosomal recessive genodermatosis with multisystem involvement. H syndrome is characterized by cutaneous hyperpigmentation and hypertrichosis, hepatosplenomegaly, heart anomalies, hypogonadism, hearing loss, short stature and hyperglycemia. H syndrome is a part of a spectrum disease named as "Histiocytosis Lymphadenopathy Plus Syndrome" with the other three allelic disorders which are Faisalabad histiocytosis, pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and sinus histiocytosis with massive lymphadenopathy. This spectrum disorder caused by biallelic mutation in the SLC29A3 gene located at 10q22.1. This gene encodes human equilibrative nucleoside transporter3 (hENT3) protein plays a role in cellular uptake of nucleosides. Herein, we present two new cases of H syndrome one of these which has a novel mutation in SLC29A3 gene.
Clinical Reports: Case 1: A 27-year-old female patient was consulted to our department from Endocrinology Clinic with the suspicion of MODY due to the diagnosis of insulin-dependent DM which started 6 months ago. Physical examination revealed symmetric hyperpigmented patches with hypertrichosis in both medial thighs. It was learned from the medical history of the patient that the skin lesions started at the age of 8 years and she has childhood-onset bilateral hearing loss. In the examinations of the patient; ESR and CRP elevation and pericardial effusion were detected. The patient had no hepatosplenomegaly, joint contractures or short stature. There was a first-degree cousin marriage between her parents. Homozygous c.1339G> A (p.Glu447Lys) mutation was found in exon 6 of SLC29A3 gene in molecular analysis. This mutation was previously described in H syndrome patients from the same region of Turkey. Case 2: A 12-year-old male patient with insulin-dependent DM was referred to our department from Pediatric Endocrinology Clinic because of his bilateral hearing loss diagnosed in early childhood and symmetric hyperpigmented patches accompanied by hypertrichosis in both thigh medials. In the examinations of the patient; ESR and CRP levels were found to be elevated. There was no hepatosplenomegaly or short stature. There was a first-degree cousin marriage between his parents. In the molecular analysis, a novel, homozygous c.1013_1013delG (p.Gly338AlafsTer67) mutation was detected in exon 6 of SLC29A3 gene.
Conclusion: H syndrome is a very rare genodermatosis and its clinic is very heterogeneous. Diagnosis of these patients is often omitted and patients are worn out with misdiagnoses, unnecessary examinations and inappropriate treatment options for many years. In this case report, it was aimed to raise awareness about this disease.

NVS12

Erythroderma in Adolescent: Netherton Syndrome

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Introduction and objective: Netherton Syndrome is an autosomal recessive skin disorder characterized by ichthyosis, atopy and hair shaft abnormalities. Mutations have been found in the SPINK5 gene located on the 5q32 chromosome gene encoding the serine protease inhibitor protein (LEKTI), which plays an important role in providing epidermal homeostasis associated with the desquamation process in the epidermis. The case is presented to draw attention to childhood erythroderma. **Materials and Methods:** A 14-year-old boy was referred to us from Kosovo with complaints of diffuse redness and scaling skin. It was learned from his medical history that his complaints were severe since his birth and that redness and scaling continued to reduce in later ages, which became more severe in the last 2 years. There was no history of collodion membrane at birth; however, it was learned that he stayed in the incubator for 4 months due to redness on the entire body at birth. His dermatological examination revealed diffuse erythema covering more than 70% of the body and on this basis, erythematous squamous plaques of 1-10 cm in diameter with double-edged scale at the margins and erythroderma appearance containing widespread 1-10 mm diameter desquamated macules (Figure 1). These findings were accompanied by significant erythema on the face, while the axillary and inguinal region were preserved. In addition, we observed moon face and a buffalo hump at the junction of nape and back. When the patient followed up for seborrheic dermatitis, atopic dermatitis, and desquamative erythroderma was admitted, he was on 3.75 mg/day of prednisolone treatment for 5 months. The patient found to have total IgE elevation as well as atopic findings was diagnosed with Cushing's syndrome by pediatric endocrinology. The skin biopsy revealed parakeratosis, acanthosis, separated stratum corneum, and mild infiltration in the dermis. Skin lesions were clinically and histopathologically consistent with ichthyosis linearis circumflexa. It was found that mutations were heterozygous (c.891C>T /p.Cys297) in exon 11 and (c.1431 -12G>A) intron 15 of the SPINK5 gene in gene analysis and the diagnosis of NS was confirmed. The microscopic evaluation of the eyebrows and hair showed trichorrhexis invaginata (Figure 2). **Results:** The case was diagnosed as Netherton Syndrome with hair shaft abnormalities, ichthyosis linearis circumflexa and atopic findings triad. Gene analysis has not yet been completed. The erythroderma of the patient, who was started on acitretine during the follow-up, increased. Vancomycin was started with the suggestion of an infectious diseases specialist and acute renal failure developed. The patient developed erythroderma complications and was transferred to pediatric inpatient clinic. **Discussion:** NS is known to be a syndrome arising at birth, or in the first few months of life, that has a high mortality rate in the neonatal period. However, there is no collodion baby phenotype. The first skin symptoms are diffuse erythema and scaling skin. Typical hair findings may occur later, which may lead to missing the diagnosis and delaying the diagnosis with different diagnoses, such as atopic dermatitis. Therefore, hair examinations should be repeated at intervals in these babies. In childhood and adolescence, NS should be kept in mind, especially in children presenting with erythroderma, and it should also be aware that the mortality rate can be high.

Erythroderma in adolescent: Netherton Syndrome

Introduction
Netherton Syndrome (NS) is characterized by an autosomal recessive transition, ichthyosis, atopy, and hair shaft abnormalities. The SPINK5 (Serine Protease Inhibitor Kazal-type 5) gene mutation in the 5q32 chromosome encoding the serine proteinase inhibitor (LEKTI-Lymphoepithelial Kazal Type Inhibitor), which plays an important role in desquamation in the epidermis, is shown as the cause[1]. The case is presented to draw attention to childhood erythroderma.

Case
A 14-year-old boy was referred to our hospital from Kosovo with complaints of diffuse redness and scaling skin. It was learned from his medical history that his complaints had been severe and ongoing since birth, that redness and scaling had decreased over time but intensified again over the last 2 years. There was no history of collodion membrane at birth; however, it was learned that he stayed in the incubator for 4 months due to redness on the entire body and a history of congenital erythroderma. In addition, he had developed infection such as colitis and cystitis at 1 month and bronchiolitis at 8 months. The patient, who also had a history of asthma, had been followed up due to infantile seborrheic dermatitis, erythroderma, and atopic dermatitis since birth in other centers. The evaluations at other centers had revealed an elevated total IgE level, and the prick test had shown a positive reaction to wheat, cereal, and rye. There was no pathological feature in his family history.
Dermatological examination revealed diffuse erythema covering more than 70% of the body and on this basis, erythematous squamous plaques of 1-10 cm in diameter with double-edged scale at the margins and erythroderma appearance containing widespread 1-10 mm diameter desquamated macules (Figure 1-2). The pustular eruption was also noted on the erythrodermic skin. These findings were accompanied by prominent erythema on the face, and the axillary and inguinal area was preserved. In addition, a moon face and a hump in the neck-back junction area were observed. The patient, who was followed up at the other center due to seborrheic dermatitis, atopic dermatitis, and desquamative erythroderma, had been receiving 3.75 mg/day prednisolone for 5 months.

The findings of the patient who was evaluated by pediatric endocrinology were consistent with Cushing Syndrome. Elevated total IgE (2400 U/I) was present and atopic dermatitis was diagnosed according to his history and Hanifin-Rajka criteria. The patient's history was evaluated with dermatological examination findings and a history of congenital erythroderma, and the most likely diagnosis was thought to be the "Inherited Syndromic Ichthyosis" group. The focus was directed to Netherton Syndrome, the most common cause of this group, and a skin biopsy was taken with a preliminary diagnosis of ichthyosis linearis circumflexa. The skin biopsy revealed parakeratosis, acanthosis, separation in the stratum corneum, and mild infiltration in the dermis. Skin lesions were clinically and histopathologically consistent with ichthyosis linearis circumflexa. Microscopic examination of the eyebrows and hair revealed trichorrhexis invaginata (Figure 3). According to the gene analysis performed to support the diagnosis, NS conforming mutations in Exon 11 (c.891C> T /p.Cys297) and Intron 15 (c.1431 -12G> A) were detected in the SPINK5 gene. The patient was diagnosed with Netherton Syndrome with hair shaft anomaly, ichthyosis linearis circumflexa, and atopic dermatitis triad, and the diagnosis was supported by gene analysis. In the follow-up phase, low-dose acitretin (0.2 mg/kg) treatment was started; the patient's erythroderma elevated at the end of the 2nd week, and the treatment of acitretin was discontinued. The leukocyte value, which increased with intermittent fever, reached 35.000. Upon the recommendation of infectious diseases specialist, the patient was started on vancomycin due to sepsis, and acute renal failure developed in the patient. The patient, who developed erythroderma complications, was transferred to the pediatric inpatient clinic and was discharged with recovery.

Discussion

For the first time in 1949, Comel described a figurative psoriasiform dermopathy in a young woman and named it ichthyosis linearis circumflexa (ILS). In 1958, Netherton identified trichorrhexis invaginata (TI) as an unknown hair shaft abnormality. Nevertheless, the relationship between ILS and TI remained unknown until 1969, and Altman and Stroud defined these two anomalies as a single clinical condition that also included atopic dermatitis. In 2000, a group of French and British researchers identified 13 families with several mutations in the SPINK5 gene that encoded the serine protease inhibitor as a cause of NS. LEKTI deficiency leads to barrier dysfunction of the skin, thereby playing a role in inflammation and pathogenesis of typical hair shaft defects[2]. The typical ILS lesion is erythematous, mildly squamous annular or polycyclic, migratory double-edged patches. In the majority of cases, the lesions are periodic, last several days, and may be overlooked[3]. In our case, the clinical findings that had begun at birth had continued for years, showing periods of exacerbation and recovery.

Mental retardation, short stature, and a tendency to develop food allergies have also been reported in association with the syndrome. Our patient had no mental retardation but had short stature. The prick test performed at the other center reported a positive reaction to wheat, grain, and rye. The relationship of the syndrome with atopic dermatitis causes diagnostic delay and different diagnoses to be made, especially in cases without a family history. It has been reported in the literature that these patients were diagnosed with diseases such as atopic dermatitis, congenital ichthyosiform erythroderma, erythroderma, infantile seborrheic dermatitis, acrodermatitis enteropathica, and erythrokeratoderma. Histopathological features vary according to the type and period of the lesion. Hyperkeratosis, parakeratosis, and thinning in the granular layer are often detected. Old ILS lesions and erythrodermas with widespread squamous lesions exhibit psoriasiform epidermal hyperplasia, papillomatosis, and perivascular mixed inflammatory infiltrate. When pustular rash occurs, spongiosis, intraepidermal vesiculopustular formation is observed[4]. In our case, biopsy taken from the pustular lesion on the erythematous floor is an important finding indicating the separation in the stratum corneum. Topical moisturization and if erythroderma has developed, rational management of erythroderma is important in treatment. In older patients with NS, retinoid therapy, which is generally useful in other ichthyoses, has been reported to not respond, even to lead to worsening by suppressing terminal differentiation[1,5]. In our case, we observed worsening of symptoms due to the treatment of acitretin and therefore ended retinoid treatment.

Netherton Syndrome is a syndrome that develops at birth or in the first few months after birth and has a high mortality rate in the neonatal period. However, there is no collodion baby phenotype. The first skin symptoms are diffuse erythema and desquamation. Typical hair findings may appear late; this may lead to a missed diagnosis or diagnostic delay with different diagnoses such as atopic dermatitis. Therefore, when NS is suspected in children, eyebrows and hair should be examined intermittently, and it should be remembered that trichoscopy is a useful diagnostic tool. In childhood and adolescence, NS should be kept in mind, especially in children presenting with erythroderma, and it should also be aware that the mortality rate can be high.

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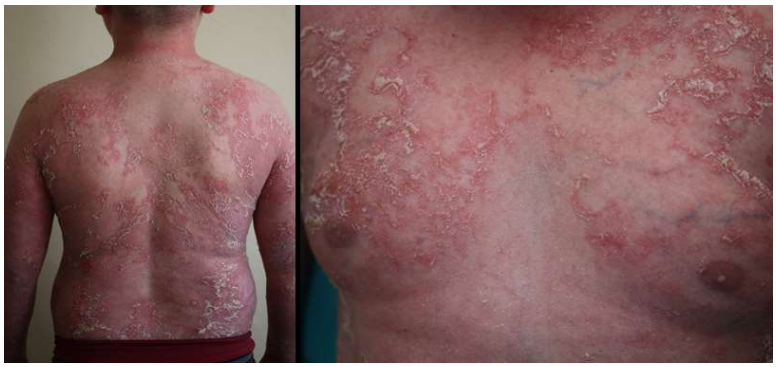

Fig 1-2: Diffuse erythema covering more than 70% of the body and on this basis, erythematous squamous plaques with double-edged scale at the margins and erythroderma appearance containing widespread desquamated macules

Fig 3: Hair shaft abnormality showed trichorrhexis invaginata on microscopic evaluation

NVS13

Familial Incontinentia Pigmenti: Two Families Four Cases

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Incontinentia Pigmenti (IP) is an X-linked dominant, multisystemic, rare neuroectodermal disease which is caused by pathogenic variants in IKBKG/NF-κB/NEMO gene and the estimated prevalence at birth is 1.2/100.0001. Affected individuals present with psychomotor retardation, intellectual disability and epilepsy along with alopecia, retinal detachment, hypodontia and nail dystrophy. Characteristic skin lesions evolve through four stages2; blistering (birth to age 4 months), wart-like rash (for several months), swirling macular hyperpigmentation (age 6 months into adulthood), and linear hypopigmentation. We aim to discuss the phenotypic effect of random X- inactivation with molecular diagnostic results and highlight the history of evolution of the skin lesions for the clinical diagnosis in IP. In the index patient of the first family (21 months), hypodontia and hyperpigmented skin lesions tracing Blaschko's lines were observed. Whereas the index of the second family (15 months), was followed up by pediatrics neurology outpatient clinics, due to hypotonia, psychomotor retardation and refractory epilepsy. The characteristics and the history of the skin lesions supported the clinical diagnosis of IP in both patients. Clinical evaluation of both mothers revealed that they are mildly affected by IP. The common heterozygote deletion mutation spanning exon 4 to 10 was shown in the index cases' and mothers' DNA samples with IKBKG specific MLPA analysis. IP has clinical variability and therefore, in familial cases, mildly affected parents may not be diagnosed until they have severely affected offspring leading to diagnosis. We will here present four cases from two families with definitive diagnoses supported by clinical and molecular findings.

NVS15

Two New Patients Diagnosed With Trichothiodystrophy Type 1

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Introduction ang Aim: Trichothiodystrophy (TTD); is a rare disorder with mostly autosomal recessive inheritance and characterized by a wide range of clinical findings such as, physical-intellectual retardation, ichthyosis, susceptibility to infections and signs of premature aging in addition to hair abnormalities. Approximately half of the patients' skins are sensitive to sunlight, and in most of these patients biallelic mutations in the ERCC2 (XPD) gene are detected. The estimated incidence of TTD is 1-1.2 per million live births and to date, approximately 200 patients have been identified in the literature, including 44 TTD1 patients associated with mutations in the ERCC2 gene. Here, we aimed to present the clinical findings and molecular analysis results of two different TTD1 patients with pathogenic mutations in the ERCC2 gene.
Patient Reports and Method:
Patient 1: According to the anamnesis of a 10-year-old girl, she had a history of premature birth, growth retardation, mild intellectual disability, ichthyosis, photosensitivity and intermittent neutropenia. Nonconsanguineous parents had a history of son who had ichthyosis, hydrocephalus and epileptic seizures, and he died at the age of two due to frequent infections. In the physical examination of Patient 1, whose anthropometric measurements were below the 3rd centile; wooly, sparse and brittle hair, dysmorphic facial features, crowded teeth, knee flexion contracture, palmoplantar hyperkeratosis, dystrophic nails and ichthyosis in thoracolumbar region with diffuse dry skin findings were noted. Cranial MRI revealed diffuse hypomyelinization and fine corpus callosum.
Patient 2: According to the anamnesis of a 14-year-old boy, he had a history of short stature, intellectual insufficiency, ichthyosis and photosensitivity, and hair loss after a while. Parents with third degree consanguinity had a history of two pregnancies that were lost with unknown etiology in the perinatal period. In the physical examination of Patient 2, whose anthropometric measurements were below the 3rd centile; wooly and brittle hair, dysmorphic facial features, crowded teeth, dystrophic nails and generalized pigmented ichthyosis findings were noted., Myelin pallor in the subcortical white matter was reported on cranial MRI. Both patients underwent whole exome sequencing analysis for molecular genetic diagnosis with a preliminary diagnosis of TTD. Findings and Conclusion: As a result of the analyses, c.1354C>T (p.Gln452Ter) and c.2164C>T (p.Arg722Trp) variants in the ERCC2 gene (NM_000400.3) were found heterozygous in Patient 1. Sanger sequence analysis of the parents revealed that these variants were in a heterozygous state. At the analyses of Patient 2; c.2164C>T (p.Arg722Trp) variant in the ERCC2 gene was detected in homozygous state. The c.2164C> T variant, which was found to be common in both patients, was previously identified as pathogenic in TTD1 patients homozygously in the literature and was associated only with TTD1. The c.1354C> T (p.Gln452Ter), one of the compound heterozygous variants in Patient 1, was identified in the literature as one of the compound heterozygous variants in a patient diagnosed with 'Xeroderma pigmentosum group D (XPD)' which is an allelic disorder of TTD1. In the case of compound heterozygosity, as in our patient, some null allele mutations common to TTD1 and XPD may be found and in this case the second mutant allele determines the clinic. Since the second mutant allele detected in the patient was associated with c.2164C>T TTD1, these results support the TTD1 clinic. Since the clinical diagnosis of Patient 1 is TTD1 which is not precancerous in contrast to XPD, even she had a null mutation previously detected in a patient with XPD, it makes differences in terms of counseling and follow-up. The patients presented here are thought to contribute to the genotype-phenotype correlation of TTD1, a rare disease.

NVS19

Rare Case Report: Localized Proteus Syndrome With Neurological Involvement

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Introduction: Proteus syndrome is a rare syndrome characterized by progressive segmental overgrowth affecting skeletal, skin, adipose tissue and central nervous system. Asymmetric growth is observed in childhood, especially in the extremities. Neurological findings such as convulsions have been reported very rarely. Specific diagnostic criteria have been developed, but the mosaic, somatic, heterozygous pathogenic variant of the AKT1 gene should be demonstrated in the affected tissues for definitive diagnosis. Cases with a genetic mutation that do not fully meet the diagnostic criteria or with limited growth in certain areas of the body are considered to be localized manifestations. Localized Proteus Syndrome with neurological involvement has not been reported in the literature. This rare case emphasizes this association and aims to contribute to the literature.

Case: A 4-year-old male patient with scoliosis, intellectual disability and delay in speech was referred to the Department of Pediatric Genetics. He was a term, small for gestational age infant with a noticeable swelling on forehead. Follow-up imaging revealed plagiocephaly in the calvarium, hyperosteosis at the frontoparietal junction and developmental cortical malformations consistent with perisilvian polymicrogyria in the right frontal lobe. At the age of 2 years, antiepileptic treatment was initiated because of significant multifocal sharp wave activity in the frontotemporal regions on electroencephalogram. On physical examination, he had scoliosis, craniofacial asymmetry, lipomatous mass located in the left alar wing of the nose, lipodermoid lesion in conjunctiva, hyperpigmented areas correlated with Blaschko lines on the face and neck, epidermal nevi, left axillary and inguinal areas hyperpigmented areas. Echocardiogram and hearing test were normal. According to the family's declaration, dysmorphic findings did not progress but scoliosis worsened. Biopsy samples taken from the affected areas demonstrated variable AKT1 mutation and diagnosis of Proteus Syndrome was confirmed.

Discussion: Proteus syndrome is a rare clinical entity with variable clinical features of progressive asymmetric overgrowth and dermatological findings. The pathogenic variant of the AKT1 gene should be demonstrated in the affected tissues for definitive diagnosis due to mosaic involvement, but the absence of mutation in the peripheral blood does not rule out the diagnosis. Typical skin findings include cerebriform connective tissue nevi, which are almost pathognomic for the syndrome. Other findings include epidermal nevi, hyperpigmented nevi on Blaschko lines, hemangiomatous and lipomatous lesions. Significantly increased predisposition to thrombosis is an important cause of morbidity and mortality. Other findings include vascular malformations, growth in visceral organs and susceptibility to tumor development. Benign tumors such as meningiomas and ovarian cystadenomas develop more frequently, but patients should be followed for malignancy. Neurological findings are rarely observed. The coexistence of localized Proteus syndrome and epilepsy in our patient is very rare and has not been reported before. The clinical findings of our patient not fully meeting the criteria and the presence of epilepsy make the differential diagnosis difficult. PTEN hamartoma tumor syndrome, PTEN-associated Cowden syndrome and SOLAMEN syndrome (segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus), CLOVE (S) syndrome (congenital lipomatous asymmetric overgrowth of the trunk, lymphatic, capillary, venous and combined type vascular malformations, epidermal nevus, skeletal and spinal anomalies), Bannayan syndrome and Klippel-Trenaunay syndrome should be considered in differential diagnosis. Treatment is symptomatic and multidisciplinary follow-up is required. Through this case, we emphasize clinical variations of Proteus syndrome, presence of localized syndromes and association of rare neurological manifestations. Early recognition of this rare association maye reduce morbidity and mortality.

NVS20

Griscelli Syndrome; Case Series and Literature Review

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Griscelli syndrome (GS) is a rare autosomal recessive genodermatosis characterized by hypopigmented skin and silvery-grey hair due to melanosome transport defect. Large melanin pigment aggregation in hair shaft under light microscopy is pathognomic for the disease. It is divided into 3 subtypes based on clinical findings and genetic aetiology; type 1 is caused by MYO5A mutations and involves neurological finding along with hypopigmented hair and skin. Type 2 is due to RAB27A mutations and patients have immunological impairment. Type 3 is related to the MLPH gene and characterized by isolated hair and skin findings. Type 2 is the most common of the three subtypes. Differential diagnosis includes Hermansky-Pudlak (HPS) and Chediak-Higashi syndrome (CHS) with silvery-grey hair and immunological findings.

In this study, we present clinical and molecular findings of 10 GS patients evaluated in Medical Genetics Department of İstanbul Medical Faculty, between 1998 and 2014. 6 cases had GS2 and 4 had GS1. Silvery-grey hair and melanin pigment aggregation were observed in all patients. As aspected, generalized hypopigmentation of skin was more common in GS2 (5/6), while hypo/hyperpigmented spots were detected in GS1 (2/4) which were not previously reported. Immunological impairment including haemophagocytic lymphohistiocytosis (5/6), pyogenic infections (6/6), hepatosplenomegaly (6/6), thrombocytopenia (4/6), anaemia (5/6), neutropenia (6/6) were present in most of the GS2 patients, but also in two of GS1 group as recurrent pyogenic infections and low immunoglobulin levels. Neurological involvement presented in GS1 with severe neuromotor retardation, intractable epilepsy (2/4), hydrocephaly, cerebral and cerebellar atrophy, delayed myelination and occipital sharp wave activity in EEG. Notably, GS2 patients displayed hypotonia (2/6), seizures (3/6), NMR (2/6) and CNS findings including cavum septum pellucidum, subependymal calcified multiple lesions. As GS2 is lethal in early childhood, 5 of the patients in this group died at an average age of 10 months.

Molecular analyses were performed in 9 patients. Five GS2 patients had homozygous known pathogenic variants in RAB27A including c.51delCT (2/5), exon 3-4 deletion, c.510delAAGCC and c.240-2A>C, while one patient had no mutations in this gene. In GS1 group, MYO5A variants were detected in two patients including c. [2893C> T];[c.4875delT]/p.[R965*];[I1625Mfs*17] and homozygous c.4830C>A (p.Y1610*) and linkage analysis revealed informative result in one patient.

Griscelli syndrome is usually lethal in early childhood. It is more common in our country due to the high rate of consanguineous marriages. As bone marrow transplantation is the only curative treatment and early diagnosis is crucial to increase the survival rate, it is important to raise awareness of geneticists, paediatricians, neurologists and dermatologists about the disease.

Keywords: Griscelli syndrome, RAB27A, MYO5A, MLPH, Chediak-Higashi, Hermansky-Pudlak

NVS21

Johnson Blizzard Syndrome

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Johanson-Blizzard syndrome (JBS) is a rare autosomal recessive disorder described by Johanson and Blizzard in 1971. This syndrome characterize with aplasia or hypoplasia of alae nasi, exocrine pancreatic insufficiency, teeth defects, midline dermal defects, growth retardation, mental retardation, hypothyroidism, congenital heart defects, pancreatic insufficiency, atresia of anus and congenital deafness. İt was shown to result from mutations of the UBR1 gene located on chromosome 15q15-21. In this case report, we presented a 3,5 months old girl who had been brought the complaints of failure to throw and who was diagnosed as JBS due to presence of hypoplasia of alae nasi, growth retardation, aplasia cutis.A novel pathogenic homozyzygous frameshift variant c.4027_4028del (p.Leu1343Valfs*7) in UBR1 (NM_174916.2) gene was detected and confirmed by sanger sequencing. Segregation within the family showed that parents were heterozygous carriers.

NVS22

Identification of a Second Gene (AP1B1) Causing Mednik (Mental Retardation, Enteropathy, Deafness, Peripheral Neuropathy, Ichthyosis, Keratodermia) Syndrome

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MEDNIK syndrome (Mental retardation, Enteropathy, Deafness, Peripheral Neuropathy, Ichthyosis, Keratodermia) is a very rare autosomal recessive disorder caused by AP1S1 gene mutation. The aim of this study is to report a second gene that could cause the disease in a Turkish patient with clinically diagnosed MEDNIK syndrome. Genetic consultation for a 11- month-old girl due to ichthyosis and developmental delay revealed short stature, growth retardation, celiac disease, deafness, ichthyosis, keratodermia and hypothyroidism. MEDNIK syndrome was diagnosed clinically but AP1S1 gene analysis was found to be normal. Whole exome sequencing analysis revealed a new biallelic missense mutation in the AP1B1 gene encoding the large subunit (β1) of the adapter protein 1 complex (AP1B1:NM_001127:exon6:c.T668C:p.L223P). This variant was confirmed by Sanger sequencing; biallelic mutation in children and heterozygous mutation in both parents were shown. There are 5 different types of adapter proteins (AP-1 to AP-5) that act as cargo proteins associated with the Golgi complex. To this date, the AP-4 group AP4B1, AP4E1, AP4M1 and AP4S1 gene biallelic mutations have been associated with spastic paraplegia. AP-1 consists of 2 large (γ1-2 / β1), 1 medium (μ1 / μ2) and 1 small (σ1A / σ1B / σ1C) subunits, and each isomer is encoded by a different gene. The AP-1 protein is also involved in regulating copper pumps (ATP7A and ATP7B) involved in intercellular traffic and has been shown to cause copper metabolism disorder. It is known that only AP1S1 gene mutation encoding σ1A unit of AP-1 protein, cause MEDNIK syndrome. In this study, a mutation was identified in AP1B1, a new gene that could cause MEDNIK syndrome

NVS23

Novel Homozygous Missense MSMO1 Mutation in Two Patients With SC4MOL Deficiency

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Introduction: Sterol-C4-methyl oxidase deficiency was recently described as an autosomal recessive condition caused by the mutations in the MSMO1 gene (also known as SC4MOL). Main features of the disease are psoriasiform dermatitis, microcephaly, and developmental delay. Here, we describe two siblings with psychomotor retardation, erythematous and ichthyotic skin lesions, and ophthalmological problems. They were treated for suspected psoriasis and ichthyosis by Dermatology Department with minimal response. Both of them had nystagmus, optic hypoplasia, myopia, strabismus, severe intellectual disability and motor delay. Materials and Methods: Because of the consanguinity present, we followed a model of rare autosomal recessive inheritance by focusing on homozygous predicted protein-altering substitutions and indels that are shared by both siblings, with a minor allele frequency of less than 0.5%. Results: This analysis revealed a homozygous missense variant (c.81A>C; p.Asn27Thr) in the MSMO1 gene, with a CADD score of 29. Segregation analysis of the c.81A>C substitution in all available members of the pedigree, including the two unaffected parents, confirmed the recessive inheritance of the mutation. Discussion: SC4MOL catalyzes demethylation of C4-methylsterols, which are meiosis activating sterols (MASs), in the cholesterol synthesis pathway. Accumulation of MASs was shown to cause hyperproliferation of patient fibroblasts and human transformed lymphoblasts, and to modify immune phenotype. Blockage of MAS accumulation and supplementation of the end product cholesterol is described as the main goal of the therapy. Accordingly, the siblings were treated with oral and topical statin-cholesterol combination and cholesterol rich diet with a better response in 2 months.

Oral Presentation Abstracts

SB5

Deficiency of Adenosine Deaminase 2 Presenting as Livedo Rasemosa

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An 14-year-old girl consultated to our department with violaceous, erythematous, irregular netlike persistant maculae, that first appeared 2 years before at the back of the hands, lower arms, legs and feet. She had raynaud, arthralgia, and sometimes headache and abdominal pain. Her growth and neuromotor development were normal. Her aunt had cerebrovascular accident at the age of 34. Screening for autoantibody profiles [anti-nuclear antibody (ANA), anti double-stranded DNA (anti-dsDNA), anti-neutrophil cytoplasmic antibodies (ANCAs), antiphospholipid antibodies], cryoglobulins, or deviations in the coagulation system found no abnormalities. Skin biopsy revealed as fibrin thrombosis of some capillary and arteriol vessels in the dermis. Based on the clinic and histopathological findings, skin lesions diagnosed as livedo racemosa. As livedo racemosa can be a sign of systemic vascular disorder, and she had arthralgia, raynaud and an early stroke story in her family, the differantial diagnoses consisted of systemic lupus erythematosus, PAN, Sneddon syndrome and deficiency of adenosine deaminase 2 (DADA2). Pediatric Rheumatology Clinic performed the genetic test and revealed the homozygot mutation in the CERC1 (ADA2) gene. The genetic data in conjunction with the clinical phenotype confirmed a diagnosis of DADA2 for this patient. The patient is currently being treated with tumor necrosis factor α (TNF-α) inhibitör Etanercept. DADA2 has a wide spectrum of clinical manifestations that can range from fatal vasculopathies to a more indolent cutaneous-limited disease. The most common clinical characteristics include PAN, fever, livedo racemosa, lacunar strokes, hepatosplenomegaly with portal hypertension, Sneddon syndrome, and B-cell immunodeficiency. These patients may be admitted to the dermatology clinic first with only cutaneous manifestation such as livedo racemosa. Earlier diagnosis of DADA2 can lead to prevention of irreversible damage such as stroke. So, pediatric dermatologist should think and consultate these patients to the pediatric rheumatology clinic for further evaluation as soon as possible.

SB7

A Rare Mutation in The Alox12b Gene In a Newborn With Autosomal Recessive Congenital Ichthyosis

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Ichthyosiform dermatoses are genetically inherited diseases characterized by crust deposition covering almost the entire surface of the skin. The clinical spectrum of the disease is quite wide. Patients may have extensive skin dryness, skin peeling and flaking, and erythroderma. The disease is divided into two groups as congenital and acquired. Congenital ichthyosis forms include classic lamellar ichthyosis, nonbullous congenital ichthyosiform erythroderma, harlequin ichthyosis. Congenital ichthyosis is autosomal recessive and occurs at a frequency of 200,000 births. The cases are born surrounded by a collodion membrane. Diagnosis is based on clinical findings and skin biopsy and molecular analysis. In this case report, we aimed to discuss the phenotypic findings of a newborn with a rare mutation in the ALOX12B gene which was diagnosed as autosomal recessive congenital ichthyosis type 2.

SB8

Genomic Changes Detected by Hereditary Cancer Panel in Maign Melanoma Patients

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Skin cancers include basal cell carcinoma, squamous cell carcinoma, and malign melanoma. Malignant melanoma rarely occurs in the mouth, intestinal tract or eye. There is also a subgroup of skin cancers associated with hereditary cancer syndromes. Familial atypical multiple mole-melanoma syndrome is caused by mutations in the CDKN2A gene, which is also detected in 40% of familial malignant melanoma cases. Mutations of the CDK4 gene also cause familial melanoma. Other hereditary cancer syndromes that increase the risk of melanoma include BAP1-associated tumor susceptibility syndrome, hereditary breast-ovarian cancer syndrome (BRCA1/BRCA2), Li-Fraumeni syndrome (TP53), and Cowden syndrome (PTEN). All five patients who were included in our study were selected from patients with unrelated, early-age diagnosed and positive family history. In the next generation sequencing (NGS), the Qiagen wide cancer panel was used. Sequencing was performed on the NGS system of llumina MiSeq. QIAGEN Clinical Insight (QCI™) program was used for data analysis. No reportable variants were detected in two patients. In three patients, PMS1:c.1271 A>T (NM_000534.4), PALB2:c.833_834 delTAinsAT (NM_024675.3), RINT1:c.2149 T>G (NM_021930.6), CHEK2:c.1427 C>T (NM_145862.2) and PMS2:c.187 G>A (NM_000535.7) variants of uncertain significance were detected. These genes are associated with melanoma in the literature. In order to clarify the effect of these, functional studies are needed. In conclusion, it is crucial to perform the hereditary cancer panel from index cases in families with high cancer incidance and molecular background has not been elucidated, for preventive health policies. In addition, the identification of common hereditary cancer genes will guide the personalized therapy planning.

SB9

Pachyonychia Congenita: A Rare Case Report

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Introduction: Pachyonychia congenita is a rare genodermatosis characterized by nail dystrophy, palmoplantar keratoderma, palmoplantar hyperhydrosis, pilosebaceous cysts, oral leukoceratosis and follicular keratosis. It is usually inherited as an autosomal dominant manner. Disease symptoms can be exacerbated by high temperature and humidity. The disease is divided into four clinical subgroups due to mutations in the KRT6A, KRT6B, KRT6C, KRT16 and KRT17 keratin genes. There are variations between the clinical findings depending on the gene affected.
Case: In this study, a case with pilosebaceous cysts, hydradenitis suppurativa, nail dystrophy and plantar keratoderma will be presented. A large number of individuals with similar clinical features as proband were noted in the patient's pedigree. Whole gene analysis of nine genes (KRT6A, KRT6B, KRT6C, KRT16, KRT17, GJB6, AAGAB, DSG1, TRPV3) was performed in "Pachyonychia Congenita Project" and heterozygous c.263T>C (p.Met88Thr) variant was detected.
Conclusion: Keratin 17 protein is produced in nails, hair follicles, the skin on the palms of the hands and soles of the feet and also sebaceous glands. Mutations in the KRT17 gene are associated with Pachyonychia congenita type-2 and Steatocystoma multiplex. The p.Met88Thr mutation we identified in our case, and was previously mentioned in the literatüre, is in the helical initiation domain of the protein. This is an evolutionarily conserved region and the mutation disrupts intermediate filament formation. After three months of anti-TNF treatment, there was a significant improvement in hydraadenitis suppurativa complaints in accordance with the literature; on the other hand, plantar keratoderma, pilosebaceous cyst and nail dystrophy were not regressed.

SB10

Socs Gene Polymorphism in Vitiligo Patients

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Vitiligo is a chronic disease characterized by depigmented macules, and patches due to melanocyte destruction. Genetic and utoimmune hypothesis is suggested. The suppressors of cytokine signaling (SOCS) proteins, especially SOCS1, and SOCS3, involved in the pathogenesis of autoimmune diseases play a critical role in the immune hemostasis. We think that the SOCS1, and SOCS3 gene polymorphisms that have not been studied in vitiligo may be involved in the pathogenesis of vitiligo by decreasing the negative control of JAK-STAT signaling pathway, and increasing the IFN sensitivity, and Th1 response. In this study, we aimed to investigate the role of SOCS1, and SOCS3 gene polymorphisms in susceptibility of the pathogenesis of vitiligo. In this study, the association of SOCS1 rs33989964, SOCS3 rs4969168, and rs4969170 polymorphisms with vitiligo development, and clinical features were evaluated in 100 patients who were nonsegmental vitiligo, and 100 healthy controls. Volunteers without autoimmune disease except vitiligo and first or second degree relatives without vitiligo disease were included in the study. TaqMan probe and polymerase chain reaction were used for genotyping and IBM SPSS2 3.0 program was used for statistical analysis. No statistically significant relationship was found between all three polymorphisms and vitiligo. SOCS1 rs33989964 del/del genotype in progressive patients (p: 0.025); SOCS3 rs4969168 AA genotype in patients with spontaneous vitiligo, and accompanied by the Koebner's phenomenon (p:0,031, p:0,049); SOCS3 rs4969170 AA genotype in patients with poliosis (p:0,024) were statistically significant. SOCS3 rs4969168 A allele frequency in patients with familial autoimmunity (p:0.036); in patients with poliozis, and leukotrichia, the SOCS3 rs4969170 A allele frequency was significantly higher (p:0.006, p:0.048). Although our case-controlled study partially contributes to the pathogenesis of vitiligo, there is a need for studies investigating polymorphisms and gene expressions together and testing SOCS mimetic agents in treatment.

SB11

Klippel-Trenaunay-Weber Syndrome: A Rare Case Presentation

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Introduction: PROS (PIK3CA-related overgrowth syndrome) is a spectrum including syndromes with overlapping findings such as CLOVES (Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/spinal), FAH (Fibroadipous hyperplasia) and MCAP (Megalencephaly-capillary malformation), caused by somatic mutations in PIK3CA gene. Recently, mutations in PIK3CA gene were also detected in Klippel-Trenaunay-Weber syndrome (KTS) and it was also added to the group of PROS. KTS is characterized by a triad of cutaneous capillary hemangioma, asymmetric bone and soft tissue growth, venous and lymphatic malformation. Tissue hypertrophy is usually observed in lower extremities as unilaterally.
Case presentation: In this study, blood, saliva samples and biopsy of the affected skin were obtained from a 16-year-old male patient with clinical diagnosis of PROS with unilateral hypertrophy of lower extremities, hyperpigmentation of skin, unilateral port-wine stain, macrodactyly, varicose dilatations in right leg, edema, and hemangiomas in back. Next-generation-sequencing analysis revealed a somatic heterozygous NM_006218.3:c.2176G>A (p.Glu726Lys) mutation in PIK3CA gene in skin biopsy sample but absent in other tissues.
Conclusion: The PIK3CA gene is a proto-oncogene that is commonly mutated in human somatic cancers. The timing and tissue specificity of postzygotic mutations in this gene are responsible for the phenotypic variability. The mutation in proband has been previously reported in MCAP patients. Congenital megalencephaly is observed in 90% of MCAP patients or it develops in the first year of life. Our patient was evaluated as KTS because his neurological examination and brain MRI were normal. In this study, p.Glu726Lys mutation in the PIK3CA gene is reported for the first time in clinically compatible KTS cases.

SB12

Determination of Functional Effect of Novel Runx2 Variants by Molecular Prediction Tools

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The RUNX2 gene encodes a member of the family of transcription factors - RUNX, which regulates amelogenesis and osteogenesis and also plays a role in osteoblast differentiation. The RUNX2 gene has the ATP binding region, glutamine / alanine rich domain (QA), Runt homologous domain (RHD) region, proline-serine-threonine rich region (PST) and nuclear matrix target signal (NMTS) region. The main part that binds primarily to the regions in the target genes and enables CBFβ heterodimerization is the Runt domain between amino acids 101 and 209 and is evolutionarily conserved. There are other genes that the Runx2 protein regulates with its transactivation and transrepression properties. Heterozygous pathogenic variants in the RUNX2 gene have been associated with Kleidocranial Dysplasia (CCD, MIM # 119600), a rare syndrome affecting 1/1 000 000 newborns. In addition to short stature, facial dysmorphism, cranial and skeletal anomalies, the main clinical findings are related to bones and teeth; hypoplastic / aplastic clavicle, such as simple tooth anomalies. In our study with 52 cases from 31 families, 9 novel pathogenic gene variants were detected in addition to 8 different mutations associated with CCD. The possible molecular effects of these variants were evaluated in bioinformatics databases and considering the functional regions and evolutionary conservation of RUNX2 gene. In addition, phenotype - genotype correlation and radiological findings were compared for these variants.

SB13

A Homozygous Frameshift Mutation of Cathepsin C Gene in Two Turkish Siblings With Papillon-Lefèvre Syndrome

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INTRODUCTION AND AIM: Papillion-Lefevre syndrome (PALS, OMIM:#245000) is an autosomal recessive disorder characterized by palmoplantar keratoderma, periodontitis, and premature loss of dentition. PALS is caused by homozygous or compound heterozygous mutation in the cathepsin C gene. The aim of this study is to report a further case of PALS having a homozygous frameshift mutation in CTSC gene with clinical findings.
METHOD: CTSC gene all exons and exon intron boundaries were sequenced via Sanger sequencing.
RESULTS: Two siblings (13 and 20 year-old girls) referred to Erzurum Region Training and Research Hospital Medical Genetics Clinic because of palmoplantar hyperkeratosis and premature tooth loss. They were born to consangiounus parents following an uneventful pregnancy. In physical examination, they had hyperkeratosis of palms and soles and premature tooth loss. They were diagnosed as PALS with these clinical findings. We found a homozygous 1bp deletion (c.1047delA, p.Gly350Vfs*10), it causes a shift in reading frame of gene resulting a premature stop codon, in CTSC gene. The mutation was reported previously as a pathogenic in Clinvar and HGMD. Their healthy parents are heterozygous for this mutation.
CONCLUSION: PALS is a rare ectodermal dysplasia characterized by palmoplantar keratoderma associated with early- onset periodontitis. The prevalence is estimated between 1/250,000 and 1/1,000,000 individuals. Two siblings with typical clinical findings of PALS syndrome are presented to contribute to the literature.

SB14

Two Families With Autosomal Recessive Hypohydrotic Ectodermal Dysplasia Associated With Edar

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Hypohidrotic ectodermal dysplasia(HED) is a rare genetically heterogeneous group of disorder characterized by impaired development of the hair, teeth, sweat glands and nail. HED is predominantly inherited in a X-linked which due to mutations in the EDA1 gene. Whereas, autosomal recessive and autosomal dominant forms are caused by EDAR, EDARADD and WNT10A genes. We present 3 patients from 2 family have an autosomal recessive form of HED in different missense mutations of EDAR gene in this study. First case is a 2 month-old male, who pesented with anhidrosis, lack of tear, sparse hair/eyelashes/eyebrows and anadontia. The parents originate from near villages. On physical examination, the patient's body weight was 5,5 kg(25-50p), height was 60 cm(50-75p) head circumference was 39 cm(25.p). Thin and hypoplastic skin, periorbital wrinkling, fine-hypochromic-decereased hair/eyelashes/eyebrows, prominent lips and micrognathia were noted. Mutational analysis of the EDAR gene demonstrated homozygous p.Cys148Arg (c.442T>C) mutation. The other patients from second family are 22 month-old male and 5 year-old male siblings, the products of a consanguineous marriage between 1,5. cousins. They presented with anhidrosis, very dry skin, sparse hair/eyelashes/eyebrows, microdontia/oligodontia and atopic dermatitis. These brothers had physical examination findings as similar as first patient and their nails are normal. Severe teeth deficiency were detected on lateral craniograms. In EDAR gene, homozygous c.314G>A missense mutation is detected in siblings and they were diagnosed as HED. Pathogenic mutations in EDA, EDAR and EDARADD genes result in indistinguishable phenotypes. On the contrary, mutations in the WNT10A gene exhibits a highly variable phenotype.

SB17

Pseudoxanthoma Elasticum and Familial Inheritance

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Pseudoxanthoma elasticum is a rare degenerative disease of elastic tissue involving the skin, eyes and blood vessels. Although the majority of cases are autosomal dominant and autosomal recessive, the disease may also occur sporadically. Patients have cutaneous, ocular and cardiovascular symptoms. Skin changes usually become prominent in adulthood, rarely in childhood. Pathogenic variations in the ABCC6 (MRP6) gene have been reported to cause PXE. Our case is a 12-year-old boy. He was born on the 6th pregnancy of a married couple of 32 years. He's the fourth and last child in the family. Parents are second degree relatives. Our patient was born with normal spontaneous vaginal route (NSVY) at term. In 2017, they applied to dermatology because there were blisters in the skin tissue on the neck and neck. Angioid streaks were detected in both eyes in the left eye due to visual loss. The patient was referred to the genetic outpatient clinic for ABCC 6 gene analysis with suspected pseudoxanthoma elasticum. After preliminary evaluation and family history of the patient, multiplex ligation-related probe amplification (MLPA) method was decided for ABCC 6 gene analysis. Today, 4200 different ABCC6 mutations have been identified. These are mainly located at the 3'-end of ABCC6 between exons 24-30. SALSA p092B kit was used for analysis. This kit contains 23 probes corresponding to ABCC6 exons 2, 4, 5, 7–15, 17, 18, 21-28 and 30 and 12 control probes for quality control. Since the P092B kit did not have probes for ABCC6 exons 1, 3, 6, 16, 19, 20, 29 and 31, ABCC1 was included in the study because ABCC1 was close to ABCC6 (6.5 kb telomeric). In conclusion, homozygous deletion of ABCC 6 was detected in our patient. We aimed to present the clinical and genomic findings of the case.

SB19

Very Rare Syndromes With Interesting Dermatological Findings

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In this study, four very rare genetic syndromes with interesting dermatological findings will be presented.
Case 1: 3 years 10 months old girl referred to our clinic due to ichthyosis starting from birth, hair loss and fragility, joint restriction, growth retardation, and neuromotor developmental delay. Microscopic examination of her hair sample revealed tricothiodystrophy. On radiological examination, osteosclerosis was detected and tricothiodystrophy type 1 with central osteosclerosis and dysmyelinization was diagnosed. The tests revealed a compound heterozygous mutation in the ERCC2 gene involved in DNA repair mechanism.
Case 2: A 3-year and 8 months old girl was referred to our clinic due to widespread erythematous rash and poikiloderma, short stature, genitourinary anomaly, recurrent fracture history and mild mental disability. In her family history, it was learned that her sister had similar skin findings. Rothmund-Thomson syndrome was considered clinically. Biallelic mutation was detected in RECQL4 gene which is responsible for cell division and repair.
Case 3: 2.5-year-old girl admitted due to sparse hair and eyebrows, microphthalmia, extremity anomalies and mental deficiency. Molecular tests revealed de novo heterozygous mutation in PORCN gene in the Wnt signaling pathway and confirmed the diagnosis of Gorlin Goltz syndrome.
Case 4: Recurrent joint dislocations, scoliosis, wide open anterior fontanel, short stature, sparse hair and eyebrow was present in a girl followed since 1 months of age .Homozygous frameshift mutation was detected in COL27A1 gene in whole exome sequencing analysis. In conclusion, dermatological findings are an important in the diagnosis of genetic diseases. Limited information is available for many very rare diseases and it may be difficult to diagnose by clinicians. Recognition of the specific findings accompanying the disease facilitates the recognition of these diseases. In all of our cases, molecular diagnosis was confirmed by whole exome sequencing analysis. In very rare diseases with atypical findings, the whole exome sequencing analysis is of great importance in making the definitive diagnosis.

SB21

Ectodermal Dysplasia / Skin Fragility Syndrome

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First ectodermal dysplasia-skin fragility (EDSF) syndrome case was described by Mcgrath in 1997 (OMIM#604536). It is a rare, autosomal recessive genodermatosis, which results from loss-of-function mutations in plakophilin 1 (PKP1) gene resulting in poorly formed desmosomes and loss of desmosomal and epidermal integrity. It is now considered as a specific suprabasal form of epidermolysis bullosa simplex.
In this report we describe a 20 years old male was born from second degree consanguineous marriage. He admitted to outpatient department of medical genetics as undiagnosed case suffered from painful perioral fissures, multiple erosions over the skin, easy blistering with minor trauma, palmoplantar hyperkeratosis with fissuring, nail dystrophy, short, sparse and easily pluckable woolly scalp hair, pruritus, hypohidrosis; complaints worsening in summer. He has short stature, normal intelligence and echocardiography. There was no personal history suggestive of lowered immunity.
We made whole exome sequencing analysis using Illumina HiSeq sequencer with Agilent SureSelect Human All Exon V5 kit and DNAnexus bioinformatics platform. We found PKP1 gene NM_000299.3:p.Arg693*/c.2077C>T novel nonsense mutation as homozygous state in patient and heterozygous state in healthy parents. Sanger DNA sequencing method confirmation was concordant with NGS. Varsome pathogenicity assessment platform interpretation is 'Pathogenic' (https://varsome.com/variant/hg19/NM_000299.3%3Ac.2077C%3ET).
To clarify undiagnosed rare disease cases exome analysis method is effective. When coexisting ectodermal dysplasia and easy skin erosions/bilistering should come to mind Ectodermal dysplasia/skin fragility syndrome as differential diagnosis.

SB24

Malignant Melanoma Coexisting With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Case of Collision Tumor

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Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is the most common lymphoid malignancy in adults which is associated with a good prognosis. It has been reported that the risk of developing a subsequent malignant melanoma or other skin cancer is remarkably increased in these patients. In cases with melanoma, lymphoproliferative disorders are usually detected incidentally during sentinel lymph node biopsy. In our case, malignant melanoma and CLL infiltration were present in the skin as a collision tumor and these two tumors were also observed as intermixed with each other in a metastatic focus. An 88-year-old male patient presented with a mass on the nasal root. He had a suspected history of CLL 25 years ago. Histopathological examination of the skin biopsy revealed an atypical spindle cell proliferation in the background of collagenous stroma that ulcerated the epidermis and infiltrated the dermis in full-thickness. Accompanying this lesion, there was a monotonous and small-sized neoplastic lymphoid cell infiltration concentrated in focal areas. In the immunohistochemical studies, spindle cells were diffusely positive for S100, focally positive for Melan-A and HMB45; neoplastic lymphoid cells were positive for CD20, CD5, and Bcl2 and negative for CD3, Bcl-6, CD10, and Cyclin D1. Histopathological and immunohistochemical findings were consistent with diagnoses of "spindle cell/desmoplastic malignant melanoma" and "CLL infiltration". Computed tomography revealed metastases in multiple lymph nodes in the abdominal and mediastinal cavities as well as in the liver. Interestingly, these two tumors with the same morphological features were detected in the liver biopsy. Molecular testing for BRAF mutation aiming at targeted therapy revealed no mutation. Due to the age and advanced stage of the disease, no other treatments were administered. In cases with CLL, melanoma development can be detected in early-stage by active surveillance. In CLL patients with metastatic melanoma, targeted kinase inhibitors and immune checkpoint inhibitors have been reported to be beneficial and tolerable.

SB27

The Clinical and Molecular Spectrum of Xeroderma Pigmentosum

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AIM: Xeroderma pigmentosum (XP) is a rare autosomal ressesive disorder. Its clinical manifestations include sun sensitivity, marked freckle-like pigmentation of the face, sunlight-induced ocular involvement such as photophobia and keratitis, and greatly increased risk of sunlight-induced cutaneous neoplasm. The prevalence of XP is approximately 2.3 per million in Western Europe. Xeroderma pigmentosum results from defects in several genes which play a role in nucleotide excision repair pathway. In this sudy, we aimed to evaluate the clinical features and molecular analysis results of five patients; while investige the phenotype and molecular spectrum of the disorder.
METHOD: Five XP patients from three different families both clinically and moleculary diagnosed, were enrolled to the study. Due to the genetic heterogenity of XP, a gene panel (TruSight Inherited Disease Sequencing Panel) was performed using a next generation sequencing platform (Illumina MiSeq). Patients histories including demographic, clinical and laboratory findings were obtained from hospital records.
RESULTS: Two of the patients were female and three were male. All displayed the clinical features of XP such as sun sensitivity and freckle like pigmentation and photophobia. Two patients had diagnosed with squamous cell carcinoma. Three different homozygous mutations were identified; two Two were nonsense (DDB2: c.726_729delAAG; c.730_733delAAAG), one was frameshift (XPC: c.2126_2129delGCTT). The c.2126_2129GCTT mutation in the XPC gene had not previously been reported in any public database.
CONCLUCION: By defining a novel mutation, this study contributes to molecular spectrum of XP, while providing further insight for genetic counselling. This study also highlights the importance of early diagnosis and follow up of the XP patients, particularly for malignancy risk in the early age.

SB28

The Importance Of Clinical Genetic Evaluation And Genetic Counseling: The Simultaneous Occurence Of Both Harlequin Type Congenital Ichthyosis And Sickle Cell Disease For Prenatal Diagnosis

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Congenital ichthyosis is a group of hereditary diseases characterized clinically by dry, thick, skin structure and histopathologically by hyperkeratosis. Mutations in the ABCA12 gene; which encode ABCA12 protein involved in lipid transport in the skin barrier, are important in the etiology of Harlequin ichthyosis, the most serious form of congenital ichthyosis.
Sickle cell anemia is a hemoglobin variant disease that occurs when the triple codon that encodes amino acid 6 in the HBB gene changes. Inherited diseases with a broad spectrum ranging from hemoglobinopathies to rare diseases affect approximately 10% of the population.
The anamnesis of a pregnant patient was taken, who was referred from the outpatient clinic of Gynecolog to Medical Genetics Department for prenatal diagnosis of sickle cell anemia and genetic counseling. Upon learning that the previous child of the couple died at the age of 35 days, clinical genetic evaluation was performed by collecting photographs and records of this baby, and Harlequin Type Congenital Ichthyosis or Epidermolysis Bullosa Dystrophica was considered as a preliminary diagnosis. Molecular analysis of ABCA12 and COL7A1 genes were performed and both parents were detected as heterozygous for the mutation (p.R2482 *; c.7444C> T) which is related to Harlequin type congenital ichthyosis. In the 11th week of pregnancy, the chorionic villus specimen was examined for mutations in the parents and it was determined that the fetus was heterozygous for the ABCA1 gene mutation but homozygous for sickle cell anemia.
Our country is quite heterogeneous genetically. Therefore the families should be evaluated in terms of different prenatal diagnosis indications, It is important in terms of public health to make clinical genetic evaluations and to provide genetic counseling in this direction.

SB28

The Importance of Clinical Genetic Evaluation and Genetic Counseling: The Simultaneous Occurence of Both Harlequin Type Congenital Ichthyosis and Sickle Cell Disease For Prenatal Diagnosis

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Congenital ichthyosis is a group of hereditary diseases characterized clinically by dry, thick, skin structure and histopathologically by hyperkeratosis. Mutations in the ABCA12 gene; which encode ABCA12 protein involved in lipid transport in the skin barrier, are important in the etiology of Harlequin ichthyosis, the most serious form of congenital ichthyosis.
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Our country is quite heterogeneous genetically. Therefore the families should be evaluated in terms of different prenatal diagnosis indications, It is important in terms of public health to make clinical genetic evaluations and to provide genetic counseling in this direction.

SB29

Autusomal Recessive Dystrophic Epidermolysis Bullosa: A Patient With a Deletion In COL7A1 Gene

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Introduction Dystrophic epidermolysis bullosa (DEB) is an ultrarare genetic disorder caused by mutations in COL7A1 gene, encoding collagen VII, it affects skin, nails and mucosal tissues. Autosomal recessive dystrophic epidermolysis bullosa (RDEB) may begin in neonatal period and is characterized by recurrent blistering of the traumatized area of the skin. There have been 581 COL7A1 mutations reported to date. Gross deletions are only responsible for a very small percent. Here we present a patient with RDEB, carrying a homozygous intragenic large deletion in the COL7A1 gene. Clinical Presentation A twelve year old patient was referred to our department with clinical diagnosis of epidermolysis bullosa. She had been diagnosed in neonatal period following blisterings and lesions beginning soon after birth. At referral, she had wounds and bullosas all over the body predominantly localised at hands and feet with pseudosyndactyly appearance of the hands due to scarring. She was born to consanguenious parents. The family history revealed a sibling with similar clinical findings who had died at 9 months old. Results Her family expressed the wiiliginance to have a further child. Due to genetic heterogenity of the disease WES was performed. There was a homozygous intragenic deletion in the chromosomal region of Chr3:48624405-48628249. It involved exon 13-24 of the COL7A1 gene. This mutation has been classified as “Pathogenic” based on ACMG-2015 classification. To date only one other patient with a homozygous deletion, and similar break points has been reported in the literature.

SB30

Clinical and Molecular Spectrum of Tuberous Sclerosis Complex Patients: Identifıcation of Fıve Novel Mutations

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Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutenous syndrome. It results from mutations in either TSC1, at 9q34, or TSC2, at 16p13.3. Skin lesions such as hypomelanotic macules, facial angiofibromas, shagreen patches, and ungual fibromas are frequently seen in these patients. Herein, we report molecular analysis results and phenotype-genotype correlations in 17 TSC patients. Eighteen patients clinically diagnosed as TSC were referred to our department for molecular analysis. TSC1 and TSC2 moleculasr analysis was performed on a next generation sequencing platform (Illumina NextSeq 500). Variant interpretation was done in accordance with American College of Medical Genetics 2015 recommendations. Sequencing failed to detect a mutation in 4 patients. On one of these patients, Multiplex ligation-dependent probe amplification (MLPA®) was performed A wide spectrum of phenotypic features was noted throughout the study group. Dermatological findings were observed in all patients. Five patients carried a heterozygous mutation in TSC1, while the remaining eight carried mutations in TSC2. Five novel mutations (one in TSC1, four in TSC2) were defined. A large deletion in the TSC1 gene was detected in one patient. In this study, in addition to the five novel mutations reported herein the spectrum of TSC1 and TSC2 gene mutations has been.

SB32

Hermasky-Pudlak Syndrome: A Case Report

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Introduction: Hermansky-Pudlak syndrome (HPS) is a genetic disorder characterized by oculocutaneous albinism, bleeding diathesis and visceral involvement such as granulomatous colitis and pulmonary fibrosis. Worldwide prevalence of disorder is known as 1-9/1000000, though in Puerto-Rico known as 1/1800. This syndrome is caused by different mutations in ten genes (HPS1, HPS3, HPS4, HPS5, HPS6, AP3B1, AP3D1, BLOC1S3, BLOC1S6, DTNBP1). Protein products of these genes take part in protein complexes (AP-3, BLOC-1, BLOC-2 and BLOC-3) functioning in intracellular vesicular formation, protein trafficking and biogenesis of lysosome-related organelles. In HPS cases, aberrant formation of melanosomes causes oculocutaneous albinism and absence of platelet-dense granules causes bleeding diathesis.

Case: Here, we present a 33-year-old woman with oculocutaneous albinism and nystagmus who was referred from gastroenterology department where she was followed for granulomatous colitis for two years. It was learned that she had continuous bleedings in her previous operations and had been treated for colitis. She had regular menstrual cycles. Her parents were fourth degree consanguinity and known as healthy. She had 32-year-old sister was followed up for colitis, nystagmus and albinism; 22-year-old brother was followed up for albinism and bleeding disorder; 27-year-old healthy sister. When she had admitted to our department she had 6-year-old healthy daughter and pregnancy. In her physical examination, oculocutaneous albinism, bilateral horizontal nystagmus and hypopigmented hair and skin were detected.

Conclusion: In genetic analysis of patient, c.1189delC; p.GlnSerfs*2 mutation in HPS1 gene was detected. The association of this mutation with the disease has been reported previously, causing preterm termination in HPS1 protein. Deficiency of HPS1 and HPS4 proteins forming BLOC3 complex cause severe form of disease presented with oculocutaneous disease, bleeding disorder, pulmonary fibrosis, granulomatous colitis.

Note: The Hermansky-Pudlak syndrome genetic panel was conducted by Harald SCHULZE in Universitätsklinikum Würzburg Institut für Experimentelle Biomedizin. By the time we submitted this abstract without Mr. SCHULZE as an author because we couldn't connect him.

SB34

Analysis Of Alterations Between Variant Annotations in Clinvar Datasets

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INTRODUCTION

ClinVar is an open access online database, showing genetic variations in humans and clinical phenotypes of these genetic variations. Genomic changes are mapped to reference sequences based on HGVS standards and then reported. ClinVar works in collaboration with many genetic and clinically based organizations and an active partner of the ClinGen project (1). It also provides access to people and information on the date of studies that contribute to the identification of variations and associated phenotypes recorded in the archive. In other words, ClinVar not only reports the clinical phenotypes estimated by the variants detected in sick people, but also processes information about the people, institutions and organizations that send this information. The accuracy of the data and its clinical estimates largely depend on the evidence supported by the sources. Since these evidences can vary, particularly in terms of new data published or submitted, ClinVar archives and constantly updates data. Those classification changes affect laboratories assumptions in terms of reporting a genetic variant. Determining the amount and degree of ClinVar annotation changes are important to show geneticist that Clinvar data are not stable and reported annotations that refer Clinvar should be checked periodically.

Publications examining the classification changes in ClinVar have produced contradictory findings, often due to the fact that annotations are not taken into account. In a comprehensive study analyzing all ClinVar variants, 81% similarity is founded between the three main classification levels: pathogenic (P) / likely pathogenic (LP), variant of insignificance (VUS), and possibly benign (LB) / benign (B). Two or more participants/senders were included in this study (2,3). Other medically significant differences (VUS /LB, P/LP) were found to be consistent with 94.1% (4).

Some studies have found that there are entries in ClinVar that cause false positive results. For example, incompatibilities have been detected between the submissions made from the BIC (Breast Cancer Information Core) database, which is not being updated currently, and the submissions made from another database, OMIM. Data causing false positive and negative variant results should not be evaluated nominally.

A second challenge is that variant reporting strategies differ across laboratories. Different laboratories can report ACMG/AMP levels in different ways. One laboratory can report a possible pathogenic variant as benign, while another laboratory can report the same variant VUS. Moreover, once a pathogenic variant has been identified, it is difficult to understand the patient-level conclusions about the relationship with the variant and its phenotype effects (5). Although the American College of Medical Genetics and Genomics (ACMG) and the Molecular Pathology Association (AMP) have established guidelines for variant classification, differences in interpreting the results create difficulties (6).

MATERIAL-METHOD

ClinVar is one of the most important databanks that investigates clinically relevant genetic variants. Unlike other web-based in-silico analysis databanks, ClinVar is comprised of submissions from individual genetic experts and institutions. Genetic variants are classified in ClinVar in terms of their effects as uncertain significance (VUS), likely pathogenic (LP) , pathogenic (P) benign (B) and likely benign (LB), As new variant submissions are added, ClinVar updates datasets weekly and because of this process, variant annotations may change over time.

In this study, we aim to analyze the alteration of variant annotations by time in the ClinVar database which has been in service since 2012. Especially alterations between benign to pathogenic or vice versa are very critical and studies to further analyze the effects of these alterations in terms of population genetics continues.

The latest version of the ClinVar dataset, published in December 2019, includes 674.786 unique variant annotations compiled from 1,025,258 submissions from 1,432 users. We analyzed two datasets from January 2017 to December 2019, published from the ClinVar Web site with the help of Python programming language.

FINDINGS

Records in the ClinVar database are coded with different access numbers. The entries in the format SCV000000000.0 of these codes, are used for the individual identification of each record sent. If there are multiple postings about the same variation/condition pair, they are collected in ClinVar's data stream and reported with a reference code in the format RCV000000000.0. Due to this model, one variant is included in multiple RCV accesses when different conditions are reported for a variant.

Finally, all records submitted for the same variation are reported with the code VCV000000000.0 (8).

XML files are paired and unique variant annotations with RCV codes are compared according to the publication date. As a result, we found that 444,933 new variant annotations were added to the dataset from 2017 and 24,664 (3.65%) annotations changed over time. According to our computer program analysis, we observed that, 48.32% (n=6.242) of VUS variants were reclassified as B/LB and 7.58% (n=473) as P/LP. 5,396 variants were previously classified as B/LB, and reclassified in the 2019 data set as VUS (2.44%) and P/LP (0.31%). Lastly, 19.42% of 4,674 variants were annotated as P/LP in the 2017 dataset and reclassified as VUS and 1.71% of them were downgraded to B/LB categories.

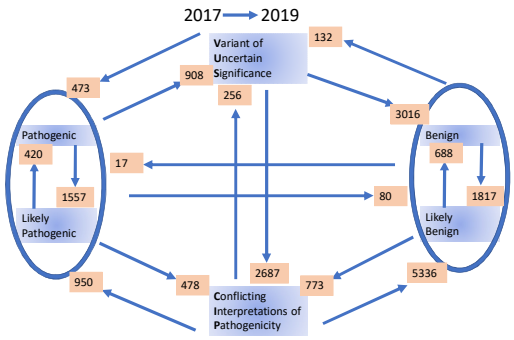

Figure 1. Variant classification changes between 2017 and 2019 years in ClinVar

RESULTS/DISCUSSION

Our analysis results conclude that annotation statues of all variants, especially VUS in ClinVar dataset, is very important in the decision-making process of a clinically relevant variant, and should be checked periodically. Classifying the role of variants in a disease requires expert review in terms of scientific evidence and should differ from the previous version. Reporting of varying differences in classification is a high priority for re-evaluation (9). It is anticipated that reconstruction of variant classifications and comparison between clinical laboratories in ClinVar contributes to the redefinition of variants and the development of different clinical diagnosis and treatment methods for individual's reports or those who are planned to be reported (10).Continuous data sharing and updating in ClinVar will improve the care and treatment of individuals with genetic disorders or those with a genetic risk in the community. In

order to understand the current status and interpretations of all genetic variants that have been gathered from patients in the past, genetic diagnostic centers should check the most recent updates in ClinVar. In this way, it will be possible for patients to receive better clinical implications for their treatments.

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SB35

Novel Mutation in CDH1 For Autism Spectrum Disorder By WES and the Importance of Parental Verification

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Autism spectrum disorder (ASD) is a developmental disorder that affects communication and behavior. Many genes and syndromes have been reported to be associated with ASD. Index patient is a ten years old boy who have been followed up for a diagnosis of autism spectrum disorder for 8 years. There is no feature in his antenatal and natal history. He developed a normal development until the age of one. We performed WES on the patient with autistic features and identified an novel inherited heterozygous mutation in CHD1 (NM__001270.2) c.4681C>T (p.His1561Tyr) in the index case and his mother and and a heterozygous mutation in the CNTNAP2 gene (NM_14141.5) c.2651G>A (p.Arg884Gln) in the index case and his father. Pilarowski-Bjornsson syndrome (PILBOS) is caused by heterozygous mutation in the CDH1 gene on chromosome 5q and an autosomal dominant neurodevelopmental disorder characterized by delayed development, intellectual disability, with autistic features. Pitt-Hopkins-like syndrome-1 (PTHSL1) is caused by homozygous or compound heterozygous mutation in the CNTNAP2 gene on chromosome 7q35-q36 and an autosomal recessive neurodevelopmental disorder characterized by delayed psychomotor development, intellectual disability, severe speech impairment or regression, and autistic behavior. The mutation in CHD1 gene has not been reported in Clinvar but it was found to be disease causing by software like Mutation Taster, SIFT and Polyphen. c.4681C>T (p.His1561Tyr) mutation is reported a novel benign variant in CDH1 gene, because of the mother has not any clinical features related autism or other psycologycal diseases.

SB36

Evaluation of Clinical and Prognosis Features of Five Patients With Epidermolysis Bullosa and Osteogenesisimperfecta

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Osteogenesis imperfecta and epidermolysis bullosa simplex coexistence was first established in 2010 in five Turkish families from the Black Sea region as a result of the biallelic c.321-353 del (p.Met107-Leu117del) mutation in the FKBP10 gene responsible for folding procollagen, and this association was attributed to the founder effect. In this study, five cases diagnosed with osteogenesis imperfecta and epidermolysis bullosa will be presented. In this study, five cases who were admitted to Cerrahpaşa Pediatric Genetics Outpatient Clinic were diagnosed as epidemolysis bullosa and osteogenesis imperfecta. The mean age of cases was 5.4 years (1 year-13 years), and the mean admission height SDS was -3.0. All patients had consanguineous marriages in their families and all originated from the Black Sea region. Severe type osteogenesis imperfecta was considered due to recurrent multiple fractures and deformity in our patients. Radiological examinations revealed severe osteopenia, severe scoliosis and bowing and deformity of long bones. Two patients had blue / gray sclera and one patient had conductive hearing loss. Dentinogenesis imperfecta was not observed in any of our cases. One patient was ex, and two patients could not continue to follow up because they lived outside the city. The follow-up period of our 12.5 and 3.5-year-old patients was 10 and 2 years, respectively. Pamidronate treatment was given to both patients. The patient, who was 12.5 years old at the last examine, was mobilized in a wheelchair due to bone deformities, could not walk without support and had no fractures for the last 6 years. Our 3.5-year-old patient could sit without support but was unable to walk. We detected homozygous c.321-353 del (p. Met107-Leu117del) founder mutation in the FKBP10 gene in five of our patients with molecular testing. In patients with recurrent fractures and bullous lesions of the skin, osteogenesis imperfecta due to FKBP10 mutation should be considered.

SB38

PIK3CA-Related Overgrowth Spectrum Syndromes: 3 Cases and a Novel Therapeutic Strategy

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Overgrowth syndromes are characterized by generalized/segmental, symmetric/asymmetric findings of overgrowth that may include various tissues. PI3K's are the members of a highly conserved family of lipid kinases that phosphorylate many intracellular signaling pathways, including the PI3K-AKT-mTOR pathway; an important regulator of normal cellular processes such as cell proliferation, metabolism, survival and apoptosis. Pathogenic variants of PIK3CA, which encodes the p110 alpha catalytic subunit of Class 1A PI3K; is commonly detected in colon, breast and endometrial cancers and various types of solid tumors. In addition to various cancer groups, this pathway is also involved in the etiopathogenesis of genetic disorders. PIK3CA-related overgrowth spectrum (PROS) is an umbrella term for rare syndromes caused by somatic mutations in the PIK3CA gene. These syndromes are defined as distinct clinical conditions with broad and overlapping findings. The main features are vascular malformations, mosaic skin lesions, acral anomalies with congenital (or early childhood) and sporadic segmental overexpression. Currently, other than symptomatic treatment, there is no specific and/or curative treatment available for the affecteds. The patients have a shortened life span and often present with the chronic pain, leading to a worsened quality of life. In this report, three patients affected by PIK3CA-related overgrowth spectrum disorders will be presented. Therapeutic strategies in PROS will be discussed by exemplifying a recently published study demonstrating the curative effects of an inhibitor called BYL719 on 19 patients with CLOVES and similar syndromes.

SB39

From Nail Findings to Diagnosıs of Two Different Autosomal Dominant Inherited Syndromes

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Nail-Patella syndrome is an autosomal dominant cartilage-bone dysplasia with a prevalence of ~1/50,000. 88% of the pathogenic changes in LMX1B gene is familial, 12% de novo. Malformations of nails, knees, elbows and the presence of iliac horns are major findings. Nail a/hypoplasia/dystrophy are prominent in the first two fingers. Nail abnormalities ranges from aplasia, transverse/longitudinal ridging, pitted/discolored nails, separation into two halves by a longitudinal cleft, to triangular lunula. Pachyonychia congenita is characterized by hypertrophic nail dystrophy, painful palmoplantar keratoderma, blistering, oral leukokeratosis, follicular keratosis on the trunk and extremities. The inheritance is autosomal dominant and 30% of cases are de novo. Diagnosis is possible by clinical findings or detection of heterozygous pathogenic change in one of the 5 keratin genes*. First family was evaluated due to pathological USG finding of fetal knee dislocation. Father had facial asymmetry and thumb nails separated into two halves by a longitudinal cleft and triangular lunula of index finger, which is pivotal minor anomaly for Nail-Patella syndrome. The LMX1B c.741+1G>T pathogenic variant in both father/baby supported familial inheritance. Thickening of nails and skin findings in the second case led to diagnosis of Pachyonychia congenita. De novo c.4106T>C change was detected in the KRT6A gene. We here report two cases from two different families whose nail findings led to the syndromic clinical diagnosis, while molecular diagnostic algorithm varied according to genetic etiopathogenesis (single/multi gene) and/or technical availabilities (gene panels/CES/WES).
AD: Autosomal Dominant, CES: Clinic Exome Sequencing, WES: Whole Exome Sequencing, *KRT6A, KRT6B, KRT6C, KRT16, KRT17

SB40

Ectodermal Dysplasia - Three Genes Three Novel Variations

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Introduction: Ectodermal dysplasia is an inherited disease associated with abnormal development of ectodermal origin structures such as teeth, nails, hair, nerve cells and sweat glands. According to the state of sweat glands, ectodermal dysplasia has two different types, the hypohydrotic type is usually X-linked recessive inheritance, while the hydrotic type is inherited as autosomal dominant. In clinical and functional classification of ectodermal dysplasia, molecular genetic basis is taken into consideration.
Aim: In this article, we aimed to present the relationship between different clinical findings of ectodermal dysplasia and different genetic variations.
Methods and Results: After the clinical evaluation of three cases with a pre-diagnosis of ectodermal dysplasia, with TruSight One Expanded (6699 gene) and Illumina NextSeq 550 system, we identified three novel pathogenic variations in three different genes: Homozygous NM_002529.3 (NTRK1): c.1177 + 2T> A, homozygous NM_001399.5 (EDA): c.610G> A (p.Gly204Arg) and heterozygous NM_003722.5 (TP63): c.580-2A> G variations. The clinical presentation of the NTRK1 gene was associated with 'Insensitivity to pain, congenital, with anhydrosis. The patient with EDA gene pathogenic variation was associated with 'Ectodermal dysplasia 1, hypohidrotic, X- linked'. The patient with TP63 gene pathogenic variation was decided as ectodermal dysplasia.
Conclusion: Since patients with ectodermal dysplasia are individuals with normal intellectual capacity and lifespan, the implementation of the necessary supportive measures and taking the necessary precautions will minimize the complications that may occur due to the syndrome. Ectodermal dysplasias are a heterogeneous group of diseases and mutations of different genes can cause different clinical presentations. Therefore, performing multiple gene panel analyzes will be more useful both to speed up the diagnosis and to reduce the cost of testing. Thus, the treatment of the patients can be started earlier and genetic counseling can be provided.

SB42

Identification of a Novel Comp Gene Variant as a Likely Cause of Pseudoachondroplasia: Fırst Case in North Cyprus

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Introduction and aim: Pseudoachondroplasia (PSACH, OMIM 177170) is a rare, autosomal dominant genetic disorder with an estimated prevalence of 1 in 30,000 worldwide. Heterozygous mutations in the cartilage oligomeric matrix protein (COMP) gene, located on chromosome 19, were found to be responsible for the disease in 1995 and since then over 60 COMP mutations were identified to be associated with PSACH. Affected individuals show severe clinical symptoms including disproportionate short stature, lower limb anomalies, early-onset osteoarthritis, loose joints and brachydactyly and diagnosis is often not possible until around 2 years of life. Accurate molecular diagnosis and identification of molecular alterations leading to PSACH is important for treatment and family planning. Methods: Here we present the first PSACH case identified in the Turkish Cypriot population. Proband is 4 years-old male, born as a second child to non-consanguineous healthy parents. DNA was isolated from the peripheral blood sample of the proband and clinical exome sequencing was performed. Results and Conclusion: Variant confirmation and co-segregation analysis was done by Sanger sequencing using DNA samples of the parents and the proband. The variant, c.1420_1422del of the COMP gene, was identified as a novel mutation responsible for this spontaneous form of PSACH. Overall, this study emphasizes the importance of revealing disease-causing variants in a particular population for immediate use in accurate diagnosis, for improved understanding of the underlying molecular mechanisms and for developing effective preventive medicine strategies.

SB43

Preconceptual Next Generation Sequencing Experıment On Six Parents Who Have Child With Epidermolysis Bullosa

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Epidermolysis bullosa (EB) is a group of heterogeneous genetic disorder that characterized by mechanical fragility, blisters and erosions of skin and mucosa. EB is caused by mutations approximately different 20 genes that encoding the proteins; contributing to intraepidermal adhesion and dermo-epidermal anchorage of skin and mucous membranes. In this study, we aimed to review of EB-NGS panel results of six unraleted families. Six couple who admitted due to having consanguineous marriage and previously died children with EB were included in this study. Genomic DNA samples of parents were used for genetic analysis and sequenced by a custom designed targeted panel that comprised all exons and exon intron junctions of COL17A1, LAMA3, LAMB3, LAMC2, ITGA3, COL7A1, KRT5, ITGB4, ITGA6, PLEC on Ion Torrent system (Thermo Fisher Scientific) because it was not able to obtain DNA samples of affected children. Seven heterozygous disease causing variants (LAMC2, LAMA3, COL17A1, COL7A1) were identified in twelve probands. Two families reconsulted following new pregnancies. In one family, the prenatal genetic analysis did not showed disease causing mutation and the mother gave a healthy birth. On the other hand, COL7A1 mutation was detected prenataly in the baby of the second. However the family regregted to end of the pregnancy. The mother gave a birth of baby with clinical findings of EB. As a consequence, we could obtain efficient genetic results with EB-NGS panel through testing only career probands and prenatal screening.

SB44

A Specific Method in The Dıagnosıs of Kindler Syndrome: Case Report

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Introduction: Kindler syndrome (KS) is an autosomal recessive dermatosis characterized by early onset of acral blister, photosensitivity, progressive poikiloderma, skin atrophy.
Results: A 30-year-old female patient presented to our clinic with brown discoloration of the arms, face and neck and deformity of her nails. It was learned from the patient's history that liquid-filled lesions developed at early ages, especially in the sun-exposed areas, and that during the recovery periods, the skin became thin and left red brown spots. There was also deformity of the nails, thinning of the fingertips, and difficulty in opening the mouth. It was noted that the patient had similar findings to his brother. On dermatological examination, poikiloderma appearance and dystrophic changes in nails were observed, which were characterized by telangiectasias, erythema and atrophy of the whole body skin, more prominent on the face, neck, ears, hands and feet.
Method: Clinical exome sequencing (Sophia Genetics) was performed and no pathogenic mutation was detected. When the FERMT1 gene was investigated for KS, one of the leading ones, exon 10-11 was not read. Due to the absence of PCR amplification with primers designed for this region, homozygous deletion was detected in exon 10 and 11 in FERMT1. There was no amplification in the same region in the brother's DNA with similar complaints.
Conclusion: KS develops with biallic mutations in the FERMT1 (MIM607900) gene, which consists of 15 exons. FERMT1 encodes the 'Fermitin family homologous 1' protein, which performs the adhesion of the actin cell skeleton to the extracellular matrix in keratinocytes. Symptoms of the syndrome include

SB49

Two Distinct Type Epidermolysis Bullosa With One Novel Gross Deletion in COL7A1

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Epidermolysis bullosa (EB) is a group of genetic skin diseases that cause the skin to blister and erode very easily. In people with EB, blisters form in response to minor injuries or friction, such as rubbing or scratching. There are four main types of EB, which are classified based on the depth, or level, of blister formation: EB simplex, Dystrophic EB, Junctional EB ve Kindler Syndrome. EB may then be further classified based on severity and specific symptoms, such as distribution (localized or generalized) and whether parts of the body other than the skin are affected. Specific sub-types may then be determined based on identifying the exact protein that is defective in a person with EB. This may be done by tests performed on a skin biopsy, or when possible, genetic testing. EB may be caused by mutations in at least 20 genes that play various roles in the structure, integrity, and repair of the skin. Inheritance may be autosomal dominant or autosomal recessive. Here, two different types of EB patients are presented. One of them is junctional type EB and the other is dystrophic type EB. The first patient was a 1-month-old male patient. The other is a 15-year-old girl. Both patients underwent molecular genetic analysis using the NGS panel for EB. One of the patients had a missense mutation in the LAMB3 gene previously described in the literature and the other had a gross deletion in the COL7A1 gene, which was not previously described in the literature.

SB50

A New Edar Gene Mutation: 7-Years Clinical Follow-Up in a Girl With Hypohidrotic Ectodermal Dysplasia

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Abstract
Hypohidrotic ectodermal dysplasia (HED) is characterized by hypotrichosis, hypodontia, and hypohidrosis. Hypohidrosis may lead to recurrent hyperthermic episodes. The scalp hair is thin, lightly pigmented, and slow-growing. The skin is thin, and dry. HED is associated with typical facial features such as a protruding forehead, sparse and fine eyebrows and eyelashes, wrinkles under the eyes, characteristic periorbital hyperpigmentation, a saddle-bridged nose, and hypoplasia of the mandible. HED is inherited in an autosomal dominant (AD), autosomal recessive (AR), or X-linked manner (XL). The majority of the patients have the XL form. HED has a prevalence of approximately 1/15.000. Only four genes, EDA, EDAR, EDARADD and WNT10A constitute more than 90% of HED cases. Mutations in EDAR gene (2q13), accounts for 10–15% of HED cases, cause both AR and AD inheritance. Here we present a girl who was diagnosed at 6 months of age and underwent clinical follow-up for 7 years. When diagnosed, she had prenatal onset growth retardation in additional to characteristic features in this syndrome. During follow-up, oligodontia and normal development was observed in the patient. Her parents were relatives. c.1198C>T (p.Arg400Cys)(R400C) homozygous mutation was detected in the sequence analysis of EDAR gene of patient. Although this variation was described before, has not been association with the disease. It is likely pathogenic according to in silico mutation tools. Afterward, her parent and two brothers were shown to be heterozygous for the same variation. We report this case because to be rare and likely to contribute to phenotype-genotype correlation.
Key Words: Hypohidrotic ectodermal dysplasia, hyperthermic episodes, EDAR gene, autosomal recessive

SB52

Homozygous Synonymous Mutation in The COL7A1 Gene: Epidermolysis Bullosa Clinic

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Epidermolysis Bullosa (EB) is a disease characterized by mechanical trauma due to increased fragility of the skin, bullae and erosion formation in the skin and mucosa, and abnormal wound healing. It is a group of heterogeneous genetic diseases with autosomal dominant or recessive inherited chronic course resulting from mutations in genes encoding proteins in the epidermis or basement membrane. It is divided into four main groups according to the current classification system; simplex, junctional, dystrophic and Kindler syndrome. In recent years, molecular diagnosis of heterogeneous hereditary diseases in which, multiple genes are responsible, has been facilitated by the next generation sequence analysis. The corresponding increase in the number of variants brought along difficulties in variant filtering and classification. A 36-year-old patient diagnosed with epidermolysis bullosa was admitted to the Ege University Medical Genetics Clinic. She had bullous lesions on her hands and feet, atrophy of her nails and erosion on her face. Epidermolysis bullosa dystrophic type was considered with clinical findings. There was first degree cousin consanguinity between his parents. Whole exome sequence analysis was performed and c.5499C> T (p.Gly1833Gly) change in COL7A1 gene was detected. Although this variant was a synonymous change, it was reported as a mutation responsible for the disease because it was described in a previous publication in association with the disease and was consistent with the patient's clinical presentation. In conclusion, especially in the next generation sequence analysis, it is emphasized once again that synonymous variants may be associated with the disease in the variant classification, and the importance of filtering related to the patient's clinic.

SB55

Detection of NF1 Whole Gene Deletion in a Neurofibromatosis Case With Severe Dysmorphic Features

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Background: Café-au-lait spots and skinfold freckling lead physician to consider neurofibromatosis type 1. The genetic diagnosis cannot be made for each patient who is fulfilling the National Institutes of Health (NIH) criterion for the clinical diagnosis. Hereby, a case is presented which has hypotonia, growth retardation, intellectual disability, severe dysmorphic features, café-au-lait spots and skinfold freckling.
Findings: She was born as 1600 gr and 42 cm after 31st week of gestation and had been hospitalized in the incubator for 45 days because of postpartum respiratory distress. In physical examination; height: 92 cm (3-10p), weight: 12.4 kg (<-2.5 SDS), head circumference: 46 cm (3-10p), wide forehead, triangular face, hypertelorism, strabismus, low-set and backward positioned ears, low, sparse eyebrows, flattened and wide nasal root, micrognatia, rocker bottom feet, multiple (> 100) café-au -lait spots, axillary and inguinal freckling were observed. On ophthalmological examination, bilateral, temporal pallor of the optic discs were detected. Lisch nodule was not present. Peripheral blood karyotype revealed 46, XX. No mutation was detected in NF-1, PTEN, SOS1 genes. A deletion was found in 17q11.2 region of NF1 gene by FISH analysis.
Results: Although large NF1 gene deletions comprise 5% of all NF1 patients, it is recommended that patients who have severe dysmorphic features and clinical findings of NF1 should be analyzed for this deletion. In order to identify the exact region of deletion, microarray analysis has been planned.

SB56

Basal Cell Nevus Syndrome: A Case With 9Q22.3 Microdeletion

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Basal cell nevus syndrome (BCNS), also known as Gorlin syndrome (OMIM #109400) is a rare genodermatosis. It is a multisystem disease with autosomal dominant inheritance. The haploinsufficiency of the genes responsible for he BCNS are PTCH1, PTCH2 and SUFU. It is characterized by multiple basal cell carcinomas, jaw cysts, bony deformities and macrocephaly. The mean age at the time of diagnosis is 25. Developmental delay/intellectual disability, macrosomia, seizures, craniosynostosis and hydrocephaly are additional findings common in 9q22.3 microdeletion. The microarray analysis of a female patient referred to Karadeniz Technical University Department of Medical Genetics for macrosomia, dysmorphic facial appearance, pectus deformity and hypotonia at two months of age revealed a 4.5 Mb loss on 9q22.3 including PTCH1 gene. The patient was followed up for the diagnosis of BCNS, and developmental delay, seizures and pleural cysts were added to the patient's findings during the follow-up. The patient, who is now three years old, is still being followed up. Due to the increasing use of microarray and next generation sequencing, patients can be diagnosed at earlier age, often before manifestation of the characteristic age-dependent BCNS features. The aim of this presentation is to draw attention to similar cases by presenting a case diagnosed in infancy by microarray analysis.

SB57

Case Series With Neurofibromatosis Type 1: Evaluation of Novel Mutations and Genetic Counseling

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Neurofibromatosis is an autosomal dominant disease affecting the skin and nervous system in one in every 2500 people. The most frequent findings include cafe-au-lait spots, freckling, plexiform neurofibromas and optic glioma and caused by heterozygous mutation in the neurofibromin gene (NF1) on chromosome 17q11. In our study, 77 patients whom had clinical findings from 65 families were sequenced by new generation sequencing method including all exon and exon-intron junctions in terms of pathogenic variants of NF1 gene. 39 pathogenic variants were detected in 53 out of 77 patients. 13 Of these mutations were novel variants and classified as pathogenic after in-silico analysis. 26 of them were previously identified. When the distribution according to mutation types is examined, the most common missense mutations (11/39) are detected, followed by mutations leading to premature stop codon (10/39), frameshift mutations (9/39), intronic mutations (6/39) and deletions (2/39). Family screening revealed that half of the cases were de novo. The most common clinical findings were cafe-au-lait (43 patients) followed by axillary freckling in 25 patients, Lisch nodules in 16 patients, neurofibroma in 10 patients and optic glioma in 9 patients. In addition, 3 patients had epilepsy and 1 patient had thyroid medullary cancer. Neurofibromatosis is one of the most common genetic diseases with complete penetrence but variable expressivity. In addition to dermatologic findings, the possibility of mental retardation, epilepsy and the risk of developing benign or malignant tumors is important for the clinical follow-up of patients. Genetic diagnosis and genetic counseling is the most important step in the treatment of the young patients whom clinical findings are not clear, because the penetrance increases with age. Furthermore, the case series presented here had great importance in terms of reporting new mutations.

SB58

Evaluation Of Clinical Findings and Surveillance of Three Patients With Bloom Syndrome From The Same Family With Growth Retardation and Pigment Disorder

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Bloom Syndrome is a disease caused by biallelic mutations in the BLM gene, characterized by proportional severe intrauterine growth retardation, photosensitivity, telangiectatic, hypo and hyperpigmented skin lesions, immunodeficiency, susceptibility to malignancy, and increased sister chromatid exchange. 4-month-old boy (whose parents were the first cousin relative) was admitted due to intrauterine growth retardation and multiple cafe au lait spots, hypopigmented areas and physical examination revealed long-narrow face, wide forehead, high palate, microcephaly, lesions, proximal thumb and mild hearing loss. His IQ was found 82. His DEB test was positive and his preliminary diagnosis was Fanconi anemia. Heterozygous mutation was found in the gene that is responsible for Fanconi anemia. It was learned that an 11-month-old girl (whose parents were the first cousin relative) with similar facial findings, microcephaly, intrauterine growth retardation and cafe au lait spots and hypopigmented areas was third cousin relative with the index patient. Increased sister chromatid exchange value was found in the Sister Chromatid Exchange test. Bloom syndrome was considered. Her 20-month-old sister also had large cafe au lait spots and hypopigmented lesions, bilateral clinodactyly, severe growth retardation, mild speech impairment, and similar facial findings. Whole Exome Sequence analysis revealed homozygous mutation NM_000057.4: c.2823 + 1G> A in BLM gene and patient was diagnosed with Bloom syndrome. In the first follow-up of the patient, anterior mediastinal mass was detected when he was 18 years old and diagnosed as Nonhogkin lymphoma. Two sisters followed up until the age of 8 and 5 did not develop any complications. Monitoring of growth and development, ensuring adequate calorie intake, screening for hematologic and solid malignancies, reducing exposure to sunlight, and treatment of accompanying immunological and endocrinological problems are important in the surveillance of patients with Bloom syndrome.

SB59

Evaluation Of Clinical Findings in Three Patients With Ectodermal Dysplasia Syndrome Caused by Eda, TP63, LMX1B Gene Mutations

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In this study, three different families with hypohydrotic ectodermal dysplasia, Ectodermal dysplasia, Ectrodactyly, Ectodermal dysplasia (EEC) syndrome and Nail patella syndrome will be presented. One year old boy referred to us due to inability to sweat, sparse hair and eyebrow, brittle and scanty hair, dry eye, marked lips, conical teeth, and hypodontia. His skin biopsy revealed significant compact orthohyperkeratosis in epidermis, vascular proliferation in papillary dermis and thin appearance in whole dermis. Similar clinical findings were present in his two brothers. Hypohydrotic ectodermal dysplasia was considered in the patient. A known hemizygous (c.871G> A) mutation was detected in the EDA gene on X chromosome associated with Ectodermal Dysplasia 1. EEC syndrome was considered in a 2-year-old child who was referred to us for operated cleft palate-lip, bilateral ectrodactyly (head and 5th fingers bifid), hypertelorism, flat nose root, thin-sparse hair and contact dermatitis on his skin. His father also had similar findings. Molecular analysis of TP63 gene revealed a heterozygous (c.1658C> T) novel mutation that was predicted as disease-causing in in-silico prediction programs. A 12-year-old patient presented with walking at the fingertip, nail dystrophy , flexion contracture of the thumb, slow growth of the hand and toe nails, and limitation of the wrist and elbow. Hypoplasic appearance of patella, bilateral radioulnar synocytosis, iliac horn detected in his X-rays. A de novo heterozygous mutation (c.571del6) was found in the LMX1B gene associated with Nail Patella Syndrome. The first two families are followed up for high fever, frequent infection, and severe feeding problems; the second family is also followed up by the department of plastic surgery and orthopedics because of ectrodactyly and the patient with nail-patella syndrome is followed up for accompanying renal and orthopedic problems.

SB61

Coexistence Of Atrichia Wıth Papular Lesions and Osteogenesis Imperfecta: A Case Report

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Introduction: Atrichia with papular lesions (APL) is a genodermatosis characterized by atrichia of the whole body and papular lesions. Osteogenesis Imperfecta (OI); is a genetic disease characterized by osteoporosis and increased bone fragility. Herein, we report a case with coexistence of APL and OI. Case report: A twenty six-years-old female patient was reffered to our clinic with the complaint of hair loss of whole body. She had hairs at birth but she lost all hair since age of two-years-old. In the early infancy, the patient had bone fractures 5 times in his lower and upper extremities and was diagnosed with OI. She was 125 cm tall and weighed 35 kg. In dermatological examination; total alopecia was observed in hair, eyebrows and body hairs. There were numerous milia like papules 1-2 mm in size on the scalp and upper eyelids. Blue sclera was present. In orthopedic examination; there were duck-like gait, multiple bone deformities in both femur, tibia, humerus and forearm bones and coxa vara. Histopathological examination of the scalp showed that hair follicles were reduced in number and miniaturized. There were numerous dilated follicular cysts containing keratin plugs. Radiological findings were consistent with OI. Based on these findings, the patient was diagnosed with OI accompanying APL and referred for genetic analysis.
Discussion: APL should be considered in patients with diffuse alopecia with papular lesions in early childhood. Type 2 rickets has been reported in patients with early-onset widespread alopecia, but no coexistence of OI has been reported. Before these patients are diagnosed as alopecia areata, they should be evaluated clinically, biochemically and radiologically in detail and biopsy should be taken. Genetic examinations should be performed from patients if necessary.

Introduction
Atrichia with papular lesions (APL) is a rare genodermatosis characterized by the complete absence of hair from the whole body occuring within a few months of birth and the presence of milia-like papules distubuted over the body (1). This phenotype has been associated with mutations in two different genes: the human hairless gene located on the 8p12 chromosome and the vitamin D receptor gene on 12q-12-q14 (2). In cases with vitamin D receptor gene mutation, atrichia is accompanied by type 2 rickets. Bone deformities in our case were compatible with osteogenesis imperfecta (OI) (3). OI is a genetic disease characterized by osteoporosis and increased bone fragility. Herein, we report a case with coexistence of APL and OI.

Case report

A twenty six-years-old female patient was reffered to our clinic with the complaint of hair loss of whole body. She had hairs at birth but she lost all hair since age of two-years-old. In the early infancy, the patient had bone fractures 5 times in her extremities and was diagnosed with OI. She was 125 cm tall and weighed 35 kg. Blue sclera was present. In orthopedic examination; there were duck-like gait, multiple bone deformities and coxa vara (figure 1).

Figure 1: Multiple bone deformities

In dermatological examination; total alopecia was observed. There were numerous milia like papules 1-2 mm in size on the scalp and upper eyelids (Figure 2). Oral mucosa, teeth, nails were normal and there was no sweating related complaint.

Figure 2: Diffuse alopecia and papular lesions

Family history was negative. In the laboratory examination, complete blood count, kidney, liver and thyroid function tests, calcium, phosphorus and alkaline phosphatase values were within normal limits. Radiological examination was compatible with OI (figüre 3).

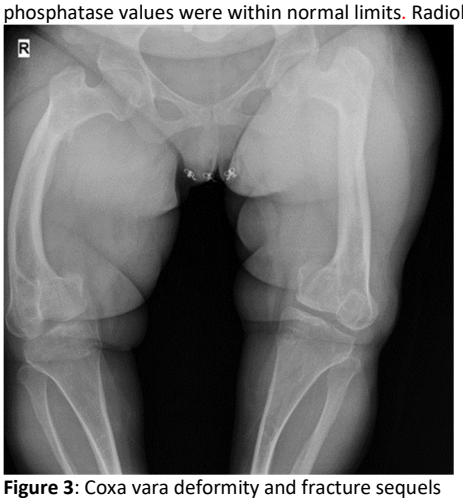

Figure 3: Coxa vara deformity and fracture sequels

In histopathological examination of the scalp, the hair follicles were reduced in number and were miniaturized. There were numerous dilated follicle cysts with keratin plugs (figüre 4).

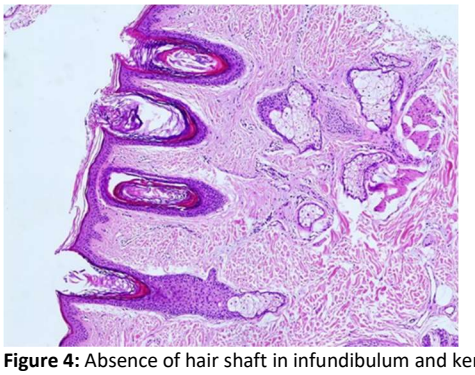

Figure 4: Absence of hair shaft in infundibulum and keratinous cysts in superficial dermis (HE,X200)

Discussion

APL is a rare form of total alopecia characterized by hair loss after birth and the development of keratin-filled cysts (4).

This form of hair loss is mainly associated with mutations in the human hairless gene located at chromosome 8p21 (5). Increasing sporadic reports in non-consanguineous individuals indicate that its prevalence may be underestimated due to the lack of awareness and frequent misdiagnosis as its alopecia universalis (1). Histologic examination shows loss of hair follicles and formation of dermal cysts filled with cornified materia (6). The rarer condition, vitamin-D-dependent rickets, also mimics APL (1). Similar to our case, in patients with skeletal deformities rickets should be ruled out orthopedic examination, radiology and laboratory findings. In addition to the main clinical features of osteogenesis imperfecta, such as recurrent bone fractures and blue sclera, laboratory and direct radiographic findings were also compatible with OI in our patient.

Yip et al, divided APL diagnostic criteria into five major and five minor and reported that at least four major criteria should be found for the diagnosis (table 1).

TABLE 1. Diagnostic criteria for APL
MAJOR CRITERIA
1. Permanent and complete absence of scalp hairs by the first few months of life.
2. Few to widespread, milia-like papules from infancy or childhood.
3. Replacement of mature hair follicle structures by follicular cysts filled with cornified material in scalp histology.
4. Mutation(s) in the human hairless gene
5. Clinical and/or molecular exclusion of vitamin-D-dependent rickets
MINOR CRITERIA
1. Family history
2.Absence of secondary axillary, pubic, or body hair growth and/or sparse eyebrows and eyelashes.
3. Normal growth and development, including normal bones, teeth, nails and sweating.
4. Whitish-hypopigmented streaks on the scalp.
5. Lack of response to any treatment.

Conclusion

APL should be considered in patients with diffuse alopecia with papular lesions in early childhood. Type 2 rickets has been reported in patients with early-onset widespread alopecia, but no coexistence of OI has been reported. Before these patients are diagnosed as alopecia areata, they should be evaluated clinically, biochemically and radiologically in detail and biopsy should be taken. Genetic examinations should be performed from patients if necessary.

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SB62

Novel PCNT Mutation in a Patient With Microcephalic Osteodysplastic Primordial Dwarfism Type II(MOPDII)

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Introduction and Aim Microcephalic osteodysplastic primordial dwarfism type II(MOPDII) is characterized by intrauterine growth retardation, severe proportionate short stature, and microcephaly. MOPDII patients often present with pre-term birth, and their size in utero is occasionally confused with fetal intrauterine growth retardation. A known genetic alteration has been described for MOPD II, a bi-allelic loss of function mutation in the Pericentrin gene (PCNT) located on chromosome 21. This gene has an important role in mitotic spindle organization; its loss prevents cell division resulting in severe growth retardation; autosomal recessive inheritance has also been described.

Material and Method: A 3 years old male referred us with oligohydramnios, growth retardation, microcephaly, premature fusion of the cranial sutures and fontanelles, aquiline nose structure, frontal bossing, cleft palate, cleft lip, syndactyly of toes 2 and 3, left inguinal hernia, spasticity of the muscles. FGFR2 and FGFR3 genes were performed with Sanger sequencing. Chromosomal microarray analysis (CMA) was performed using Agilent Technologies 4x180K SurePrint G3 Human CGH+SNP Platform. MLPA P034 and P035 probes were used for DMD deletion analyses. Trusight One Expanded panel was used on Illumina NextSeq 550.

Result: CMA analysis, FGFR2 and FGFR3 gene Sanger sequencing analyses, DMD MLPA analyses were evaluated as normal. The homozygous ENST00000359568.5(PCNT):c.541C>T (p.Gln181Ter) variation determined in Trusight One Expanded panel. This variation was determined as pathogenic according to ACMG-2015 classification (PVS1, PM2, PP3).

Discussion: ENST00000359568.5(PCNT):c.541C>T(p.Gln181Ter) mutation was not previously reported in the literature. Therefore, our finding is considered as the first case report of this mutation in MOPDII patient.

SB65

Optic Glioma in Neurofibromatosis:
A Novel Mutation and Review of The Literature

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INTRODUCTİON: Neurofibromatosis Type 1 (NF1) is a neurocutaneous disorder inherited as an autosomal dominant trait. Optic glioma prevalence is 10-15 % in children with NF1. NF-1 gene encodes neurofibromin, a tumor supressor protein. Neurofibromin inactivates RAS by activating the signal activity of GTPase. Mutations in this cascade may cause function loss in somatic tissue and tumors like optic glioma. MATERİAL-METHODS: A sixteen year old proband with a clinical diagnosis of NF and optic glioma was genetically diagnosed with molecular genetics analysis. RESULTS: A molecular genetic analysis to NF1(NM_001042492) gene revealed a novel, pathogenic, heterozygous c.1260+1G>T mutation in the splice donor site in the intron 11. In recent publications, the risk of optic glioma was increased in mutations in exon 1-22 and exon 11-17 (cysteine/serine rich region). CONCLUSİON: Mutations in first 20 exons (Upper 5' tertile), especially in cysteine/serine rich exons (exon 11-17) is associated with the development of optic glioma. The relationship of optic glioma and the pathogenic mutation was consistent of ones in the literature in our case. In addition, yearly ophthalmologic examinations are important for screening optic glioma in patients with NF.

SB66

Molecular Genetic Analysis of a Family With Severe Palmoplantar Keratoderma

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Background: Hereditary palmoplantar keratodermas (PPK) are a heterogeneous group of keratinizing disorders characterized by hyperkeratotic thickening of the palms and soles. Studies on the molecular basis of PPK indicated the mutations in the genes encoding proteins involved in the keratinization process, such as keratins, desmosomes, loricrin, cathepsin C, gap junction proteins, and many others. Patients and Methods: Keratinized tissue deposition on the palms, soles, toes and gluteal tissue was determined in a three-month-old baby girl born at the first pregnancy of a two-year married non- consanguineous couple. The 24-year-old mother also had severe keratosis on her hands, feet, and neck. Both of them were thought to be palmoplantar keratoderma.Genomic DNA was isolated from peripheral blood and libraries containing 4811 genes were prepared according to the TruSight ™ One (Illumina) protocol. The resulting libraries were sequenced in the Illumina Miseq system and data were analyzed using the Genomize Seq Software. Results: Heterozygous NM_006121.3 (KRT1): c.623T>C (p.Leu208Pro) variation was determined in the patient and the affected mother. This variation has been previously reported as a pathogenic variation in the ClinVar database and we classified this variation as a likely pathogenic variation (PP5, PM2, PP3, PP2, PP1) according to ACMG 2015. Conclusion: Pathogenic/likely pathogenic variations of the KRT1 gene have been associated with autosomal dominant Ichthyosis histrix, Curth-Macklin type, Ichthyosis, cyclic, with epidermolytic hyperkeratosis, Palmoplantar keratoderma, epidermolytic, Palmoplantar keratoderma, nonepidermolytic, and autosomal recessive/autosomal dominant Epidermolytic hyperkeratosis. Evaluation of molecular genetic analysis results together with the physical examination of the patient were offered after detailed genetic counseling was provided.

SB69

Comprehensive Bioinformatic Analyses Of BRCA1/2 Variants Identified in Individuals With Personal and/or Family Hıstory of Brca-Related Cancers

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Pathogenic variants in the coding regions of the BRCA1/2 genes lead dysfunctional or nonfunctional BRCA proteins and non-coding BRCA1/2 gene variants were known to increase BRCA-related disease risk. In this study, the next-generation sequencing (NGS) data produced by targeting the exon and exon-intron junctions of the BRCA1/2 genes in 125 Turkish individuals were comprehensively analyzed using in silico analyses. A total of 59 coding and 37 non-coding variants were identified and multiple bioinformatic tools were used for characterising their functional and regulatory impacts as well as linkage disequilibrium plots were generated by Haploview. The NGS approach to screen BRCA1/2 genes in BRCA-related cancers, not only allowed us to to identify several known coding and non-coding variants but also identify 8 novel variants that were not reported in any public databases. We identified 11 missense variants that potentially affect protein function predicted in at least two common in silico tools and 22 coding variants were also found to likely alter different types of post-translational modifications. Multiple non-coding BRCA1/2 variants including the top putative regulator rs799923 (RegulomeDB score=1f) were found to reside in the critical regulatory regions and acting as eQTL in GTeX database. Notably, identified eQTLs were found to have role in cis-regulation and likely affect the NBR2 gene expression. Our results suggest non-coding variants in the BRCA1/2 have regulatory potential and act as eQTL by contributing gene regulation. Further research is needed to elucidate the roles of suggested putative regulatory and functional variants and uncover their associations with BRCA-related cancers.

SB71

A Case Followed Up With PRE-B All is Diagnosed With Bloom Syndrome

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Bloom syndrome is one of the autosomal recessive inherited chromosomal instability syndromes characterized by growth retardation, photosensitivity, telangiectasia, skin pigmentation abnormalities, immune deficiency and susceptibility to malignancy. It can cause early mortality due to cancer predisposition, the most common being leukemias and lymphomas. The case presented here is a 17-year-old male patient presented with complaints of weight loss and fatigue. There was consanguineous marriage between his parents (second degree cousins) and there was no significant feature in the birth and family history. Physical examination revealed weight 43 kg (<3p), height 149 cm (<3p), head circumference 50.5 cm (<3p), long and narrow face, epicanthus, anteverted ears, butterfly-shaped telangiectatic rash on face and thin upper lip. In addition, numerous hypopigmented and hyperpigmented lesions were observed on the skin. The patient was referred to EUTF Pediatric Hematology Department for further investigation due to pancytopenia on hemogram and horseshoe kidney and hepatosplenomegaly detected by abdominal ultrasonography. After peripheral smear and bone marrow biopsy, he was diagnosed with pre- B acute lymphoblastic leukemia (ALL). Patients' ALL associated molecular and molecular cytogenetic tests were normal, he responded well to ALL treatment but the side effects of chemotherapy were severe. Karyotype obtained from peripheral blood and bone marrow was 46,XY. Together with dysmorphic, clinical and laboratory findings of the patient, Bloom syndrome was considered. Molecular genetic analysis revealed a homozygous c.572_573delGA (p.Arg191LysfsTer4) variant in the BLM gene. This mutation is classified as pathogenic and it is important in that it is a rare variant of a rare syndrome and it is diagnostic in our patient.

SB72

Three Genetic Syndromes Which Diagnosed Based on Dermatological Manifestations

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Many genetic syndromes have dermatologic manifestations that are useful to diagnose. Papillion-Lefevre, LEOPARD, and Waardenburg syndrome are examples of these syndromes. Papillion-Lefevre syndrome is an autosomal recessive disorder characterized by palmoplantar keratoderma, periodontitis, and premature loss of dentition LEOPARD is an acronym for the manifestations of this syndrome: multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness. Waardenburg syndrome type 1 is an autosomal dominant syndrome characterized by pigmentary abnormalities of the hair, skin, and eyes; sensorineural hearing loss; and dystopia canthorum. Here we present three cases in which clinical diagnose based on dermatological findings and confirmed diagnoses by targeted gene sequencing. The first case has hyperkeratosis of palms and soles and prematüre teeth loss. Thus, we clinically diagnosed as Papillion- Lefevre syndrome. Molecular genetic analyses revealed a homozygous pathogenic c.1340A>G variant on CTSC Gene The second case has sensorineural deafness and 1-5mm dark lentigines on the neck and trunk. The father also has 1-5mm dark lentigines on the whole body. We clinically diagnosed as LEOPARD syndrome. Molecular genetic analyses revealed a heterozygous pathogenic c.1402A>C variant on PTPN11 gene. The third case referred to the clinic because of dysmorphic facial features. A small white forelock was seen during the examination. We clinically diagnosed with Waardenburg syndrome. Molecular genetic analyses revealed a heterozygous pathogenic c.668G>A variant on the PAX3 gene. Dermatological manifestations are important to recognize genetic syndromes. Thus, targeted molecular genetic analyses lead to earlier and low cost diagnose.

SB75

CAFE-AU-LAIT Spots And Hypopigmented Macules: Constitutional Mismatch Repair Deficiency Syndrome

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Introduction and Aim: Cafe-au-lait spots are common macular lesions in children and may increase in size from 1-2 mm to 20 cm. Although the first diagnosis that comes to mind when Café-au-lait spots are seen in children is neurofibromatosis type 1, Legius Syndrome, Noonan Syndrome, McCune Albright Syndrome, Constitutional Mismatch Repair Deficiency Syndrome and other rare genetic diseases should be considered. Patients with Constitutional Mismatch Repair Deficiency Syndrome can be distinguished from patients with neurofibromatosis type 1 with Cafe-au-lait spots and associated hypopigmented macules on their skin, and in case of doubt, genetic diagnosis can be made by mutation analysis in PMS2, MLH1, MSH2 or MSH6 genes.
Method: In this presentation, a family of 5 , the older brother who was diagnosed as T-cell lymphoblastic lymphoma at the age of 2, healed with treatment and diagnosed with brain tumor 4 years later, sibling diagnosed with brain tumor, mother who died of endometrial carcinoma and a father recovered from ileal adenocarcinoma, is described.
Results: The patient, whose parents were first-degree relatives, had Cafe-au-lait spots and hypopigmented spots on dermatological examination. It was shown that homozygous MSH2 mutation in both brothers developed several cancers. Father and sister were reported to carry the same mutation in heterozygous state.
Discussion: In patients with Constitutional Mismatch Repair Deficiency Syndrome, the genetic stability is impaired as a result of DNA repair mechanism disorder, resulting in predisposition to brain tumors, lymphoma and other childhood cancers. Early diagnosis of these patients before cancer development and inclusion in cancer follow-up programs will have a positive effect on morbidity and mortality.
Introduction and Aim:
Cafe-au-lait spots (CAL) are common macular lesions in children and may increase in size from 1-2 mm to 20 cm (1). Although the first diagnosis that comes to mind when CAL are seen in children is neurofibromatosis type 1 (NF1); Legius Syndrome, Noonan Syndrome with lentigines, McCune Albright Syndrome, Constitutional Mismatch Repair Deficiency Syndrome (CMMRD) and other rare genetic diseases should be considered (2).
Patients with CMMRD can be distinguished from patients with NF1 with CAL and associated hypopigmented macules on their skin. In case of doubt, genetic diagnosis can be made by mutation analysis in PMS2, MLH1, MSH2 and MSH6 genes (3).

Method:
In this report, a family of 5 persons, in which 4 of them had cancer, is reported. Two brothers were shown to have CMMRD. The older brother with CAL was diagnosed with T-cell lymphoblastic lymphoma at the age of 2, recovered after treatment and 4 years later he was diagnosed with a central nervous system (CNS) tumor (glioblastoma multiforme) while his sibling was also diagnosed with another brain tumor (medulloepithelioma). Mother died of endometrial carcinoma at age of 40 and the father recovered from ileal adenocarcinoma at age of 38.
Also, other diseases that can overlap with NF-1 are discussed in details afterwards.

Results:
The patient, whose parents were first-degree relatives, had CAL and hypopigmented spots on dermatological examination. After occurence of second tumor in the child and tumors in the parents, a preliminary diagnosis of CMMRD was considered. It was shown that both brothers had homozygous MSH2 mutation while their sister and parents carried the same mutation in heterozygous state.

Discussion:
Although CAL are seen in 10-20% of normal individuals, observing multiple macules should raise the clinical suspicion of NF1 and other CAL associated genetic syndromes; Legius Syndrome, Noonan Syndrome, McCune Albright Syndrome and CMMRD (2). These genetic diseases may have clinical features that overlap with NF1.
In patients with CMMRD, the genetic stability is impaired as a result of DNA repair mechanism disorder, resulting in predisposition to brain tumors, lymphoma and other childhood cancers (4). Autosomal recessive inheritance pattern of CMMRD requires biallelic germline mutations but monoallelic mutation also brings the Lynch Syndrome in which cancer risk significantly increases in patients' early 30s to 40s (3). CMMRD patients may present with CAL and other clinical features including neurofibromas, Lisch nodule, skinfold freckling and pseudoarthrosis (2).
Early diagnosis of these CMMRD patients before cancer development and inclusion in cancer follow-up programs will have a positive effect on morbidity and mortality (5).
Legius Syndrome, also known as NF-1 like syndrome, is caused by pathogenic mutations in SPRED1, which is responsible for production of Spred-1 protein that regulates the Ras/mitogen-activated protein kinase signaling pathway involved in cell proliferation, differentiation, apoptosis and cell movement. Before description of Legius Syndrome in 2007, it was misdiagnosed as NF-1 but these patients don't develop optic pathway gliomas, Lisch nodules, neurofibromas, bone dysplasia, or CNS tumors although they can have CAL and axillary/inguinal freckling (6).
In Noonan Syndrome with lentigines, brown skin spots called lentigines similar to freckles, hypertelorism, heart defects, short stature, and chest wall deformities are the characteristic features. These lentigines mostly first appear in mid-childhood, but CAL usually develop before lentigines, in the first year of life. Noonan Syndrome patients have been shown to have increased risk of developing cancer (2).
The other disease to remember with presence of CAL is McCune-Albright syndrome, in which the borders of these lesions are irregular compared to other diseases (7). Patients have abnormal scar-like tissue in their bones, called polyostotic fibrous dysplasia. Endocrine problems, such as early puberty, hyperthyroidism, acromegaly, can occur.
In conclusion, encountering CAL requires questioning of several syndromes apart from NF-1. Diagnosis of CMMRD, though rare, should be kept in mind and efforts should be made to identify the disease if suspected.

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SB79

Variegate Porphyria: A Case Report

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Abstract
Variegate porphyria (VP) is a rare genetic disease caused by disease-related variants in the PPOX gene, leading to the accumulation of porphyrins and porphyrin precursors in the organism. In patients, the symptoms of this disease may show a wide clinical variation as skin symptoms and/or neurological symptoms. We present a young male patient who has adenoma sebaceous on the cheek and right nasolabial sulcus and was diagnosed with tuberous sclerosis by the clinician. CT imaging of the patient who did not have any feature in the background and the family history revealed nodular lesions in the right kidney and simple cortical cyst in the left kidney. Genetic analysis of the patient was performed by NGS method and revealed heterozygous genomic change NM_001122764.3 (PPOX): c.767C> G (p.Pro256Arg) classified as a possible pathogenic variant. Based on this genetic result, the patient was reassessed by the clinician for VP. To date, many variants have been identified in the PPOX gene, an autosomal dominant inheritance pattern, and some individuals with disease-causing variants in this gene are asymptomatic. However, VP patients have an increased risk of liver hepatocellular carcinoma and chronic kidney disease and should be checked regularly. Findings from genetic tests can provide the correct treatment and necessary precautions by changing the clinical diagnosis of the patients.

VARIEGATE PORPHYRIA: A CASE REPORT

Variegate porphyria (VP) is a rare genetic disease caused by disease-related variants in the PPOX gene, leading to the accumulation of porphyrins and porphyrin precursors in the organism. In patients, the symptoms of this disease may show a wide clinical variation as skin symptoms and/or neurological symptoms. We present a young male patient who has adenoma sebaceous on the cheek and right nasolabial sulcus and was diagnosed with tuberous sclerosis by the clinician. CT imaging of the patient who did not have any feature in the backgroundand the family history revealed nodular lesions in the right kidney and simple cortical cyst in the left kidney. Genetic analysis of the patient was performed by NGS method and revealed heterozygous genomic change NM_001122764.3 (PPOX): c.767C>G (p.Pro256Arg) classified as a likely pathogenic variant. Based on this genetic result, the patient was reassessed by the clinician for VP. To date, many variants have been identified in the PPOX gene, an autosomal dominant inheritance pattern, and some individuals with disease-causing variants in this gene are asymptomatic. However, VP patients have an increased risk of liver hepatocellular carcinoma and chronic kidney disease and should be checked regularly. Findings from genetic tests can provide the correct treatment and necessary precautions by changing the clinical diagnosis of the patients.

Introduction

Variegate porphyria is an autosomal dominant inherited and rare genetic metabolic disease. Due to insufficient function of the enzyme protoporphyrinogen oxidase, haem biosynthesis failure and excessive porphyrin accumulation are observed in this disease.Patients can experience neurological symptoms along with increased photosensitivity and skin lesions (hyperpigmentation, hypertrichosis, milia, blister, etc). The following is a case report of a male patient with skin lesions and kidney nodules who carries a PPOX gene mutation.

Case report

A 21-year-old man presented with recurrent skin lesions and kidney nodules. These adenoma sebaceous skin lesions, which sometimes disappear on the face and back and reappear, were first noticed 3 years ago. The patient had no history of neurological system. There was no remarkable information in the background and family history. There was no history of drug use that could lead to skin lesions. Physical examination revealed adenoma sebaceous on the cheek and right nasolabial sulcus. The patient had skin lesions in his back area, some of which were covered with excision or shell and some healed with atrophic scars. Other than these, no signs of hyperpigmentation or hypertrichosis were observed on the patient's skin. The patient also did not have a genetically. The patient previously examined by CT imaging tecnique and has announced that showed nodular lesions in the right kidney and a simple cortical cyst in the left kidney. The patient's complete blood table, liver and kidney function tests and ferritin levels were normal. The patient was followed up in the occupational diseases hospital with the clinical diagnosis of tuberous sclerosis. He was referred to us because tuberosclerosis was reported as normal as a result of genetic analysis previously investigated. Clinical exome sequencing (CES) analysis was performed. Genetic analysis of NM_001122764.3(PPOX): c.767C> G (p.Pro256Arg) was determined as heterozygous and classified by criteria of The American College of Medical Genetics and Genomics (ACMG) as likely pathogenic variant.

Discussion

The prevalence of VP is thought to be around 1/100,000 in European countries. VP is an autosomal dominant genetic disorder caused by disease-related variants of the PPOX gene. PPOX is a gene which is located at 1q23.3 region on chromosome 1, has 13 exons and is approximately 8 kb long. Until today, a number of different mutations have been identified in this gene, such as missense, frameshift, splice site and nonsense. These mutations cause partial deficiency of the haem synthesis enzyme and cause the formation of the clinic. Specific symptoms to this disease can vary greatly from one person to another. VP patients can get a diagnosis when they apply because of psychosis, depressivity, anxiety, thin skin, cutaneous photosensitivity, hypopigmented skin patches, seizures, confusion, muscle weaknes, tachycardia, vomiting, nause and vomiting, constipation, abdominal pain, visual hallucination, paralysis, motor polyneuropathy, abnormal blistering of the skin, peripheral neuropathy, porphyrinuria, and scarring complaints. Some individuals may have this disease asymptomatic.Herein, we present a patient with a heterozygous possible pathogenic variant in the PPOX gene and previously followed up with a clinical diagnosis of tuberosclerosis. It was planned to clinically re-evaluate our patient in order to confirm the diagnosis of VP and to ensure the genotype-phenotype correlation.

Conclusion

Genetic testing is crucial for the correct diagnosis and treatment of patients. these tests can help diagnose even asymptomatic individuals.The effect of the findings from genetic analyses on the patient's clinic should be investigated and patients should be re-evaluated in terms of genotype-phenotype correlation.

SB80

A Rare Genodermatosis: Carvajal Syndrome

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Carvajal Syndrome (CS OMIM # 605676) is a rare disease characterized by keratoderma, woolly hair and dilated cardiomyopathy. Biallelic mutations of DSP gene which encodes desmoplakin, a crucial component of desmosomes are responsible for CS. In this study we report two novel mutations in two Turkish CS patients. First case was a 2-year-old boy having dry skin, hypotrichosis, entropion and hypohydrosis. He was born via caesarean section due to oligohydroamnios to a consanguineous marriage parents. He has speech delay. Physical examination revealed dry skin structure, hypotricosis, entropion on the lower eyelids and dystrophic nails. No mutations were detected in EDA and EDAR genes from the older siblings with normal karyotype. Second case was a 6-yearold girl referred to us because of dry and coarse hair and dilated cardiomyopathy. Prenatal, natal, postnatal histories and neuromotor development were normal First cousin marriage was reported between parents. Systemic examination was normal except dilated cardiomyopathy and hepatomegaly. We sequenced 33 genes in genodermatoses panel via next-generation sequencing. We detected homozygous c.1445G> A (p.Cys482Tyr) and c.4297C> T (p.Gln1433 *) mutations in DSP gene respectively. Both were novel and segregated with the disease. Insilico analysis predicted the mutations as pathogenic. CS is associated with increased risk of sudden cardiac death and progressive heart failure developes more than 90% of patients in their early teens. Therefore molecular dignosis may be lifesaving in CS patients.This is the first report of molecularly prooved CS in Turkish patients and the study expands the mutation spectrum of DSP gene.

SB83

An Ultra-Rare Disease: Giant Axonal Neuropathy: A Case Report

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Giant Axonal Neuropathy (GAN) is a very rare progressive sensorimotor polyneuropathy with autosomal recessive inheritance. Patients typically have coarse and curly hair. In this case report, we aimed to present a 16-year-old patient diagnosed with GAN, a very rare genetic disease, in the light of clinical and genetically updated literature findings. A 16-year-old male patient who was previously examined for motor mental retardation at the external center but could not be diagnosed was admitted to our pediatric neurology outpatient clinic. His history revealed that he had continuous falling attacks when he was walking at the age of two and a half and was only crawling at the age of ten. The patient was admitted in a wheelchair-dependent manner. On physical examination, he had curly hair, tight hair, and extensive hyperkeratotic areas on his body. There was atrophy in the distal muscles and atrophy in bilateral thenar and hypotenar muscles. Deep tendon reflexes could not be obtained globally. MR imaging showed symmetrical hyperintense signal areas in the brain stem and dentate nucleus. EMG examination revealed demyelinating sensory motor polyneuropathy-related changes and the patient was referred to medical genetics department with the preliminary diagnosis of giant axonal neuropathy. It was learned that her parents were first-degree relatives and her eleven-year-old brother had a similar history. Whole gene sequence analysis of GAN gene for DAN etiology was studied. Homozygous c.1709G> A mutation was detected in GAN gene. There are approximately 60 cases in the literature about GAN that can be recognized by physical examination such as hair type and characteristic brain MR findings. It is emphasized once again in this case report that the etiology of polyneuropathy should not be forgotten.

SB84

Ehlers Danlos Syndrome Which Was Diagnosed by Evaluating Low Coverage Regions

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Ehlers-Danlos Syndromes(EDS) are a group of inheritable connective tissue disorders with wide range of phenotypic-genotypic variability. The triad of joint hypermobility, skin hyperextensibility, soft tissue/vascular fragility were shared within the subtypes. Among, arthrochalasis EDS(aEDS) stands out as a rare subtype with generalized joint laxity, congenital bilateral hip dislocation, and recurrent subluxations. Heterozygous variants causing skipping of exon 6 in COL1A1/COL1A2 are responsible for aEDS. Here we present 7-year-old patient diagnosed with aEDS due to a heterozygous mutation in COL1A2. He was referred to our clinic and had joint laxity, skin hyperextansibilty, multiple atrophic skin scars in physical examination. In medical history congenital hip dislocation, recurrent bone fractures were noted, his father also had similar health problems since the infancy. Based on clinical findings and family history, EDS was suspected and clinical exome sequencing was performed due to genetic heterogenity. Sequencing was carried out using IlluminaV2 chemicals on the Illumina NextSeq500 platform. Bioinformatics analyzes and variant calling were performed by using Sophia-DDM-V3 analysis program. No pathogenic variant was found. However, when low coverage areas were examined, it was found that reads of the COL1A2 gene exon 3-6 were low for confident variant analysis. Then we had looked the filtered out variants. A likely pathogenic missense c.279G>A variant in COL1A2 was detected resulting in altered splicing in exon 6. Sanger sequencing confirmed the diagnosis in patient and the father. By reporting this case, we would like to note that detailed evaluation of low-coverage regions may be a clue to identify pathogenic variants.

SB85

Congenital Insensitivity to Pain With Anhidrosis (CIPA)

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Hereditary sensory and autonomic neuropathy (HSAN) is a heterogenous group of disorder characterized by insensivity to pain and autonomic disfunction. HSAN type 4, also known as CIPA, shows anhidrosis in addition to the typical findings of HSAN. Homozygous or compound heterozygous mutations in NTRK1 gene cause CIPA phenotype. The aim of this study was to discuss the genotype-phenotype correlations of three families in which we identified mutations in the NTRK1 gene. Three patients from two Syrian families and three patients from one Turkish family were referred to our clinic because of recurrent fever, anhidrosis, insensivity topain, delayed healing of woundsand self-mutilation. Although prenatal, natal and postnatal history of the patients were not significant, all patients had hospitalizations due to recurrent fever. All families had a first cousin consanguienous marriage. On physical examination, bite marks on the tongue, amputation of the distal phalanx in the hands and feet due to burning and non-healing wounds on the body were common among all patients. Index patient from Turkish family and her brother had osteomyelitis. All karyotypes from the patients were normal. After DNA isolation from peripheral blood, all exon and exon-intron boundaries of NTRK1 gene were sequenced by Sanger sequencing. For exons suspected of deletion, exon-specific PCR was performed and visualized on gel electrophoresis. Homozygous c.200delA (p.Asn67Thrfs*2) mutation was detected in the first family and homozygous deletion between exon 9-17, was detected in the second family. In the Turkish family, homozygous c.353_359+2delGTCGCCTGT founder mutation was detected. Although CIPA is a rare genetic disease, molecular diagnosis is important for screening individuals at risk in the family, and for appropriate genetic counseling, prenatal diagnosis and follow-up of patients.

SB86

Five Patients From Two Different Families With Epidermodysplasia Verruciformis

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Introduction and Objectives Epidermodysplasia verruciformis is a rare, inherited disorder characterized by a spectrum of wart-like verrucous lesions and pityriasis versicolor–like spots. Epidermodysplasia verruciformis prevalence is unknown. It is caused by mutations in the EVER1(TMC6), EVER2(TMC8) or CIB1 gene. EVER1 and EVER2 are located on chromosome 17q25.This genes encode integral membrane proteins that localize to the endoplasmic reticulum and are predicted to form transmembrane channels. Lesions start in early childhood on the face, dorsum of the hands and legs. These lesions are caused by infection with specific human papillomavirus types that usually do not cause any clinical symptoms in the general population. It is estimated that 30%-60% of EV patients develop squamous cell carcinoma or other types of non-melanoma skin cancer. Methods Targeted next generation sequencing Findings We presented five patients, from two different families with classical features of epidermodysplasia verruciformis. All of the patients had a wart-like verrucous lesions on the hands and Pityriasis versicolor–like spots on the face and neck. Histopathology of the skin biopsies was consistent with epidermodysplasia verruciformis. Molecular analysis revealed a homozygous c.1127+1G>C mutation in the splice site of IVS9 of TMC8 gene in all the patients. Result Cases are presented to contribute to the literature because of its rarity.

SB88

Hpomyelination Spastik Paraplegia and Ictiosis Due to Possibble Inheritance of ELOVL1 Gene Pathology

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Two siblings with delayed motor development, imbalance problems, spasticity of the lower extremities, and dry and thickened skin were included in a exome sequencing study at Acıbadem University. As a result, previously not reported homozygous splice site region variant in ELOVL1 gene was determined. This gene pathology was first described in 2018 with autosomal dominant inheritance. Our primary goal is to confirm the diagnosis of patients with ataxia, hypomyelination, lower extremity spasticity and ichthyosis. In this newly defined gene pathology, we aim to investigate the supporting findings of the disease and recessive inheritance by in vitro studies.

Very long chain fatty acids (VLCFAs) are vital and they are the essential for myelin, photoreceptors and epidermal barriers. The mammalian VLCFA synthesis is carried out by the seven-member family of proteins (ELongation Of VLCFAs proteins; ELOVL1–7). From this family, ELOVL1 catalyzes the elongation of saturated and monounsaturated fatty acids in the synthesis of C22-C26-VLCFAs. VLCFAs form components of sphingolipids (ceramides and sphingomyelin) and glycerophospholipids. VLCFAs produced with ELOVL1 are important for myelin. Myelin-producing cells (oligodendrocytes and Schwann cells) mainly use C24-sphingolipids catalyzed by ELOVL1.

In this study, we aimed to make a functional study of the novel, homozygous variant ELOVL1 which was detected by exome sequencing in two siblings with skin involvement and hypomyelination in central nervous system. Knock-out mice are lethal ELOVL1 shown to be essential. Variants that eliminate enzyme activity in humans have not been identified. The number of reported patients suffering from this disease is only two and is associated with heterozygous variants leading to decreased enzyme activity. We predict that the novel homozygous mutation, which we detected in our patients, probably leads to a short and less effective protein synthesis. We aim to test the variant effects in vitro: the measurement of the enzymatic activity and the sphingolipid levels are critic for the confimation of the pathogeny of the variant.

SB89

Investigation of PON1 Q192R Gene Polymorphism in Vitiligo Patients

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Introduction and Objective: Vitiligo is an autoimmune disease characterized by the destruction of the skin melanocytes, observed by depigmented macules. Although the etiopathogenesis is not known, genetic, immunological and environmental factors are thought to play a role. Recent studies have focused on oxidative stress in the pathogenesis of vitiligo. Paraoxonase 1 (PON1) is an antioxidant enzyme bound to plasma high-density lipoprotein, it has been shown to protect low-density lipoprotein against oxidation and reduce oxidative stress. In this study, we aimed to investigate the possible relationship between vitiligo and PON1 Q192R gene polymorphism.
Methods: Sixty patients with vitiligo and 70 healthy controls were included in the study. DNA was isolated from the blood samples by phenol / chloroform method. PON1 Q192R gene polymorphism was determined by polymerase chain reaction (PCR) - restriction fragment length polymorphism (RFLP) method, and genotype and allele frequencies were compared between groups.
Results: Genotype frequencies of PON1 Q192R gene polymorphism were statistically significant between patients and controls (p = 0.05), but there was no significant difference in allele frequencies (p = 0.16). The QQ genotype was found to be significantly lower, and the QR genotype was significantly higher, in patients with vitiligo than the control group (p = 0.05). In addition, the frequency of the QR genotype was found to be higher in patients with a family history of vitiligo than the QQ genotype (47.4%, 22.5%, respectively) (p = 0.05).
Conclusion: According to our findings; We think that PON1 Q192R gene polymorphism may play a role in the development of vitiligo and QR genotype may be a risk for vitiligo. However, in order to support the results of this study, more comprehensive studies in different ethnic groups are needed in the future.

SB91

Two Patients With Epidermolysis Bullosa

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Introduction and Aim Epidermolysis bullosa (EB) is described as rare inherited heterogeneous group of diseases characterized by blister formation and erosions as a result of mild trauma or minor injury. It usually manifests by blister formation and erosions as a result of mild trauma. Changes in genes encoding structural proteins found in dermoepidermal junction components and keratinocytes, causes blister formation on the skin. In the light of current knowledge EB is classified into four main subgroups according to the location of the skin layer in which blister originates. These four main subgroups are EB simplex that occurs by intraepidermal cleavage, junctional EB that occurs by cleavage within the lamina lucida, dystrophic EB that occurs by separation of lamina densa and lastly Kindler syndrome that occurs by cleavage of both lamina densa and lamina lucida. Herein, you can find the report of patients with two main subgroups of EB that are Kindler syndrome and junctional EB variants. Major symptoms of Kindler Syndrome (OMIM # 173650) are photosensitivity, skin atrophy and acral skin blistering. However, unlike the other types of epidermolysis bullosa, poikiloderma is seen in Kindler Syndrome(KS). KS is resulted from mutations causing biallelic loss of function of FERMT1 (Fermitin Family, Member 1) gene. Junctional epidermolysis bullosa (OMIM # 226650) is a rare autosomal recessively inherited subgroup of EB with the main properties of fragility of skin and mucosal membranes and is characterized by blister formation as a result of mild traumas. There are more than one gene responsible for the etiology of Junctional epidermolysis bullosa (JEB) and it is hard to differentiate JEB from other EB subgroups clinically. Our aim with this report is to emphasize the importance of molecular diagnosis in terms of making definite diagnosis of disease, giving counseling and evaluation of future pregnancies, and also make contribution to literature about phenotype–genotype correlations. Patient's Information and Method Patient 1: A 10-year-old male patient presented to our clinic with complaints of photosensitivity, urethral synechia, and blisters started in the neonatal period. Physical examination revealed widespread scars on the skin, pseudosyndactyly, dystrophic fingernails. There was consanguinity between the parents. Since it was hard to make differentiation among EB subtypes clinically and because of the genetic heterogeneity of EB, it was decided to perform Whole Exome Sequence (WES) analysis for Patient 1. Patient 2: A 19-year-old male patient presented with complaints of photosensitivity, esophageal and anal synechia, and blisters started in the neonatal period. His physical examination revealed widespread scars on the skin, pseudosyndactyly, dystrophic fingernails. Kindler Syndrome is considered, due to presence of poikiloderma and whole coding regions of FERMT1 gene are sequenced. Findings and Result: In Patient 1, a homozygous frameshift variant (NM_017671.4) c.456_457delAGinsT (p.Lys152AsnfsTer9) in the FERMT1 gene was detected. This variant, which is expected to cause truncation in protein, was interpreted as pathogenic. In Patient 2, all EB and morbid OMIM genes were analyzed and no pathogenic variant was detected. In addition, a silent homozygous variant of c.346C> A (p.Arg116 =) was identified in the ITGB4 gene (NM_000213.5), which was interpreted as an unknown clinical significance. This variant is suspected to be the variant that can explain the molecular etiology of the Patient 2, as it is very rare in the heterozygous state in the population (GnomAD) and is not homozygous at all, and the clinical findings of the Patient 2 are consistent with the EB clinic. Studies are planned to evaluate the possible effects of the mentioned variant on protein function or expression.

SB92

A Report of Two Siblings Diagnosed With Cutis Laxa

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Introduction and Aim: Cutis laxa is a rare heterogeneous group of clinical entity of connective tissue. Its major clinical findings include skin laxity, loose, redundant and wrinkled skin. Its prevalence is even less than 1/1000000. Patients are usually presented with prematurely aged appearance. Both inherited and acquired types of cutis laxa can be seen . Inherited types can be autosomal recessive (AR), autosomal dominant (AD) and X-linked. One of the autosomal recessively inherited type is AR cutis laxa type IIA (ARCL2A). It results from biallelic mutations in ATP6V0A2 gene and this type shows a variable degree of clinical spectrum including growth retardation, late closure of the anterior fontanelle and rare but severe neurodegenerative findings in addition to the major findings of cutis laxa. Diagnosis of ARCL2A is based on characteristic findings on clinical examination of the skin, serum isoelectric focusing (IEF) for apolipoprotein C III and serum sialotransferrin and molecular genetic testing of ATP6V0A2 gene . The aim of this study is to present the clinical findings and molecular genetic results of two siblings diagnosed with cutis laxa and homozygous mutation in ATP6V0A2 gene.
Patient Information and Method: Two siblings: a three-year-old girl (Patient 1) and a three-month-old boy (Patient 2) were admitted to our clinic because of their sagging skin appearance. While both had a medical history of prematurity, ventricular septal defect (VSD) and a wide anterior fontanelle; Patient 1 had additionally easy bruising and normal time span of wound healing and Patient 2 had hydronephrosis. There was no history of consanguinity between the parents and known family history. Physical examination of both patients revealed microcephaly, redundant skin especially in neck and abdominal region, dysmorphic facial features and umbilical hernia. Additionally, hypospadias was detected in patient 2, whose clinical findings were milder. As there was no clear distinction between the present findings and cutis laxa subtypes, it was decided to perform a Whole Exome Sequencing (WES) analysis of Patient 1.
Findings and Conclusion: In the WES analysis performed of patient 1, a homozygous c.187C> T (p.Arg63Ter) variant in the ATP6V0A2 gene was found. This variant was previously interpreted as pathogen in AR Cutis Laxa Type IIA patients. Mentioned variant was detected as homozygous in patient 2 by Sanger DNA sequencing. It is considered that the application of larger scale analyzes such as NGS panels containing all known genes of cutis laxa syndromes or WES, rather than single gene analyzes, is important in terms of time and cost effectiveness, since the high genetic heterogeneity of cutis laxa, the overlapping phenotypes of the subtypes, and the different inheritance patterns that are possible in our patients.

SB93

Incontinentia Pigmenti : 4 Stage Genodermatosis

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Introduction: Incontinentia pigmenti (IP) is a rare genodermatosis with X linked dominant inheritance, usually lethal for male before birth. IP is caused by loss of function in the NEMO gene, which encodes the nuclear factor –kappa- B essential modulator involved in cell survival, inflammation and immunity. Skin findings are seen in 4 stages. These stages are characterized by vesicular, verrucous, hyperpigmented and hypopigmented skin rash. In addition to ectodermal organ involvement such as hair, nail, tooth defects, ocular and neurological involvement may be accompanied.
Case: A girl baby, 33 weeks old and weighed 2265 gr, was delivered by a 26 year old mother, by cesarean section due to plesenta previa totalis. The mother had diabetes mellitus and was smoking. The patient was hospitalized in the pediatric clinic, and widespread pustular lesions were detected on the baby's trunk and extremities. Swab and culture were examined for stained microscopy and fungal examination. Skin biopsies were performed with the preliminary diagnoses of eosinophilic pustular folliculitis, erythema toxicum neonatarum, incontinentia pigmenti and neonatal candidiasis. A large number of polymorphonuclear leukocytes were detected in the stained examination, culture was negative for bacterial and fungal infections. Histopathological examination revealed spongiosis in the epidermis, intraepidermal pustules containing multiple eosinophils, interstitial and perivascular eosinophils in the dermis. The patient had marked eosinophils (17.5%) on the hemogram. Biochemical markers were in normal limits, viral markers and immunoglobulin levels were normal except mild Ig G elevation. During hospitalization, pustular lesions were opened and secondary infection developed and systemic ampicillin (7 days) and topical mupirocin cream was started twice daily. On the 13th day of hospitalization, vesicular and pustular lesions on the erythematous floor had a linear appearance especially on the extremities and blaschkoid spread on the trunk detected and diagnosed as incontinentia pigmenti. Genetic, neurology and eye consultation was requested. Genetic analysis of DNA mutation was requested but not completed yet. Eye and neurological examination were normal. The patient were advised to be periodically checked and discharged.
Discussion: Skin findings of Incontinentia Pigmenti appear in the first week after birth. Although these lesions are well defined in the literature, it may be difficult to differentiate from many vesicular and pustular diseases such as congenital herpes simplex, varicella, staphylococcal and streptococcal infections, eosinophilic pustular folliculitis, erythema toxicum neonatorum and neonatal candidiasis. Diagnosis of IP in these patients will prevent patients from receiving unnecessary drug treatments and will provide early recognition of retinal decomposition that may develop and early treatment of future neurological and dental problems. This case is presented to emphasize to pediatricians and dermatologists, the necessity of suggesting IP in cases with linearly arranged vesicles and pustules especially in extremities, resistant to treatment in the neonatal period.

SB94

A Rare Cause of Acanthosıs Nigricans; Crouzen Syndrome

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Crouzon syndrome is an autosomal dominant disorder characterized by craniocinostosis and dysmorphic facial appearance. The diagnosis is made during the neonatal period or infant period according to the degree of dysmorphic features. The incidence varies according to race, region and ethnicity and it is reported that the incidence is 16 / 1.000.000 according to the literature. The clinical picture is the result of mutations in Fibroblast Growth Factor receptor-3 (FGFR-3). In Crouzon syndrome, acrocephaly or brachycephaly may be seen, especially as a result of early closure of coranal sutures and sagittal sutures. In addition, patients may have prominent exophthalmus, ptosis, hypertelorism, beak-like nose, ear and palate abnormalities. Crouzen syndrome may also be accompanied by cutaneous findings. The most common dermatological examination finding is widespread and atypical located acantosis nigricans. Here; A 17 - year - old girl with mild mental retardation with maxillary hypoplasia, craniofacial asymmetry, brachiecephaly and oxycephaly, perioral, perinasal and diffuse acanthosis nigricans lesions is presented because of its rarity.

SB95

Rare Ectodermal Dysplasia Case Diagnosed by Wes Analysis

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Ectodermal dysplasia (ED) is characterized by developmental and morphological anomalies of anatomical structures of ectoderm origin; hair (hypotrichosis), tooth (anodontia or hypodontia) and sweat gland (anhydrosis or hypohidrosis) is a disease that shows genetic heterogeneity that affects the development or function. Hypohydrotic ectodermal dysplasia is one of more than 100 types of ectodermal dysplasia, characterized by an impaired or underdevelopment of ectodermal derivatives in the process of embryonic development, and is the most common type of ectodermal dysplasia that can be caused by mutations in one of the EDA, EDAR, EDARADD and WNT10A genes. .
Rare eyebrow structure, dry thin hair structure, nail dystrophy, palmoplantar in a 10-year-old girl who was referred to Ege University Faculty of Dentistry, Department of Orthodontics for Medical Genetics Department due to decreased oligodontia decreased lower facial height, decreased upper-upper vermilion. Keratosis findings were recorded. The homozygous WNT10A c.686T> G (p.Leu229Arg) mutation was detected in the Whole Exome Sequence Analysis performed for the differential diagnosis of the patient who was diagnosed with ectordermal dysplasia. Parents and healthy siblings were shown to carry the heterozygous WNT10A c.686T> G (p.Leu229Arg) mutation. WNT10A gene mutations are associated with odontoonicodermal dysplasia, also known as Schopf-Schulz-Passarge syndrome, and is a rare type of ectodermal dysplasia with autosomal recessive inheritance. It is characterized by palmoplantar keratoderma, hypodontia, hypotrichosis, nail dystrophy, and multiple periocular and eyelid apocrine hydrocystomas.
Here, we present a 10-year-old girl with WNT10A c.686T> G (p.Leu229Arg) mutation that was diagnosed by reverse phenotyping, which is one of the rarest types of hypohydrotic ectodermal dysplasia by WES analysis..

SB96

A Rare Case of X-Linked Mental Retardation Diagnosed by Reverse Phenotyping With KDM5C Mutation After Wes Analysis

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The patient was referred to the Department of Medical Genetics in order to perform whole exome sequencing because of mental retardation and dysmorphic findings. A 13-year-old male patient who had no consanguinity between the parents and a similar family history, had no features other than congenital cardiopathy and operation due to pyloric stenosis at 1 month of age. In physical examination, height, weight and head circumference were below the 3rd percentile. The initial diagnosis was Kabuki syndrome with the findings of anteverted ears, triangular face, and previously performed Fragile X and array-CGH analyzes were found to be normal. Whole exome sequencing (WES) analyzes were performed on the Ion Torrent S5 platform. After WES analysis, hemizygous c.912T> A (p.C304X) mutation was detected in KDM5C gene. This mutation, which was not previously reported in the databases, was classified as pathogenic according to the ACMG classification. After confirmation with Sanger sequencing, segregation analysis was performed and the mother was found to have heterozygous mutation. The KDM5C gene which encodes specific H3K4me3 and H3K4me2 demethylase casuses X-linked Claes-Jensen- type syndromic mental retardation. It is thought to be responsible for 2-3% of X-linked mental retardation cases. We report a case of Kabuki syndrome with growth and mental retardation and dysmorphic features and diagnosed with reverse phenotyping after WES analysis.

SB97

Estimating The Most Appropriate Treatment Methods for Psoriasis by Approaching Back Propagation Artificial Neural Networks

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Artificial intelligence (AI) applications have gained momentum with the emergence of high-performance computers, recently. Studies have observed and confirmed the ability of AI in diagnose for many diseases are accurate and quick. AI systems are generally able to learn data based on mathematical models and obtain information inferences after learning. In this study, back propagation artificial neural network is used. Back propagation neural networks consist of the input layer, the hidden layer and the output layer. Inputs introduced to the input layer are used by the neurons in the hidden layer for learning with mathematical functions. The back-propagation of learning takes place in neural networks, from input to output, from output to input, and with the ability of each neuron to update itself. While self-updating of knowledge can lead to increased success, in very rare cases it may lead to a decrease in success. In artificial neural networks used a mathematically model of the human brain's neural structure. The purpose of this study was to estimate the most appropriate treatment methods for psoriasis by approaching back propagation artificial neural networks. Here, data set containing clinical features recorded in 21 categories of 108 different vitiligo patients were used. The back propagation artificial neural network trained with the data set used and indicated a success of 55%. Clearly, the prediction can be much higher by increasing the number of sample data. The ultimate goal of AI is to better serve specialists and patients in diagnosis, treatment, and precise and preventive medicine.

SB98

Estimatıng The Most Appropıate Treatment Methods For Psoriasis by Approaching Back Propagation Artificial Neural Networks

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Improvements in the performance of parallel processors have contributed greatly to the rapid increase in artificial intelligence (AI) applications. Compared to traditional processors, parallel processors can perform artificial learning operations within in a minute that will last for months. AI revolution has been made in many fields today. Artificial neural networks, a subset of AI, is a science based on mathematical modeling of the human brain. Artificial neural networks are generally based on two learning states with backward and forward spread. In this study, back propagation artificial neural network was used. Back-propagating neural networks perform learning by feeding with examples such as standard artificial neural networks. In feedforward neural networks, learning takes place only in the input layer towards the output layer, while in the feedforward neural networks, the learning progresses towards the input layer in the output layer, as well as learning within the layer can confirm itself. Confirmation can be considered as self-updating of the value corresponding to any information. Here, we present the study of estimating the most successful treatment method for psoriasis patients with feedback artificial neural networks. In this study, the success of the artificial neural network trained in eight categories of 100 psoriasis patients' clinical data. Age, disease type, family history, arthritis, pitting, smoking, stress and gender were evaluated. Results has been reported as 30%, but it is planned to improve studies by increasing patient's data. In the future, the introduction and innovation of AI theory and technology, will bring more professional, accurate and personalized assistive diagnosis and treatment in medical divisions.

SB99

A Rare Disease: Two Siblings With Autosomal Recessive Self-Healing Congenital Ichthyosis

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Introduction: Congenital ichthyosis is a disease characterized by dry skin, hyperkeratosis, skin scaling. It is frequently associated with erythroderma and genotype and phenotype present heterogeneity. Self-healing congenital ichthyosis is a subtype of autosomal recessive congenital ichthyosis and has been associated with mutations in the ALOX12B, ALOXE3 and TGM1 genes. Case Report: A girl with extensive hyperkeratotic membranes was admitted to the neonatal intensive care unit. She was delivered at 36 weeks, weight 2900g (50-75p). There was no consanguineousity between her parents. The patient was covered with collodion membranes, and there were edema and erythema in the hands and feet, ectropion and the eclabium. Her 12-year-old sister was followed in the neonatal intensive care unit with similar complaints in the neonatal period. Homozygous c.340C>T (R114W) mutation was detected in the ALOX12B gene by Whole Exom Sequencing due to the genetic etiology of congenital ichthyosis. Homozygous c.340C>T mutation was also detected in the sister of the patient. On the 24th day of hospitalization, the patient had complete regression of pathological skin findings. Discussion: She was diagnosed as autosomal recessive inherited congenital ichthyosis and the prevalence of this disease is extremely rare, as 1/1,000,000. Even in this type of ichthyosis cases, important health problems such as heat instability, dehydration, infection, hearing loss and skin cancers can be seen. In the diagnosis of congenital ichthyosis, genetic evaluation is important to confirm the diagnosis, to determine the prognosis, to manage the process, to provide genetic counseling and to plan the birth under appropriate conditions in subsequent pregnancies.

SB100

Rare Desmoplakin Phenotype: Skin Fragility / Woolly Hair Syndrome

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The cytoplasmic plaque protein desmoplakin found in desmosomes plays an important role in epithelial and muscle cell adhesion by binding transmembranous cadherins to the cytoplasmic intermediate filament network. Mutations in the desmoplakin (DSP) gene encoding desmoplakin protein can cause autosomal dominant/recessive inherited different phenotypes such as striate palmoplantar keratoderma, arrhythmogenic right ventricular dysplasia, fragile skin / wool hair syndrome, lethal acantholytic epidermolysis bullosa and Carvajal syndrome. In this case report, we aimed to present two siblings with ectodermal findings. A 6-year-old girl and a 2-year-old boy admitted to the Medical Genetics Outpatient Clinic; with palmoplantar keratoderma, wooly hair, dystrophic nail structure, skin dryness, and especially palmar facial peeling. Cardiac examination, electrocardiography and echocardiography were normal, skin biopsy supported hyperkeratosis and spongyosis. Our cases are of Syrian origin, and the parents had a second degree cousin marriage. A 4-year-old sister was followed-up with a preliminary diagnosis of CLOVES in addition to similar findings, but she died after surgery. Phenotypes related to CAST, DSP and JUP genes were considered in the molecular pathology. As a result of targeted next generation sequencing, c.7097G> A (p.Arg2366His) variation in the DSP gene was found in the proband in homozygous manner. The identified variation has been previously described in the literature and been reported disease causing variation for autosomal recessive inherited fragile skin / wool hair syndrome, Family segregation studies showed that the same variation was homozygous in the affected sibling, heterozygous DSP mutations were shown in her mother and father, demonstrating true homozygosity. The genotype-phenotype correlation for DSP-related phenotypes is not clear due to the complex structure of desmosomes and the existance of the related different. The phenotype of our case was consistent with 5 families reported in the literature diagnosed with fragile skin / wool hair syndrome. Because DSP-related cardiac findings occur at different ages and can be fatal, it is very important to follow up the patients .

SB106

3 Family Case Presentation With Hypodontia, Hypohydrosis, Hypotrichosis and Skin Findings

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Hypohidrotic Ectodermal Dysplasia (HED) is a genetic human disorder which affects structures of ectodermal origin. X-linked is the most frequent form of the disease. Inherited ichthyoses are a group of genetic disorders characterized by generalized dry skin, scaling and hyperkeratosis, and often associated with erythroderma. In this study we present 5 cases with ichtiyosis and/or HED from three family. A 5-year-old male from the first family admitted to the Medical Genetics Outpatient Clinic; with anhydrosis, hypodontia, hypothricosis and skin dryness, Next generation sequencing (NGS), revealed c.958+4C>G novel variation in STS gene in the proband in hemizygous manner and predicted as VUS according to the ACMG criteria. The second case was a 17 years old female with hypohydrosis, hypodontia, microdontia, hair loss and conic teeth. EDA: c.852delT (p.Phe284Leufs*88) variation was found in the proband in heterozygous manner. Analysis of family segregation showed that this novel variant was de novo and patogenic according to the ACMG criteria. The cases from the third family were a 21 years old male with skin dryness, ichtyotic skin, hyperkeratoses in hands and foot, 13 years old male with skin dryness, hyperkeratoses in hands and foot, bilaterally fifth finger nail hypoplasia, oligodontia, hypodontia, conic teeth, curly hair and a 10 years old female with hypothrichosis, oligodontia, hypodontia and conic teeth. As a result of NGS, c.852delT (p.Phe284Leufs*88) variant in FLG gene was found in the 21 years old male and c.463 C>T variant in EDA gene was detected in 13 years old female sibling in heterozygous manner, respectively.. Sanger confirmation of the detected variants in the family members are on the way. These unique cases will be discussed in the perspective of genotype-phenotype correlation.

SB107

Development of a New Web-Based Tool

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The widespread adoption of the next-generation sequencing has enabled scientists to document millions of variations in the human genomes, and a number of different databases human variants have been established to store the human genetic variations. Though many independent tools have been developed to infer the functional effects of genetic variants, functional inference of many variants obtained via tools may not always be accurate, requiring additional efforts.
We have therefore developed a new web-based platform that incorporates variations from various resources into a single database, including ClinVar, gnomAD, dbSNP and COSMIC, Wormbase, and C. elegans Million Mutation Project and Mutagenetix. We performed multiple sequence alignments together with the visualization of all genetic variations. Our final results will be discussed at the upcoming conference.
KEYWORDS: SNP,variation,pathogenic

Poster Presentatn Abstracts

PB15

Novel Edaradd Mutation in Three Affected Siblings With Ectodermal Dysplasia

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Ectodermal dysplasias(ED) is a clinically and genetically heterogeneous group of disorder characterized by the impaired development of2or more of the hair, nails, teeth and exocrine glands and is seen in approximately 1/10,000 frequency. Hypohydrotic/anhydrotic ectodermal dysplasia(HED) is the most common type which is inherited X-linked recessive, autosomal recessive/dominant. In the X-linked inherited form, the EDA1 (ectodysplasin) gene is responsible for 65-75% of all HEDs. In autosomal forms, EDAR (ectodysplasin receptor) accounts for 10-15% and EDARADD (EDAR associated death domain) causes 1-2%. In this study, we present a family of 3 affected children with c.424G>A homozygous mutation in the EDARADD gene. Two sisters aged 16, 3.5 and 11 year-old-male siblings were admitted to anhidrosis, absence of tear, hypotrichosis, oligodontia, and dry skin. In addition, the 11-year-old-brother also suffered from asthma allergy. It was learned that there were frequent recurrent fever and hospitalizations in infancy. There was a first cousin marriage between their parents. At 3 and 6 months of age, there were sibling deaths due to febrile seizures. Physical examination revealed dry-rough skin, scars due to scratching, oligo/anodontia, sparse hair/eyebrows/eyelashes, periorbital wrinkling and hyperpigmentation, prominent lips, ichthyosis-like appearance of the hands and feet, clubbing of the nails. A 16-year-old sister had bilateral amastia. In EDARADD gene analysis, c.424G>A homozygous mutation was detected and diagnosed as autosomal recessive HED. EDA1, EDAR and EDARADD proteins are members of the Tumor Necrosis Factor (TNF)-like EDA signaling pathway. The EDARADD gene is located in 1q42 and has a total of 11 mutations identified in HGMD

PB20

A Case of Erythroderma Due to Generalized Tinea Corporis Hidden by Ichthyosis Vulgaris

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Abstract
Erythroderma is defined as a generalized erythema and scaling involving more than 90% of the body surface area. Dermatophytosis is one of the etiologic factors of erythroderma. Generalized tinea infection may be caused by atypical lesions of tinea corporis in ichthyosis group diseases with widespread flaking as a result of keratinization disorder. Eventhough, dermatophytosis and ichthyosis vulgaris are relatively common diseases in the community, cases of coexistence have rarely been reported in the literature. The accompanying diseases such as atopic dermatitis, malignancy and diabetes may facilitate the occurance of widespread dermatophythosis. Herein, we present a 66-year-old female patient with erythroderma caused by generalized tinea corporis on ichthyosis vulgaris. We observed numerous hyphae on KOH examination of skin scrapings obtained from face, trunk and extremities. Additionally, intramucosal colon cancer that was detected during gastrointestinal system scans for the investigation of other causes of erythroderma may have facilitated spread of dermatophytosis in our patient.
Keywords: erythroderma, ichthyosis, dermatophytosis, cancer

Introduction
Ichthyosis is the name given to diseases that can be hereditary or acquired and progress with a diffuse scaling of the skin. Ichthyosis vulgaris with autosomal dominant transition is the most common and mild form of ichthyosis (1). It is characterized by ichthyosis, slowing of stratum corneum shedding, thickening (retention hyperkeratosis), changes in sebaceous and sweat gland functions. This creates an ideal natural environment for dermatophytes fed from keratinized tissues (2). Ichthyosis and diffuse dermatophytoses can cause a similar clinical presantation. Conventional ring-shaped lesions of tinea corporis may not always be seen in patients with ichthyosis. These two conditions may lead to dermatophyte overlook and spread of disease (3).
Erythroderma is a disorder in which more than 90% of the skin surface is covered with redness and scaling. Erythroderma may be idiopathic or it may occur due to dermatoses, drugs, malignancies (4). Dermatophytoses are among the dermatoses capable of erythroderma.
The atypical course of tinea corporis in patients with ichthyosis may be delayed diagnosis. Even experienced dermatologists may not be able to diagnose dermatophytosis in these cases. Therefore, we would like to remind that dermatophyte infections can be skipped in patients with ichthyosis, and dermatophytoses may result in erythroderma. As a conclusion, careful dermatological and direct mycological examination is needed in these patients.

Case report
A sixty-six-year-old woman presented to our clinic with complaints of redness, itching and burning in her body, which had been going on for about a month. The patient stated that she has had dryness on her skin since childhood, but a cream she has used as a moisturizer has caused redness with excessive itching for the past month.
It was determined that there was a diagnosis of ichthyosis vulgaris in his background,. In dermatological examination; on the extensor surfaces of the bilateral lower extremities, there were thin scales of white color on the back, dry appearance on the skin, erythematous patches and plaques on the trunk and left arm extensor surface (Figure 1,2). Biopsy was performed with the prediagnosis of mycosis fungoides and allergic contact dermatitis. The patient was recommended to use emollient containing 10% urea. (Figure 3-6) In histopathological examination of the skin biopsy taken from the erythematous papule on the trunk, numerous hyphae were observed with PAS. The patient was hospitalized with a erythroderma one month later. We observed numerous hyphae on KOH examination of skin scrapings obtained from face, trunk and extremities. There was no growing in the fungal culture.

Discussion
Deterioration in the skin barrier, cellular immune defect against tinea rubrum, delay in shedding in the keratin layer, atopic dermatit may lead to the formation of widespread and chronic dermatophytoses in patients with ichthyosis (5,6). Nevertheless, despite this environment is suitable for dermatophytes, cases where the two are together are rarely reported in the literature (2,3).
Dermatophytoses is usually localized. immunodeficiency, diabetes, steroid treatment, tinea incognito may lead to generalization of dermatophytoses. (3,7). It has been reported that atypical lesions of tinea corporis in ichthyosis vulgaris delay the diagnosis and form generalized involvement (8). The atypical appearance in our case delayed the diagnosis of dermatophytoses.
Despite the environment favorable to dermatophytes in ichthyosis, the association of generalized tinea corporis and ichthyosis in the literature is rare. The reason for this may be that ichthyosis hides generalized tinea corporis or generalized forms do not occur very often because in patients with ichthyosis, generalized tinea corporis usually occurs in the presence of facilitating factors such as atopic dermatitis, malignancy and diabetes. The underlying intramucosal colon cancer in our case may be a factor that facilitates the genaralization.

It is known that dermatophytoses can cause erythroderma. (4) In a study of 80 cases investigating the underlying dermatoses in the etiology of erythroderma, psoriasis is the most common dermatoses, and the frequency of dermatophytoses has been reported as 3.8%. (9).
Malignancies have been accused particulary in the etiology of treatment-resistant, recurrent erythroderma. These often include cutaneous T cell lymphomas. Although gastric and esophageal cancers are rarely reported in its etiology, we did not find any erythroderma cases related to colon cancer in the literature (10). We think that the erythroderma was due to generalized tinea corporis because of no suspected drug history, not showing resistance to treatment, and observing hyphae on KOH examinations.
As a conclude; in patients with ichthyosis, dermatophytoses may become generalized and chronic and overlooking of dermatophytoses may result in erythroderma. Therefore, careful dermatological and mycological examinations should be carried out in the presence of erythematous, papular symptoms, especially in cases of itched , clinically flaring or treatment-resistant ichthyosis .

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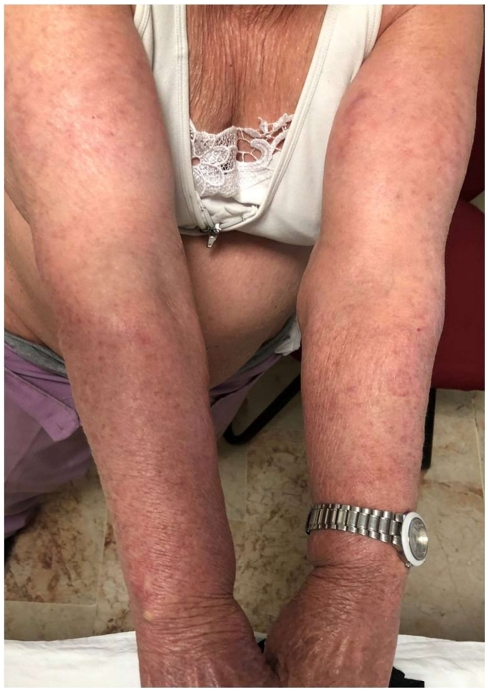

Figure 1: Appearance of the arms in the first dermatological examination
Erythematous annular plaque on the left forearm and erythematous patches and plaques on both hands and dorsal side of the forearm.

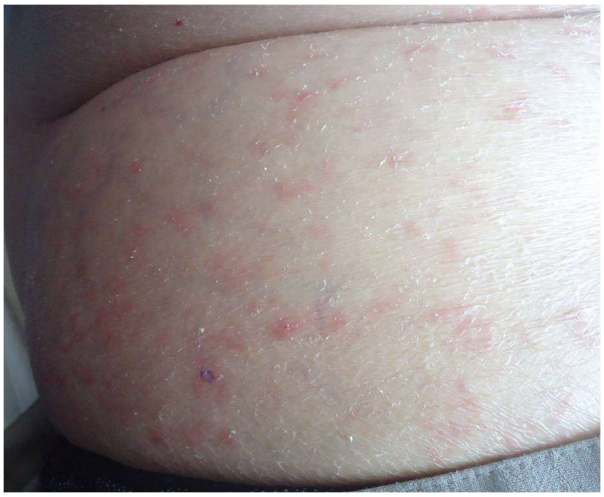

Figure 2: The appearance of the trunk in the first dermatological examination
Erythematous papules and plaques on ichthyosiform skin

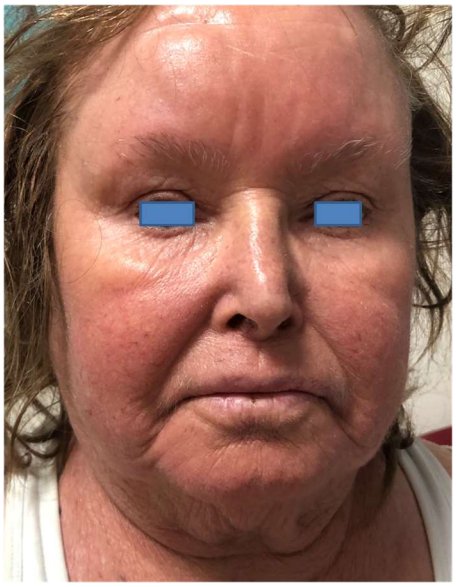

Figure 3: Facial appearance of the erythrodermic case

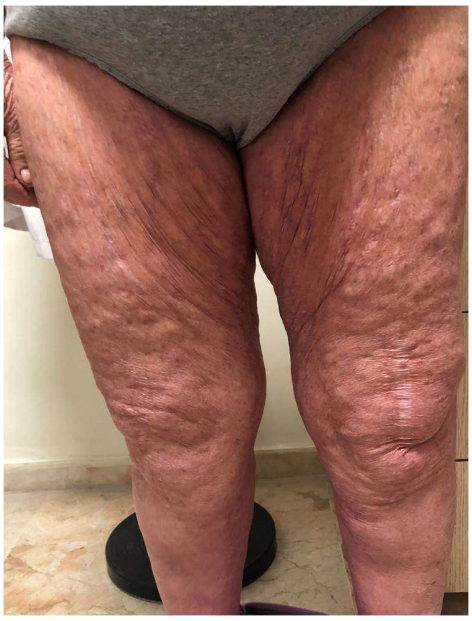

Figure 4: Appearance of the lower extremities of the erythrodermic case

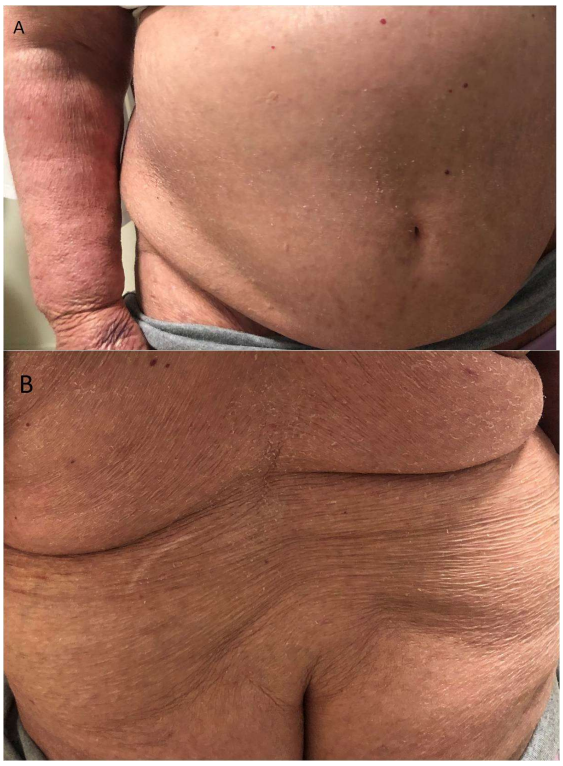

Figure 5: Anterior (A) and posterior (B) appearance of the trunk in erythrodermic patient

PB22

An Oculocutaneous Albinism Patient With a Deletion in TYR Gene

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Introduction-Aim: Oculocutaneous albinism (OCA) is an autosomal recessive disease caused by the complete absence or decrease of melanin biosynthesis. The primary clinical characteristic clinical is hypopigmentation of skin, hair and eyes. Ocular manifestations include nystagmus, iris hypopigmentation, foveal hypoplasia, reduced visual acuity and refractive errors. Oculocutaneous albinism is a genetic heterogen disease and divided into seven subgroups based on the affected genes. In this study we present an OCA Type 1A patient carrying a deletion in TYR gene.
Case Report: A ten-year-old patient with white hair and eyelashes was referred to our clinic. She was the second child of consanguineous parents. She had white hair, eyebrows, eyelashes, reddish blue coloured eyes and depigmented skin. Her ophthalmologic examination revealed iris translucency, retinal depigmentation and foveal hypoplasia. Physical examination revealed no additional pathologic signs. She was clinically diagnosed with OCA, and whole exome sequencing (WES) was performed due to the genetic heterogeneity of the disease. No disease causing variant was found following variant filtering. Due to the spesific clinical diagnosis of the patient, the genes responsible for OCA were reevaluated using IGV (The Integrative Genomics Viewer). And a sequencing failure in exon 3 of TYR gene was detected. A homozygous deletion of exon 3 was then confirmed using MLPA (Multiplex Ligation-dependent Probe Amplification) analysis.
Conclusion: Deletion mutations reported in the TYR gene are very rare (2%). In case of high clinical suspicion, where WES has been unable to provide confirmation, intragenic large deletions should be considered and evaluated via alternative methods.

PB25

A Case of Aplasia Cutis Congenita Multiple Lesion on Scalp and Limb

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Introduction: Aplasia cutis congenita (ACC) is a rare heterogeneous group of diseases characterized by non-inflammatory, well- circumscribed lesions occurring every 3 / 10,000 births regardless of race and gender. Although sporadic cases are typically seen, OD and OR inharitations have also been reported. Although disease natüre is isolated and bening, rarely it may present as components of anomalies and syndromes.
Case: A 22-year-old mother deliver 39 weeks and 4 days baby from the first pregnancy by normal spontaneous vaginal delivery. The dermatological examination of the baby revealed 2 ulcers on scalp 10x8mm diameter and 3x3 mm with hemorrhagic crusts. Bone tissue was palpated on the lesion floor. A 15x10mm epithelial defect extending from the medial metatarsal area to the proximal of the thumb was observed on the dorsal face of the baby's left foot. There was no consanguinity between the parents and the patients family had no history of similar scalp defects or other genetic diseases. There were no defects in the brain parenchyma and bone structures on left foot direct X-ray and cranial MRI. There aren't any syndromic findings. Gestational history didn't include any suspected of infection or medication.
Discussion: This case was evaluated as a sporadic case in group 1 and group 7 in Frieden classification because there was no underlying family history and genetic disease risk factors, no congenital malformation and syndromic findings, and no gestational history suspected for infection and drug. In this case, we wanted to draw attention to the fact that ACC can be seen with many congenital malformations and may be a part of syndromes as well as sporadic cases.

PB26

A Rare Case of Late Onset Unilateral Segmental Lentiginous

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Segmental lentiginous is a rare pigmentation disorder with typical lentigo histopathology characterized by unilateral and dermatomal localization of multiple, brown macules on skin.
Case: A 55-year-old female patient presented to clinic for spots on right half of her body. When she was 25 years old, she first noticed these spots on her right breast and spread to the trunk. She did not have any similar history in her family and denied additional systemic disease and drug use. Dermatological examination revealed multiple brown macules in the size of 1–15 mm located on the right breast, abdomen and back. Histopathology revealed lentigo findings characterized by melanocytic hyperplasia in the basal layer and prolonged rete ridge. Based on these findings, the patient was diagnosed as segmental lentiginous.
Discussion: Segmental or partial lentiginosis, lentiginous mosaicism are other terms used to describe this disease. In the pathogenesis, somatic mosaicism hypothesis has been proposed during embryonic development, possibly due to limited mutation to neural crest melanoblasts. Since it is seen in somatic cells, it cannot be seen in germ cells. Some segmental lentiginous cases have been shown to be associated with segmental neurofibromatosis and segmental Café au lait spots, which may be associated with somatic mosaism and postzigotic mutations. Neurological and opthalmologic pathologies were also found in a small number of patients. In our case, we highlight importance of somatic mosaicism in the differential diagnosis of pigmentation disorders due to the presence of lentigines on dermatomal localization, histological examination consistent with lentigo as unilateral segmental lentiginous.

PB33

A Sporadic Case of Mal De Meleda With 82DELT Mutation in The Gene Encoding SLURP-1

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Mal de Meleda (MDM) is a rare autosomal recessive genodermatosis characterized by transgredient palmoplantar keratoderma. Mutations in the gene encoding secreted mammalian lymphocyte antigen 6/urokinase-type plasminogen activator receptor related protein-1 (SLURP-1) have been identified in patients with MDM. Herein, we present a 56 year old Turkish male with erythematous and hyperkeratotic transgressive lesions on his feet and hands in a glove-and-sock pattern that have begun to develop in infancy. The palmoplantar skin revealed maceration with hyperhidrosis. Palmoplantar hyperkeratosis was severe with digital contractures. Nail changes included subungual hyperkeratosis, hyperconvexity and yellow-brown discoloration. Perioral erythema with angular cheilitis were noted. Teeth, hair and general physical examination were unremarkable. None of the family members were affected and consanguinity was not present. Histological examination of the skin biopsy that was taken from the dorsum of his right hand revealed hyperorthokeratosis, hypergranulosis, psoriasiform hyperplasia, acanthosis in epidermis and perivascular inflammatory infiltration, dilation of eccrine ducts in dermis. Genomic DNA was extracted from peripheral blood for mutation analysis and used for PCR amplification of the SLURP-1 gene. Direct sequencing of all PCR products of SLURP-1 gene was performed to identify the mutation. The 82delT mutation was detected in the SLURP-1 gene in our patient.

PB37

A Novel Combined C.1630T>C AND C.1579G>A Point Mutations in ALOX12B Gene in A Rare Autosomal Recessive Congenital Ichthyosis: A Case Report

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Objective and Aim: Ichthyosis is a clinically and etiologically heterogeneous group of diseases characterized by diffuse keratinization and cornification of the skin. Two combined heterozygous pathogenic mutations in ALOX12B gene in a rare case of ARCI were presented.
Case: A one-day-old female infant born from nonconsanguineus parents with 3700 gr weight, by spontaneous vaginal delivery at 39 weeks of gestation was referred to our medical genetics department.She had a healthy sister. Physical examination revealed diffuse lamellar peeling, scabbing on her skin, diffuse erythroderma, ectropion in both eyes, eclabium, blisters on oral mucosa, edema in her hands and feet.
Methods: Genomic DNA was isolated from peripheral blood and target genes were sequenced in Congenital Ichthyosis panel on IonTorrent S5 NGS platform , analyzed with ionreporter and IGV.Results: We detected two pathogenic heterozygous variants (c.1630T>C; C544R and c.1579G>A; V527M) in ALOX12B gene in the presented case report. The ALOX12B gene is associated with congenital ichthyosis type 2. Although individuals with pathogenic variant in the ALOX12B gene have been reported to exhibit congenital ichthyosiform erythroderma or intermediate phenotype, colloidone ichthyosis have also been reported as our case. The first point mutation of c.1630T>C (C544R) that detected in the current case has not been reported in the literature yet.
Conclusion and Discussion: Here we suggested that the novel point mutations that detected in the current case would provide a valuable resources for further clinical assessment in rare and different forms of ARCI. KeyWords: ALOX12B gene; c.1630T>C and c.1579G>A point mutations; NGS; ARCI

PB41

A Famıly With X-Lınked Recessive Hypohidrotic Ectodermal Dysplasia Due to EDA c.895G>A Mutation

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INTRODUCTION: Hypohydrotic ectodermal dysplasia (HED) is a rare hereditary disorder that is characterized by spare scalp and body hair (hypotricotic), hypohydrosis (less sweating) and hypodontia. HED is usually inherited in an X-linked manner, usually manifested only in males. The prevalence of the HED is estimated between 1:10000 and 1:100000 in male live births.Here, we report a Turkish family in which mother is a completely unaffected carrier of EDA c.895G>A with three affected sons and one unaffected daughter.
MATERIALS-METHODS: Family members (mother, three sons and a daughter) were clinically assessed, family history and peripheral blood samples were obtained for karyotyping and next generation sequencing with Sophia®hereditary disorder solution panel.
RESULTS: Karyotyping results were normal. Clinical exam results indicated that all family members had an EDA c.895G>A variant. Variant was observed heterozygously in mother and her daughter of whom were unaffected carriers. However, all boys were affected with typical features of hypohydrotic ectodermal dysplasia and had hemizygous EDA c.895G>A variant. This variant was previously reported to be disease causing mutation in HGMD in another case.
CONCLUSION: According to our knowledge, this is the first family from Turkey that is reported to be an X-linked HED due to EDA c.895G>A.
Keywords: EDA gene, EDA c.895G>A, X-linked hypohydrotic ectodermal dysplasia, rare disease

PB45

Intraoral Findings of Two Siblings With Aggressive Periodontitis Associated With Cathepsin C Gene Mutation

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Introduction and Aim: Cathepsin C(CTSC); proteolytically active lysosomal protease. Mutations in this gene are involved in etiology of syndromes such as Haim-Munk syndrome, Papillon-Lefevre syndrome, Aggressive periodontitis. In this case, we aimed to evaluate dental, systemic, genetic aspects of two siblings with spontaneous tooth loss, mobility.
Case Report: Two siblings, boys and girls, aged 11 and 9, applied to Marmara University Faculty of Dentistry, Department of Pedodontics with complaints of mobility and pain in the teeth. Intraoral examination of the patients revealed that all primary teeth were lost; gingival inflammation, first molars and lower incisors showed severe mobility and deep caries. Radiographic examination revealed no missing tooth germ and loss of alveolar bone in all permanent teeth. There were no signs of palmoplantar hyperkeratosis in siblings. Apart from periodontitis, other systemic or genetic diseases that could cause premature tooth loss were excluded. All exome sequence analysis study of hereditary, autosomal recessive inherited early tooth loss revealed c:919G>A,(p.Ala 307Thr) homozygous VUS(NM_001814.5) in the CSTC gene. This variant; Clinvar and HGMD were absent, VarSome was LG, and a possible pathogen novel mutation to explain the disease. During the dental treatment, female patient, 16,46 teeth; male patient spontaneously lost all his first molars. Patients received periodontal treatment; lower incisors were splinted. In the follow-up of patients, it was decided to extract 41 of female patient and 32-42 teeth of male patient.
Conclusion: According to intraoral findings and CSTCc:919G>A homozygous gene mutation, patients are thought to have aggressive periodontitis. The follow-up of patients continues.

PB46

Ectodermal Dysplasia Pronounced With Tooth Agenesis Due to WNT10A Gene Mutation

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Introduction and Aim: Many studies showing that WNT signaling pathway regulates programmed cell death(apoptosis) through various mechanisms.Mutations in this gene are involved in etiology of syndromes such as Odontoonycodermal dysplasia, Schopf-schulz-passarge syndrome, tooth agenesis.In this case report, we aimed to evaluate dental, systemic and genetic aspects of a female patient with oligodontia, malformed teeth with cone-shaped and dental caries.
Case Report:A 12-year-old girl who had a history of sparse hair and eyebrows since she was born and a history of non-shedding of primary teeth after 7 years of age applied to Department of Pedodontics with complaints of malformation and pain in teeth. Intraoral examination of patients revealed that there were 55-52,62,63,65,71-73,75,81-83,85 and 17,13,11,21,27,33,37,43,47 and primary molars have deep caries. In the radiographic examination; there were no permanent tooth germs 12,14-16,22-26,34-36,31,32,41,42,44-46.During the treatment process, 54 was extracted; endodontic and restorative treatments of 55,65,75,85,11,21 were done. In genetic examination of patient, it was found that intraoral sparse, conical teeth, hair loss on the forehead and eyebrows, dryness of skin, fracture of fingernails and elongation of the toes, bilateral second finger nails were dystrophic, and the fingernails were hypoplasic. Sweating and tears were present. The parents of patient were relatives. The patient was considered an ectordemal dysplasia predominantly oligodontia.
Conclusion: In whole exome sequence analysis(WES), c.831G>T,(p.Try277Cys) homozygous VUS(NM_25216.2) was detected in WNT10A gene. This variant, HGMD:CM149001/DM?/Tooth agenesis is indicated as VUS in Clinvar and VarSome and is considered as a possible pathogen novel mutation explaining tooth agenesis with mild ectodermal findings in our patient.

PB47

A Case of Hereditary Benign Telangiectasia

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Hereditary benign telangiectasia (HBT) is an autosomal dominant disease with telangiectasis on the face, upper trunk and the extensor face of the extremities. HBT does not show mucosal involvement, unlike hereditary hemorrhagic telangiectasia (HHT), where skin telangiectasias occur at a late age and early signs of bleeding such as epistaxis in childhood are observed. It is more common in women. It is important to make a differential diagnosis of good clinical course of HBT, which causes only cosmetic problems, from HHT, which can cause serious clinical conditions. Herein, we present a rare case of a 17-year-old girl with HBT who had similar findings in her mother and grandmother.

PB48

Dowling-Degos Disease in a Turkish Family

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Dowling-Degos disease (DDD) is a rare autosomal dominant reticular pigmentary disorder. The onset of the disease usually occurs in the third or fourth decade. A 56-year-old female presented with symetrically distributed pigmented macules on her neck, axilla, inframammary region, inguinal folds and abdomen that slowly appeared in 25 years. Comedo-like hyperkeratotic dark papules were seen on her face, neck and popliteal region. Pitted perioral acneiform scars were noted. She reported that her son, two daughters, sister, mother, grandfather and sister's children had similar dermatological conditions. Her 32-year-old daughter had reticular brownish pigmentation involving axillae, neck, inguinal folds and inframammary area for ten years. Comedo-like hyperkeratotic dark papules were seen on her face and neck. Pitted perioral acneiform scars were present. Teeth, nail, hair and general physical examination were unremarkable in both patients. Histological examination of the pigmented lesions revealed slender rete ridge elongation with antler-like pattern and basillary pigmentation was remarkable. Acantholysis was not detected. There were no evidence of mutation of all exons of the KRT5 gene on genetic analysis in the present family. Up to date, KRT5, POGLUT1, POFUT1 and PSENEN gene mutations were reported in cases with DDD in literature.

PB51

Control of T and B Cell Development by TREC/KREC Analysis in Primary Immunodeficiency Patients and Healthy Controls

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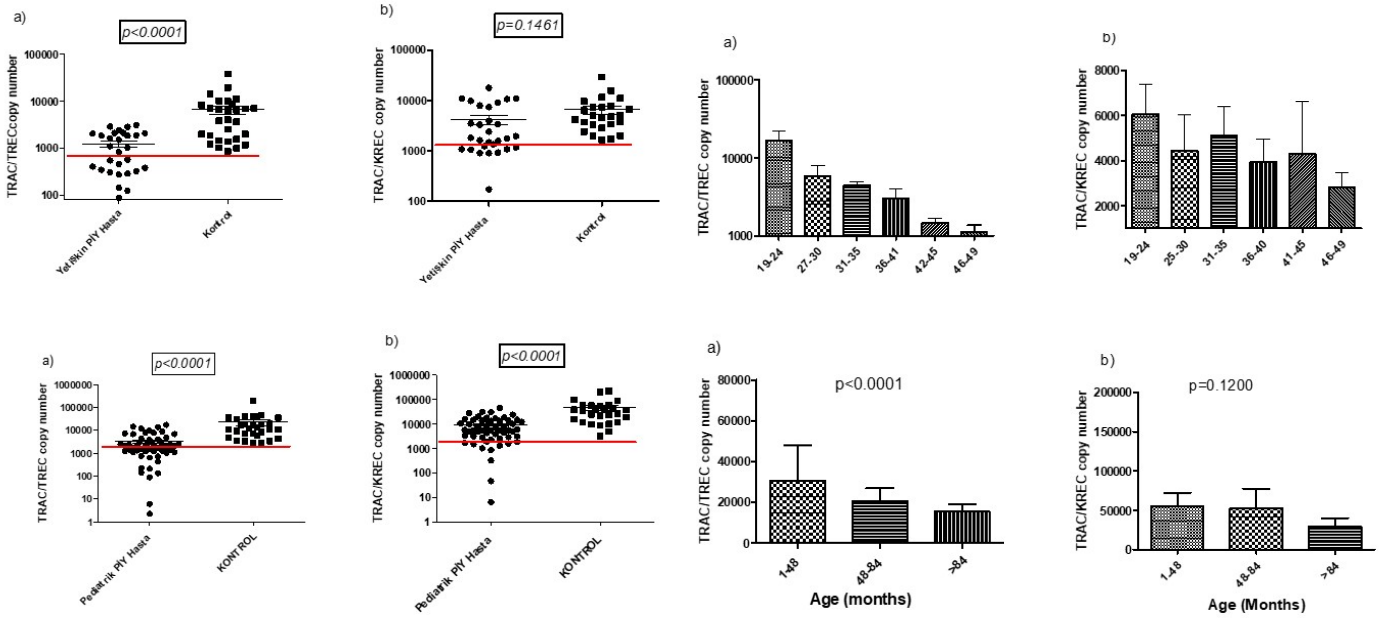
Introduction: Primary immunodeficiency (PID) is a rare, genetic disease that disrupts the function of the immune system. It is important to examine T and B cell development for the early diagnosis of PID. T cell receptor excision circle (TREC) and kappa-deleting excision circle (KREC) are circular, permanent DNA fragments that are formed during somatic recombinations in T and B cells receptor development. They reflect the number of lymphocytes and can be used as biomarkers in prediagnosis of PIDs.The aim of this study is to determine TREC/KREC copies in pediatric and adult patients with pre-diagnosis of PID and to establish a method for PID screening
Method: Fifty six pediatric, 29 adult patients were and 29 adults and 51 pediatric healthy controls were studied. After DNA isolation, TREC / KREC copy number analysis was performed by qRT-PCR. For absolute quantification, plasmids with known TRAC,TREC AND KREC copy numbers were used.
Conclusion: TREC copies of adult PID patients was significantly lower than the control group. KREC copies were also lower than controls but was not statisticaly significant. In pediatric PID patients, TREC / KREC copy numbers were significantly lower than controls and TREC numbers were decreasing in older ages. But the KREC copies did not change depending on age. The inability of T and B cells to mature during gene recombination in individuals with PID causes low TREC / KREC copy, counts. It is thought that thymus activity decreases with age which can explain low TREC copy numbers in older ages..



PB53

Dystrophic Epidermolysis Bullosa: Intrafamilial Clinical Heterogeneity

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Dystrophic epidermolysis bullosa (DEB) is a rare genodermatosis characterized by blisters caused by mutations in the COL7A1 gene. COL7A1 encodes the alpha chain of type 7 collagen which is the major component of anchoring fibrils at the dermal-epidermal junction. There are two types of DEB as autosomal dominant and autosomal recessive. Blisters accompanying nail dystrophy is observed in the autosomal dominant form which is usually milder. The blisters usually occurs at infancy. Heterozygous glycine substitutions are the most common mutations in autosomal dominant form of DEB. Glycine substitutions disrupt collagen VII anchoring fibril formation through dominant-negative interference. Here we present three siblings with epidermolysis bullosa that exhibit intrafamilial phenotypic variability. Younger sister manifested blisters on her feet at birth; later her lesions progressed to knees, elbows, hands and trunk. She had nail dystrophies of right hand and feet. Skin biopsy of the patient revealed superficial perivascular and interstitial dermatitis with full-thickness epidermal loss and milia as a result of sub-epidermal separation. Onset of her siblings' blisters was at infancy and their course was milder. Their skin biopsy showed vesiculobullous dermatitis characterized by sub-epidermal separation. Genomic DNA was isolated from peripheral blood samples of the patients and exon 73 of COL7A1 was sequenced. Heterozygous c.6127G>A (p.Gly2043Arg) mutation was found in the siblings; but wasn't found in their parents. These results suggested that one of parents has gametic mosaicism for p.Gly2043Arg mutation. This family demonstrates clinical heterogeneity of dominant DEB.

PB54

A Case of Mal De Meleda Presenting With a Novel Mutation in the SLURP1 Gene

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Mal de Meleda is a rare autosomal recessive palmoplantar keratoderma (PPK) disease with an estimated prevalence of 1/100000. Clinically, the onset of the disease is typically soon after birth and features a transgrediens and progrediens pattern of hyperkeratosis of the palms and soles. Disease is assosiated with LY6/urokinase-type plasminogen activator receptor (uPAR)-related protein-1 (SLURP-1) mutation. Two years old girl admitted to our dermatology clinic with complaints of thickening of the skin at the palmoplantar faces of hands and feet and spreading to the dorsal surfaces of fingers. There is no consanguinity between the parents; but similar history was described in distant relatives. Dermatological examination revealed hyperkeratotic plaques with well demarcated erythematous borders on palmoplantar regions spreading to extensor surfaces, premature decay of teeth and erythematous plaque on genital region. Histopathology established hyperkeratotic epidermis showing hypergranulosis and spongiosis, and mild perivasculer lymphocytic infiltration in upper dermis. Sequence analysis of SLURP1 revealed a novel variant (c.149 G>A, p.Cys50Tyr) which was classified as a variant of unknown significance according to ACMG 2015 criteria. Segregation analysis of parents and sibling is continuing.

PB60

A Rare Mandibuloacral Dysplasia Case Due to LMNA Gene Mutation

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Mandibuloacral Dysplasia is a rare syndrome with autosomal recessive inheritance characterized by mandibular hypoplasia, skeletal abnormalities, progeroid appearance and growth delay.Homozygous or compound heterozygous mutations in the LMNA gene, which encodes Lamin A and Lamin C proteins in the nuclear membrane, are responsible for the phenotype.The aim of this study is to discuss the phenotype and genotype correlation of this rare syndrome. After DNA isolation from peripheral blood, all exon and exon-intron boundaries of the LMNA gene were sequenced using the Next-Generation Sequencing (NGS) method. A 21-year-old female patient was consulted to our clinic because of growth and developmental delay and dysmorphism. There was no similar history in the family and her parents had a first cousin consanguineous marriage. Her neuromotor development was not delayed.All anthropometric measurements were below the 3rd percentile. Dysmorphologic examination revealed sparse hair and eyelashes, fine eyebrows, exophthalmic eyes, beak nose structure, maxillary and mandibular hypoplasia, decayed and irregular teeth, low-set-ears. She had also thin skin structure, shortness and contracture of distal phalanges of fingers and toes. X-ray films revealed mandibular hypoplasia, narrow chest structure, short clavicula, and osteolysis of the distal phalanx. Homozygous c.1580G>A (p.Arg527His) pathogenic mutation was detected in LMNA gene sequencing. Segregation analysis was recommended for parents. Although mandibuloacral dysplasia is a rare syndrome, it can be diagnosed clinically by detecting progeroid appearance, skeletal anomalies and mandibular hypoplasia. , LMNA gene mutation analysis is important to differentiate other laminopathies such as lipodystrophies and Hutchinson-Gilford progeria syndrome and to provide appropriate genetic counseling.

PB63

Gene Defining by Whole Exome Reanalysis

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Whole exome sequencing is an important genetic diagnosis tool, and its success rate is 30-35%. However, this rate can be increased with the re-analysis approach by using clinical findings and literature. Here, we present our process on re-analysis of exome sequencing by a case in which an exome sequencing was performed and no clinically relevant variant detected. A 57- year-old female patient suffering for 10 years from abjunction, weakness, flushing, and wasting of the face and palpitation after frequent sit-ups especially after eating (tropical fruits) was applied to the clinic. Low plasma levels of renin activity, arterial blood gas respiratory alkalosis, hypokalemia, and hypertension. Exome sequencing was performed and no clinically relevant variant was found. The patient applied to ACURARE for re-analyzing the exome data. The data were analyzed by bioinformatics methods. The patient was also evaluated for heterozygous de novo mutations as she was the only known case in the family. Also, the patients' clinical data were analyzed with the 'Phenomizer' tool in the Human Phenotype Ontology database, and genes that could be associated with the disease were prioritized. As a result, a heterozygous with a MAF value of less than 0.001 was detected in CACNA1H gene. CACNA1H was associated with familial hyperaldosteronism type IV, and the clinic confirmed that the clinic was. These results indicate that the re-analyzing approach in exome sequencing together with clinical data is very important in explaining the molecular backgrounds of the diseases.

Table 1 – Bioinformatic methods used

Used bioinformatic methods
Quality Control (Samstat-1.5.1)
Marking and Removing Duplicates (Picard-2.20.7)
Creating Variant Lists (GATK-4.1.3.0)
Annotation (ANNOVAR)
Finding related genes with the clinic (Phenomizer by HPO)
Used filters
Exonic, splicing variants
Missense/Nonsense variants
Potential disease-causing variants (SIFT, PolyPhen2, MutationTaster)
Heterozygous
Minor allele frequencies < 0,01
de novo variants
Genes, related with the clinic

Introduction

A 57-year-old female patient presented to the clinic for 10 years after eating (especially tropical fruits such as bananas) with complaints of abjunction, weakness, flushing and wasting of the face and palpitation after frequent sit-ups, and after the examination and tests, she had low plasma levels renin activity, arterial blood gas respiratory alkalosis, hypokalemia, hypertension. The patient sample was then sent for whole exome sequencing. As the results of the company did not comply with the patient clinic, the data was sent to Acıbadem University Rare Diseases and Orphan Drugs Application and Research Center.

Material - Method

All bioinformatic applications and analysis done with a notebook computer which has Intel i7 7700K CPU, NVIDIA Geforce GTX 1050 4GB GPU, 8GB RAM. The data which sequenced and mapped to hg19 referance genome is filtered from spoil reads and oligonucleotides which used for sequencing by Picard (2.20.7) tool's 'MarkDuplicates' and 'REMOVE DUPLICATES' functions. The .bam file used for calling single nucleotide polymorphisms (SNP) and insertion-deletion variants and remove bad scored readings by Genome Analysis Toolkit's (GATK-4.1.3.0) 'HaplotypeCaller' function. For prepare the SNP and INDEL data to analyze, ANNOVAR tool used for to call online database informations of variants. For filtering "dbnsfp30a (for preditcion tools' reports of variants), gnomad_exome and exac03(for minor allel frequencies of variants), cytoBand (for chromosomal locations of variants), avsnp147 (for rs codes of variants), cosmic68 (for variant informations in COSMIC)" commands used and the data ready for analysis.
On analysis; 'exonic', 'nonsynonymous SNV', 'frameshift DEL', 'frameshift INS' variants filtered. After that variants which minor allel frequencies (MAF) lower than 0.01 and disease causing variants by prediction tools (SIFT, PolyPhen2, MutationTaster) filtered. When we couldn't get any variant that gives a result, we used 'Phenomizer by Human Phenotype Ontology' for to find related genes with patient's condition and founded genes added to filter.

Results

As a result of these filtering, we found a mutation in the CACNA1H gene with heterozygous and MAF below 0.001. Mutations in this gene have led to familial hyperaldosteronism, type IV, and generalized idiopathic epilepsy. When the patient's epicrisis was compatible with familial hyperaldosteronism, type IV, the doctor was informated. The patient sample has been sent to Sanger sequencing for confirmation.

PB64

ELOVL4 Mutation in a Case With Ichthyosis, Spastic Quadrıplegia, and Mental Retardation Syndrome (ISQMR)

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Ichthyosis, spastic quadriplegia and mental retardation syndrome (ISQMR) is a autosomal recessive disorder which is characterized by ichthyosis, profound psychomotor retardation, spastic quadriplegia and seizures. ISQMR syndrome is caused by biallelic mutation in the ELOVL4 gene on chromosome 6q14.
Case with congenital ichthyosis, psychomotor retardation and epilepsy who had consanguinity between her parents was referred to us for evaluation of genetic diseases. Firstly, we performed ALDH3A2 gene sequence analysis and did not detect any mutation. In the second stage, we planned Whole Exome Sequencing (WES) with preliminary diagnosis of epileptic encephalopathy and congenital ichthyosis. Genes associated with epilepsy and ichthyosis phenotypes were filtered from Human Phenotype Ontology (HPO). We detected p.H192R (c.575A>G) homozygous mutation in ELOVL4 gene which is reported with 'Ichthyosis, underdevelopment and microcephaly' phenotype before. We aimed to emphasize that we should be kept in mind ELOVL4 gene together with the ALDH3A2 gene in patients with congenital ichthyosis, psychomotor retardation and seizures.

PB67

Case Report: Epidermolytic Hyperkeratosis

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Introduction: Epidermolytic hyperkeratosis is an autosomal dominant, mostly sporadic, rare disease characterized by keratinization disorder of the epidermis. Classically, skin redness, squamation and blistering are observed at birth or soon after birth, followed by marked hyperkeratosis. The characteristic histopathological findings differ from other congenital ichthyoses, but the gold standard for diagnosis is to show missense mutation in the keratin 1 (KRT1) or keratin 10 (KRT10) genes. This case aims to emphasize that the best approach in single gene diseases of the skin, especially when the differential diagnosis is challenging, is genome-level examinations and can guide the treatment.
Case Report: A 10-month-old girl born to non-consanguineous parents, presented with complaints of bullae, redness, peeling and flaking on the skin from birth. Patient was previously treated with the preliminary diagnosis of Ritter's disease and epidermolysis bullosa but no response was seen. There were no individuals with similar skin findings in the family. The patient, who had no dysmorphic appearance and had normal development, had yellow-gray lamellar hyperkeratotic dandruff on the scalp, extremities and whole trunk, dried bulls and erosions on the hands and arms. The palms, soles, hair and teeth were normal. Biopsy was reported as diffuse epidermolytic hyperkeratosis. The patient was referred to the pediatric genetics department and heterozygous missense mutation in the KRT10 gene was demonstrated by whole genome sequencing (WGS). The patient was started on oral acitretin 5 mg every other day for 3 months.
Conclusion: Epidermolytic hyperkeratosis, a rare disease, is the only keratin disease with genetic mosaicism in humans. Congenital ichthyosis such as ichthyosis bullosa, lamellar ichthyosis, epidermolysis bullosa should be considered in the differential diagnosis. Skin barrier dysfunction increases the risk of infection, dehydration and electrolyte imbalance. The treatment approach is symptomatic, mainly includes hydration, lubrication and keratolysis. Oral or topical retinoids have been shown to be beneficial in patients with KRT10 mutations.

PB68

Waardenburg Syndrome: A Report of Three Sibling

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OBJECTIVES: Waardenburg Syndrome is a group of diseases that are associated with deafness and pigmentation changes in hair, skin, and eyes. Waardenburg syndrome affects an estimated 1 in 40,000 people. Patients with this syndrome have pale blue eyes or heterochromia. White or gray hair in the local area of hair is another symptom of this syndrome. The features may be different even in patients in the same family.
CASE: Recently, H. A., a newborn referred to the medical genetics clinic of Eskişehir Şehir Hospital by his pediatrician for evaluation of partial hair color difference and congenital deafness(positive Otoacoustic Emission-OAE- test result). He was the third child of consanguineous parents. All three siblings had bright blue eyes but the second one without deafness and any depigmentation sign of the current syndrome. However, molecular genetic analysis of the second child are performed due to suspicion of the syndrome. The Sequence analysis of patients continues to be examined.
CONCLUSION: In this study, we presented three siblings from the family who were clinically diagnosed with Waardenburg Syndrome. All pediatricians and family physicians should remember that hearing tests should be performed when they examine children with white forelock and bright blue eyes. Early diagnosis and treatment of hearing loss are important for the psychological and mental development of patients with this rare disease. After the genetic analysis of mutation, genetic counseling patients and their relatives about the clinical course of the syndrome are also useful.
Keywords: Waardenburg Syndrome, Rare Disease, Sequence analysis

PB70

Novel Missense Mutation in Phospholipase C-Gamma-2 Gene (PLCG2) Causes Cold-Induced Psorıasıs: A Case Report

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The PLCG2 gene encodes phospholipase PLCγ2 enzyme that plays a critical regulatory role in various immune and inflammatory pathways. Mutated gene profiles were reported in ''Familial cold autoinflammatory syndrome 3 (FCAS3)", In the current case it was aimed to find out the possible role of PLCG2 gene in cold- induced psoriasis pathogenesis. DNA sample was genotyped for Autoinflammatory panel including target 12 genes (MEFV, TNFRSF1A, NLRP3, MVK, NOD2, IL1RN, IL10RA, IL10RB, IL10, PSTPIP1, LPIN2, PLCG2) by IonTorrent S5 NGS platform and analysed with IonReporter and Parseq-VariFind™AIP assay. We reported a 63-year-old female Turkish patient from Çanakkale, diagnosed as Psoriazis since she was 7 years old. Also she has short stature, psoriatic arthritis, patella subluxation, celiac disease, migraine. Dramatically, psoriatic plaques immediately appeared on her body as soon as she arrived in Uludağ for her winter vacation and she has benefit from the thermal spring. We identified a novel heterozygous missense mutation in PLCG2 gene (c.3504G>T, p.Lys1168Asn)which is patogenic mutation; in silico assessment was as follows; SIFT:0.004, MutationTaster Disease Causing, DANN:0.9989, FATHMM-MKL damaging, DEOGEN2damaging, EIGENpathogenic Population frequency: 0.00000884 (Non Finnish European). L1168A mutation in PLGC2 gene has not been reported in the literature yet. In conclusion, enhanced PLCγ2 activity due to p.Lys1168Asn point mutation may be provoke cold-induced psoriatic pathogenesis by the leukocyte hyperactivities as a inflammatory and immune-related disease in the presented case.
Keywords: PLCG2 gene; novel point mutation; c.3504G>T; NGS; cold-induced psoriasis

PB73

A Novel Try Gene Variant in Oculocutaneous Albinism Disorder

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Introduction-Aim: Albinism is the general term for rare and genetic diseases that are characterized by lack or no production of melanin, resulting in no pigmentation in the skin, hair, and eyes. Albinism is classified into three main groups: oculocutaneous (whole melanin deficiency), ocular (melanin deficiency only in the eyes) or syndromic and as the molecular basis, variants on more than twenty genes have been identified. The most common variant is determined in the TYR gene (40%). High heterogeneity observed both clinically and genetically leads to the difficulty in genotype-phenotype correlation and under-diagnosis, misdiagnosis or delayed diagnosis. Here we present a novel variant in TYR gene in our study for TRY variant screening in our population.
Method: A two years old girl who was diagnosed as oculocutaneous albinism was screened for TYR gene. Following DNA isolation, all exons of TYR gene were studied by PCR and direct sequencing and analyzed by the CLC workbench program.
Results and Conclusion: A homozygous chr11:c.1259 A>G, p.His420Arg variant was determined in the patient. The variant has been identified for the first the in the literature. Various in silico algorithms were used to the predict the effect; according to "MutationTaster", mutation was predicted to be "disease-causing" with the score of 29, according to "PolyPhen", it was predicted to be "probably damaging" with a score of 0.993, according to "SIFT", it was predicted to be "damaging" with a score of "0". The responsible TYR gene locates on chromosome 11q14.3, encodes tyrosinase enzyme, is a gene 65 kb long and containing 5 exons. The variant we identified is close to the copper-binding site (Cu-A active site). A different variant was previously defined in the same region (rs61754392) and variant has been pathogenically associated with tyrosinase-negative oculocutaneous albinism in ClinVar (variation ID: 3792). Furthermore, the variant region is highly conserved in various species. All these data indicate that the identified novel variant may be associated with albinism observed in the patient, however, it should be shown that the amount and activity of tyrosinase are affected by functional analyzes. Blood samples were requested from the parents of the patient for familial segregation studies.

A NOVEL TRY GENE VARIANT IN OCULOCUTANEOUS ALBINISM DISORDER

Introduction-Aim: Organelles, in which the melanin pigment that gives color to our body is produced, are called melanocytes. After melanin production, melanosomes are placed in the follicles of hair, skin, eyes and inner ear by melanosomes. The process of melanin synthesis is multi-step and damage to genes in which the proteins involved in any of these steps are produced can cause diseases with pigment deficiency. Albinism is the general term for rare and genetic diseases that are characterized by the lack or no production of melanin, resulting in no pigmentation in the skin, hair, and eyes. One of the major problems caused by albinism is severe visual impairment and the other is an increased risk of skin cancer. Albinism is classified into three main groups: oculocutaneous (lack of formation of melanin pigment throughout the body), ocular (melanin deficiency only in the eyes) or syndromic and as the molecular basis, variants on more than twenty genes have been identified. According to the current situation in the literature, 23 genes have been associated with albinism or hypopigmentation diseases. The most common variant is determined in the TYR gene (40%). High heterogeneity observed both clinically and genetically leads to the difficulty in genotype-phenotype correlation and under-diagnosis, misdiagnosis or delayed diagnosis. Here we present a novel variant in the TYR gene in our study to TRY variant screening in our population.
Method: A 10-ml peripheral blood sample was taken from an albinism patient, a two-year-old girl diagnosed with a clinical evaluation scale, by ophthalmology and dermatology specialists. Sample preparation and storage conditions were performed according to the instructions of Acıbadem Mehmet Ali Aydınlar University Biobank. DNA isolation was performed with a filter-based isolation kit that provides standard isolation with high quality. The quality and quantity of the patient sample were evaluated with the Nanodrop device. Following DNA isolation, all exons of the TYR gene were studied by PCR direct sequencing with sequencing primers designed and analyzed by the CLC workbench program.
Results and Conclusion: A homozygous chr11:c.1259 A>G, p.His420Arg variant was determined in the patient.

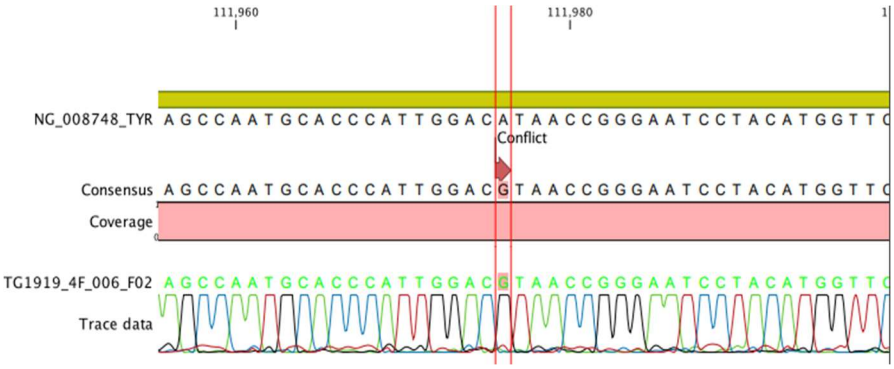

Figure 1: Identification of c.1259 A> G mutation in TYR gene by Sanger sequencing

The variant has been identified for the first in the literature. Various in silico algorithms were used to the predict the effect; according to "MutationTaster", mutation was predicted to be "disease-causing" with the score of 29, according to "PolyPhen", it was predicted to be "probably damaging" with a score of 0.993, according to "SIFT", it was predicted to be "damaging" with a score of "0". The responsible TYR gene locates on chromosome 11q14.3, encodes tyrosinase enzyme, is a gene 65 kb long and contains 5 exons. The variant we identified is close to the copper-binding site (Cu-A active site). A different variant was previously defined in the same region (rs61754392) and variant has been pathogenically associated with tyrosinase-negative oculocutaneous albinism in ClinVar (variation ID: 3792).

Algorithm	Score	Prediction
SIFT	0	Damaging
Polyphen-2_HDIV	0.993	Probably damaging
MutationTaster	29	Disease causing
MutationAssessor	3.51	Func. Impact: High
FATHMM	-5.14	Damaging
PROVEAN	-5.925	Deleterious
M-CAP	0.611	Possibly Pathogenic
CADD	26.4	Likely deleterious
FATHMM_MKL	0.98523	Damaging
MutPred 1.2	0.479	> 0.5 could be considered as 'harmful'

Table 1: Scores and effects of the found variant in silico prediction tools

Furthermore, His residue is a highly conserved amino acid of various species, including Ptroglodytes, Mmulatta, Mmusculus, Ggallus, Trubripes, Drerio and Xtropicalis.

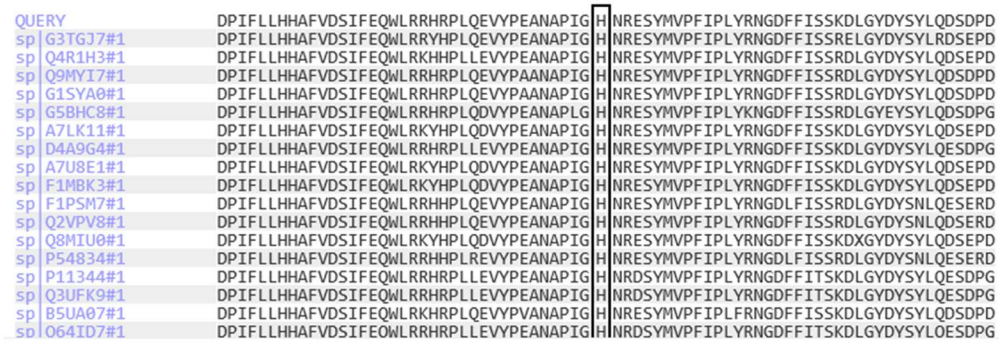

Figure 2: Preservation of His residues among species

All these data indicate that the identified novel variant may be associated with albinism observed in the patient, however, it should be shown that the amount and activity of tyrosinase are affected by functional analyzes. Blood samples were requested from the parents of the patient for familial segregation studies.

PB77

Ellis Van Creveld Syndrome With Immun Deficiency

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Ellis Van Creveld(EVC) disease is an autosomal recessive chondral and ectodermal dysplasia.It is a very rare disease due to EVC and EVC2 mutations.In particular,the EVC2 protein is thought to help regulate a signaling pathway known as Sonic Hedgehog,which plays a role in cell growth,Specialization and normal shaping of many parts of the body.EVC syndrome follows short ribs,polydactyly,growth retardation,Ectodermal and heart defects.Cognitive and motor development is normal. In this case, we aimed to evaluate this rare disease genetically. 39w3d,2475 gr born 6-year-old patient due to congenital heart defect in the neonatal period was admitted to the intensive care unit.Post-natal echocardiography showed atrioventricular septal defect,single AV valve,inlet wide VSD and wide primum ASD.During the physical examination of our patient,post-axial polydactyly in bilateral hands and syndactyly in bilateral feet (2-3),disproportionate short stature,rhizomelic shortness in extremities,narrow rib cage,flattened nasal root,hypodontic and nail dysplasia were present.In addition the patient with bronchopulner dysplasia was accompanied by immunodeficiency and was receiving IVIG.In our case,homozygous c.709G> T mutation was detected by EVC2 gene sequence analysis.Mutationtaster and Varsome and in silico genetic prediction evaluation,this change was interpreted pathologically.This interesting disease,also called hast 'six-fingered dwarfism',has many aspects waiting to be solved.EVC-related gene mutations are thought to be associated with a group of diseases called ciliopathy.In our case,immunodeficiency,bronchopulmonary dysplasia and cholelithiasis are associated with different cases reported in the literature.In order to increase the life expectancy of EVC patients,it is important to adopt a multidisciplinary approach to various clinical problems that may be seen in this process.

PB78

Bırt-Hogg-Dube Syndrome, A Rare Case

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Birt-hogg dube syndrome(BHD),a very rare disease,is an autosomal dominant disorder due to mutations in the FLCN gene.FLCN gene mutations are frameshift,nonsense or splice site mutations predicted to truncate and presumably inactivate the FLCN protein.This protein is believed to be tumor supreesor.BHD affects the skin and lungs and increases the risk of certain types of tumors.Disease severity can vary significantly even within the same family.Our patient had bilateral multifocal lung cysts,while her sister had skin lesions.The aim of this case report is to share the rarely seen BHD syndrome in which spontaneous pneumothorax may be familial.A 49-year-old female patient had occasional chest pain and dyspnea.Spontaneous pneumothorax history was present in previous years.No skin lesions were detected.In thorax CT,peribroncovascular-subpleural multiple air cysts and bullae were observed in the lower zones of both lungs.There was no renal pathology in abdominal USG.The patient had no known history of additional disease except atrial fibrillation.The patient has a history of isolated lung lesions in five family members in the family tree.One sister has isolated skin lesions.FLCN gene heterozygous c.350_357delTCTTCAGC /p.L117HfsTer13 mutation was found.Genetic counseling was given to the patient.BHD syndrome is characterized by three organ involvement.Skin fibrofolliculoma,lung cysts and increased risk of renal tumors.They may be present in a patient at the same time or may be independent of each other.BHD syndrome should be considered in the differential diagnosis for patients with only lung involvement and thus with single organ involvement.In this case,we tried to emphasize the importance of family history and multidisciplinary approach.

PB81

Coexistence Of Psoriasis and Pemphigus Vulgaris: Overview of Co-Pathogenesis Through a Case

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Psoriasis is a polygenic, immune-mediated, chronic inflammatory skin disease. Psoriasis can be associated with other autoimmune diseases involving autoreactive T cells in pathogenesis such as vitiligo, alopecia areata and autoimmune thyroiditis. Pemphigus is an autoimmune vesiculobullous disease characterized by lesions in the skin and mucous membranes. After the first report by Bloom in 1929, case reports of autoimmune vesiculobullous diseases in patients with psoriasis increased gradually. Most common coexisting diseases with psoriazis are bullous pemphigoid and pemphigus foliaceus. Sporadic cases have been reported with other pemphigus variants such as pemphigus vulgaris, IgA pemphigus and pemphigus herpetiformis. The various opinions raised about the biological mechanisms underlying this relationship: hyperactive immunological / inflammatory status in psoriasis patients causing tolerance loss to pemphigus antigens in T and B cells, epitope spread phenomena, plasminogen activation. Since HLA DRB1 alleles are associated with both psoriasis and pemphigus, common genetic pathogenesis has been emphasized. Various drugs used in the treatment of psoriasis such as topical (ditranol, salicylic acid), systemic (cyclosporine A, etanercept) agents, phototherapy ; and sometimes enalapril used in concomitant systemic diseases have also been discussed as pemphigus triggers. There are also cases in the literature related to the development of pemphigus vulgaris during phototherapy and cyclosporine A use in the treatment of psoriasis.Here we report a case of pemphigus vulgaris presenting with oral mucosal lesions in a 59-year-old male patient who was diagnosed with psoriasis 1 year ago and followed with topical steroid treatment. The patient's HLA gene analysis is ongoing. With this case, we wanted to draw attention to the addition of immunosuppressive agents to the treatment considering the risk of exacerbation of psoriasis during dose reduction of systemic steroids in the management of psoriasis and vesiculobullous diseases.

PB82

A Case of Waardenburg Syndrome With Ophthalmological and Skin Findings

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Waardenburg Syndrome (WS) is a rare genetic disease characterized by congenital sensorineural hearing loss and craniofacial abnormalities characterized by varying degrees of melanocytes in the skin, hair, and eyes. In this case report, we present a 5-year- old male patient with congenital cataract in both eyes and characteristic features of Waardenburg syndrome type 2. She had bilateral cataract surgery due to congenital cataract at the age of 4 months. The patient was followed up in the ophthalmology department with the diagnosis of secondary glaucoma in the right eye. Physical examination revealed early graying of the scalp and whitening of the inner eyebrows along with a white forelock (poliosis) found in the anterior region of the scalp. There were numerous vitiligo-like hypopigmented areas on the forehead, trunk anterior face and both forearm flexor face. Two siblings, mother, and grandmother had similar physical findings. Otoscopic findings were normal. No pathology was detected in the audiometric examination. On ophthalmologic evaluation, visual acuity was binocular at 0.2 level and bilateral aphakic. He had horizontal nystagmus. There was no heterochromia in the iris. Fundus examination revealed morning glory anomaly on bilateral optic discs. VEP was within normal limits. The “W” index was calculated as 1.82. There was no dystopia canthorum. The patient was diagnosed as type 2 WS with the available findings. WS is one of the syndromes that have heterogeneous features both clinically and genetically. Although many ophthalmologic findings accompanying Waardenburg syndrome have been reported in the literature, to the best of our knowledge, this case report is the first to report the association of WS type 2 with congenital cataract.

PB87

Xeroderma Pigmentosum: Report of Three New Cases

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Introduction and Objectives: Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder caused by defects in the repair of damaged DNA. The estimated incidence is approximately one per million live births. Xeroderma pigmentosum has been classified into eight subgroups due to mutations in DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, XPA and XPC genes. Clinical manifestations of XP include extreme sun sensitivity and freckle-like pigmentation, ocular abnormalities, and markedly increased risk of developing cutaneous neoplasms, particularly in sun-exposed areas. In addition, approximately 25-30% of affected individuals have progressive neurodegenerative symptoms such as microcephaly, ataxia, hearing loss and seizure. Methods Targeted next generation sequencing Findings In this study, we described three patients from unrelated three families with classical features of Xeroderma pigmentosum. All of the patients had sun sensitivity and marked freckle-like pigmentation on the face. One patient had a basal cell carcinoma in her lower lip at the age of ten years. The results of the molecular analysis revealed that while a patient had a homozygous c.1735C>T (p.Arg579Ter) mutation, the other patient was detected a homozygous c.413-9T>A mutation in the XPC gene. In the third patient, a novel homozygous mutation of the POLH gene was identified that has not previously been reported in databases [c.454C>T (p.Gln152Ter)]. Result Xeroderma pigmentosum is a genetically heterogeneous rare disease. Therefore, although the next generation sequencing plays an important role in the molecular diagnosis of the disease, clinical findings and community frequency dependent gene selection are also important.

PB90

'In Silico' Approach to Melanoma and Long Non-Coding RNAs

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Melanoma has the highest mortality rate in skin cancers and highly aggressive and metastatic phenotype. Latest studies have shed new perspectives into melanoma development whereas the interference of regulatory non-coding RNAs remains unclear. Long non-coding RNAs (lncRNAs) can modulate essential pathways including cell cycle, cell proliferation, immune response by regulating gene expression at multiple levels. The purpose of this study is to expand the knowledge of the possible roles of lncRNAs in melanoma and their potential in clinical application. In this study, two possible lncRNAs [DRAIC (Downregulated RNA in Androgen Independent Cells) and PCAT29 (Prostate Cancer Associated Transcript 29)] (score for both lncRNAs: 0.9786) and their target genes associated with the pathogenesis of melanoma were identified using the LncRNADisease (v.2.0) database. Scoring was performed according to four algorithms LRLSLDA, LDAP, RWRlncD and LncDisease, and the closer score to 1, the more accurate the result. DRAIC is downregulated in cancer and play the role of inhibitor in cell invasion and migration. PCAT29 identified the first time in prostate cancer and may contribute suppress tumor formation. The target genes of DRAIC are PAQR5, KIF23, RPLP1 identified via LncRNADisease database, but genes targeted by PCAT29 were undetermined. Functional analysis in a study showed that DRAIC represses migration and invasion just as PCAT29. Both lncRNAs are negative regulator of AR gene, and positive regulator of FOXA1, NKX3-1 genes. Two lncRNAs are known to play as a tumor suppressor role, but their effect in melanoma remains unknown. As a result, we determined the relationship between melanoma formation and lncRNAs (DRAIC and PCAT29) by in silico, but it should be validated experimentally with further studies.

"IN SILICO" APPROACH TO MELANOMA AND LONG NON-CODING RNAs

INTRODUCTION

Melanoma has the highest mortality rate in skin cancers and highly aggressive and metastatic phenotype. The incidence of the melanoma has been increasing in these days and is usually higher in the fair-skinned population. Although early melanoma diagnosis increases survival rate, there is no sensitive and specific biomarker for melanoma has been detected due to uncertain molecular pathogenesis [1,2]. However, the histopathological diagnosis of melanoma is difficult for dermatopathologists [2].

More than 90% of transcripts from the human genome are not converted into proteins, and non-coding RNAs play an important role in regulating gene expression and their dysregulation is effective in the development of different types of cancer [3,4]. Long non-coding RNAs (lncRNAs, > 200 bp) can modulate essential pathways including cell cycle, cell proliferation, the immune response by regulating gene expression at multiple levels [1,2,5]. LncRNAs play role in a variety of mechanisms, including chromatin modification, transcriptional activation/representation, RNA editing/splicing/degradation, and regulation of translational efficiency [2].

Latest studies have shed new perspectives into melanoma development whereas the interference of regulatory non-coding RNAs remains unclear. The purpose of this study is to expand the knowledge of the possible roles of lncRNAs in melanoma and their potential in clinical application.

METHODS

The LncRNADisease database is updated in 2019 and predicts lncRNA-disease relationships with literature-based experimental datasets (http://www.rnanut.net/lncrnadisease/) and contains more than 200,000 lncRNA-disease relationship information. LncRNADisease 2.0 version includes determining the transcriptional regulatory relationships among lncRNA, mRNA and miRNA and providing a confidence score for each lncRNA-disease association. Scoring is based on according to four algorithms LRLSLDA, LDAP, RWRlncD and LncDisease, and the closer score to 1, the more accurate the result [6]. In our study, potential lncRNAs related to melanoma pathogenesis were investigated and target mRNAs were determined using the LncRNADisease (v.2.0) database.

RESULTS

In this study, two possible lncRNAs [DRAIC (Downregulated RNA in Androgen Independent Cells) and PCAT29 (Prostate Cancer Associated Transcript 29)] and their target genes associated with the pathogenesis of melanoma were identified using the LncRNADisease (v.2.0) database.

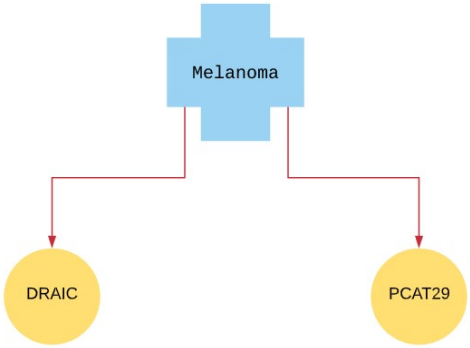

Figure 1: LncRNAs-melanoma interaction.

Table 1: LncRNAs associated with melanoma pathogenesis.

LncRNA	Chromosome	Start Site (bp)	End Site (bp)	Cellular location	Score
DRAIC	15	69463026	69571440	Cytoplasm	0.9786
PCAT29	15	69592129	69695750	Nucleus	0.9786

The target genes of DRAIC are PAQR5, KIF23, RPLP1 identified via LncRNADisease database, but genes targeted by PCAT29 were undetermined.

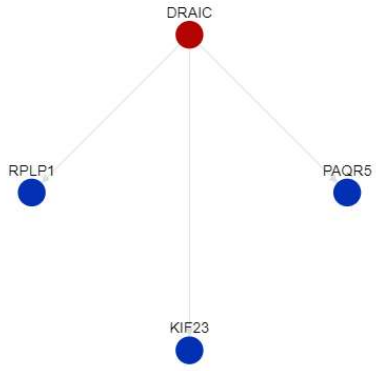

Figure 2: The targeted mRNAs of DRAIC.

DISCUSSION

Melanoma is the major cause of skin cancer-related deaths and is characterized by high metastatic potential [2]. Although recent genetic and epigenetic studies have brought new insights into melanoma formation processes, the role of non-coding RNAs remains uncertain. We have identified two candidate lncRNAs (DRAIC and PCAT29) that may be associated with melanoma with our bioinformatics analysis.

DRAIC is downregulated in cancer and play the role of inhibitor in cell invasion and migration, while PCAT29 identified the first time in prostate cancer and may contribute suppress tumor formation. TCGA analysis has shown that DRAIC expression predicts good prognosis in a wide variety of malignancies (bladder, lung, stomach, hepatocellular carcinoma, melanoma). Sakurai et al. showed that DRAIC/PCAT29 expression levels may show a prognostic biomarker for prostate cancer [1].

Functional analysis in a study showed that DRAIC represses migration and invasion just as PCAT29. In addition, silencing of DRAIC suppressed proliferation, while silencing of PCAT29 triggered. Both lncRNAs are the negative regulator of AR gene, and a positive regulator of FOXA1, NKX3-1 genes [1,2]. Two lncRNAs are known to play as a tumor suppressor role, but their effect in melanoma remains unknown. In this study, the relationship between melanoma formation and potential lncRNAs (DRAIC and PCAT29) was determined by in silico and should be validated experimentally with further studies.

CONCLUSION

In this study, the clinical applications of two tumor suppressor lncRNAs (DRAIC and PCAT29), which may be biomarkers for the early diagnosis of melanoma, were examined with a new and different perspective. The clinical benefits of lncRNAs in melanoma are still not fully determined. Further research is needed to clarify the mechanisms as well as the clinical effects of lncRNA dysregulation in melanoma.

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Netherton Syndrome Due to SPINK5 Gene Mutation

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Netherton syndrome (NS, OMIM #256500) is a rare and severe skin disorder characterized by congenital erythroderma, a specific hair-shaft abnormality(bamboo hair) and hypotrichosis. Atopic manifestations with high IgE levels and immundeficiency can also be part of this syndrome. Biallelic mutations in the SPINK5 gene encoding a serine protease inhibitor are responsible for the phenotype.The aim of this study is to discuss this rare genetic syndrome based on the clinical findings of our patient. A 3-year-old girl was referred to us because of skin dryness and erythroderma. It is reported that her clinical findings were present at birth, she had brittle hair, sun sensitivity, hypohidrosis and strabismus. She was born at 35th gestational-week and had intensive care for 3 months. Neuromotor developmental milestones were normal. She is the second child of consanguineous parents. Anthropometric measurements were Height: 98 cm (90p), Body weight: 10 kg (3p), Head circumference: 49cm (50-75p). Physical examination of the patient revealed frontal bossing, ectropion, downslanting palpebral fissures, flattened nose root, thin upper lip, prominent and low-set ear, normal nail structure, dry and erythrodermia and hypotricosis. Patient's karyotype was normal. Analysis of genodermatoses panel including 34 genes revealed homozygous c.1048C> T p. (Arg350*) mutation in SPINK5 gene. SPINK5 gene encodes LEKTI, a serine protease inhibitor, which is important in antiinflammatory processes. Mutations in SPINK5 are responsible for NS. In this study a recurrent nonsense mutation was reported in a Turkish NS patient and discussed with her clinical findings. Molecular diagnosis is important for management of the patient and preimplantation and prenatal genetic testing.

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Applications of Precision Medicine to Dermatogenetic Diseases

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Advances in techology and increased patient demands for genetic testing enabled detection of underlying genetic changes in many diseases, that resulted in clinical advantages. Diagnosis and mutation detection workflows in five patients consulted to our department in the last five years were regarded individually. Five different patients' data affected with three different rare genetic disorders Ichthyosis Vulgaris (IV), Epidermolysis Bullosa (EB), and Ectodermal Dysplasia (ED) are presented. The first patient was consulted to a dermatologist and a pathologist, and to the foundation for ichthyosis forum to provide the diagnosis as IV. The patient wanted to learn the risk for future pregnancies related to her consanguineous marriage. We explained that the condition is autosomal dominant and is inherited regardless of consanguinity. The second family had a child with epidermolysis bullosa. Genetic analysis was performed on parents and a heterozygous mutation was detected at the LAMC2 gene, exon 23 (c.3365T>G, p.Leu1122*). Prenatal diagnosis was performed for the ongoing pregnancy. The fetus was also a heterozygous carrier of the same mutation. Genetic counseling was given to three families with children with ectodermal dysplasia. Two did not want to have genetic testing. The third family wanted to have genetic testing, and a mutation was detected. As the follow up of the disease is according to the clinical signs and symptoms of patients regardless of mutations, follow up without mutation testing does not affect patient management. Dermatogenetic disorders deserve individual approach because they are rare diseases, and show a very wide phenotypic spectrum.