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Erciyes Üniversitesi Tıp Fakültesi tarafından 21–23 Şubat 2019 tarihleri arasında Kayseri'de, Erciyes Üniversitesi ev sahipliğinde düzenlenecek olan "Uluslararası Katılımlı Erciyes Tıp Genetik Günleri 2019"a sizleri davet etmekten mutluluk duyarız.

Zengin bir bilimsel programa sahip olan kongremize, Tıbbi Genetik camiasının yüksek katılımı hedeflenmektedir.

Sizleri 21–23 Şubat 2019 tarihlerinde Kayseri'de aramızda görmeyi umuyor, değerli katkılarınızla da hedefe ulaşmış bir kongreye ev sahipliği yapmayı diliyoruz.

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INVITED SPEAKER ABSTRACTS (IS)

IS-001

Importance of functional genomics in medical genetics

Cagri Gulec

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The primary purpose of medical genetics is to identify genetic variations responsible for pathological phenotypes. Advanced sequencing technologies yield great number of genetic variants which are then evaluated with in silico and segregation analysis. Though supported by these analyses, identified variation may not be still the disease-causing mutation. To claim that the identified variation is the mutation underlying a disease, functional relation between variant-genotype and disease-phenotype or a disease-specific biomarker, should be tested. Studies dealing such genotype-phenotype relationship are called as functional studies and have gene-based or genome-wide approaches. Functional studies might become necessary especially for missense and regulatory mutations. On the other hand, due to their low feasibility and high cost, functional studies could not be performed for each case. Therefore, it is important to know when a functional study is performable. Depending on the type of mutation, and the function of mutant gene product, various RNA-, protein-, and/or cell-based techniques can be included in a functional study. One of critical issues for starting point is the accessibility of mutant gene product. In some cases, mutant gene-product can be obtained from blood or skin fibroblast of the patient. In the case of inaccessible mutant gene-product, additional advanced methods like in vitro mutagenesis and mutant animal model might be needed. In both cases, functional study is performed in the presence of mutant gene product. While gene-based approach is proper for mutations in both regulatory and structural genes, genome-wide or functional genomic approach is more reasonable for mutations in regulatory genes.

IS-002

Current approaches in the breast cancer

Haluk Akin

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Breast cancer is the second most common diagnosed cancer in woman. In USA, lifetime development risk of an invasive breast cancer risk for a woman is approximately one in eight. Particular gene mutations associated with breast cancer are more common among certain geographic or ethnic groups, such as people of Ashkenazi Jewish or Dutch ancestry and Norwegian and Icelandic people. A small percentage of all breast cancers cluster in families. These cancers are described as hereditary and are associated with inherited gene mutations. Hereditary breast cancers tend to develop earlier in life than sporadic cases, and primary tumors are more likely to develop in both breasts. Because of first gene mutations associated to increased susceptibility to breast and ovarian cancer are the pathogenic germline alterations in *BRCA 1/2*, these mutations have been studied a lot, but many additional genes have now been discovered that also increase breast cancer risk. By the more genes associated with hereditary breast cancer syndromes, there is increased clinical use of multigene panel testing to evaluate patients with a suspected genetic predisposition to breast cancer. While this is most certainly a cost-effective approach, broader testing strategies have resulted in a higher likelihood of identifying moderate-penetrance genes. On the other hand, the testing of more genes has led to increased detection of variants of uncertain significance. It will be discussed the developing strategies in the genetic approach against the breast cancer by a brief description in this presentation. On the other hand, the novel aspects added into regular genetic counseling knowledge of breast cancer and important issues of the counseling process will be emphasized.

IS-003

Phenotypic contradictions: Dual effect

Ferda Emriye Percin

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The phenotypic complexity of genetic disease in persons may present a challenge for the physician. The interference of two distinct disease phenotypes in a single patient may suggest that it is a new clinical phenotype. Alternatively, two overlapping disease phenotypes may be incorrectly interpreted as an atypical or expanded phenotypic presentation of a single disease. Clinical presentations complicated by multiple genetic diagnoses in a single patient have been named with different terminologies in the literature; such as “dual diagnoses”, “two diagnosis”, “blended phenotypes” and “multilocus genomic variations” have been used to characterize such instances. The next generation sequencing analysis methods such as Whole-exome sequencing (WES) has provided a distinct advantage in the diagnosis of such clinically challenging patients. In selected large cohort reports (by WES analysis); rate of multiple genetic diagnosis in a single patient is differs between %0,9-1,4 even though this rate is high as high %4.5 in some reports. Thus, it is not surprising that patients with more than one genetic diseases are being increasingly mentioned in the literature, due to WES becomes increasingly available in the Medical Genetics clinics. The incidence of multiple diagnoses in consanguineous families might be increased over the overall rates. The comprehensive clinical phenotyping of family members with dual phenotypes is important for ultimately provide accurate genetic counseling. Especially we should keep in mind dual phenotypes due to in our country is high consanguinity marriage rates.

IS-004

Novel gene identification via whole exome sequencing in patients diagnosed with primary autosomal recessive primary microcephaly

Ahmet Okay Caglayan

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The introduction of next-generation DNA sequencing platforms led to opportunities for gene discovery in structural brain disorders (SBDs), resulting in the identification of novel genes essential in human brain development. Under light of these success on novel gene discovery, the classification of SBDs has moved from clinical and imaging approach to rely more heavily on genetics. In addition, these studies also provided significant challenges associated with disease gene discovery in these disorders supporting, their locus and phenotypic heterogeneity. The discovery of novel rare, autosomal recessive, and highly penetrant mutations in SBDs patients from consanguineous families not only will advance the understanding of molecular mechanisms underlying these disorders and lead to better family planning, but also can suggest treatment strategies. I'll present my studies in which novel genes were identified as a cause of autosomal recessively inherited microcephaly using whole exome sequencing with a novel bioinformatics approach.

IS-005

Current developments in Huntington disease

Ayse Caglar Sarilar

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Huntington's Disease (HD) is the most common among nine known polyglutamine disorders. HD is an autosomal dominantly inherited neurodegenerative disorder of the central nervous system, characterized by involuntary movements, impaired motor coordination, cognitive loss and psychiatric abnormalities. The disease gene (IT-15), localized to chromosome 4, 180kb long, is composed of 67 exons. The gene product is a 348 kDa protein, called huntingtin, whose function is not known yet. The mutation causing HD is the expansion of the CAG triplet repeat in the first exon of the IT-15 gene. In Huntington's Disease, there are many studies about the predictors of disease, follow-up methods for prognosis and treatment. The inverse relationship between the number of CAG recurrences and the age of onset is shown. However, many variables have been analyzed and the predictive methods for the onset of the disease are among the most recently studied subjects. In addition, how and with which markers the disease can be followed in the research has come forward. Therefore, electrophysiological methods (such as EEG changes, sleep analysis, SEP, MEP, sympathetic skin response) were used for the prognosis of the disease. In addition, some neurobiological markers (such as brain PDE 10 A enzyme) are being studied. Many agents for treatment of the disease (pridopidine, cannabionoid, nilotinib, resveratrol, caffeine, ubiquinol, coenzyme Q10, laquinimod, phosphodiesterase inhibitors) have been tried. In addition, deep brain stimulation, physical activity exercises, dance therapy, and computerized cognitive therapy are also tried in the treatment. In this talk, current developments will be discussed.

IS-006

Cardiovascular Diseases and Genetics

Hakan Gurkan

Department of Medical Genetics, Trakya University Faculty of Medicine, Edirne, Turkey

Congenital Heart Disease: Congenital heart disease is the most common malformation related to the heart in the fetal and neonatal period and represents a heterogeneous group whose cause is less known. The incidence of congenital heart disease is approximately 0.5-0.8% in all live births, this rate increases to 3-4% in stillbirths, 10-25% in spontaneous abortions and 2% in premature newborns. It includes a broad and heterogeneous spectrum of heart disease, including inherited heart disease, cardiomyopathies, and arrhythmic diseases in structurally normal hearts, ie, canalopathies. Familial Hypercholesterolemia: It is a disease that causes LDL elevation, increased risk of coronary artery disease at a young age, xanthomas in skin and tendons, atherosclerotic plaque formation in arteries. The prevalence of familial hypercholesterolemia is 1 / 200-500. Familial hypercholesterolemia increases the risk of coronary heart disease by a factor of 20 when not treated. Pathogenic variations of *LDLR*, *APOB*, *PCSK9* are responsible for 60-80% of familial hypercholesterolemia. Long QT Syndrome (LQTS): On the ECG; Cardiac electrophysiology disorder characterized by QT prolongation and T wave anomalies and ventricular tachycardia. Prevalence of 1/2000. The most common symptom is syncope and usually occurs as a result of exercise and excessive excitement. Ventricular tachycardia; it may result in ventricular fibrillation and cardiac arrest or sudden death. Most often occurs in the 20s.

IS-007

Inborn errors of metabolic diseases with dysmorphological findings

Ozgur Cogulu

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Inborn errors of metabolism (IEM) are genetically determined disorders caused by the absence or abnormality of an enzyme. This leads to the pathway of the enzyme to work defective. It generally results with the accumulation or depletion of a specific metabolite. IEM are inherited generally as autosomal recessive, however autosomal dominant, X-linked and mitochondrial types of inheritance have also been reported. Diseases caused by inborn errors of metabolism are classified into 3 main groups composed of large complex molecule diseases such as complex lipid degradation, mucopolysaccharidoses, peroxisomal disorders; small molecule diseases such as amino acid, organic acid, purines and pyrimidine metabolism disorders, and other diseases such as metal, lipoprotein metabolism disorders and porphyria. On the other hand some other classifications have also been reported. The Society for the Study of Inborn Errors of Metabolism classified this group of diseases under 15 titles;

1. Disorders of amino acid and peptide metabolism
2. Disorders of carbohydrate metabolism
3. Disorders of fatty acid and ketone body metabolism
4. Disorders of energy metabolism
5. Disorders in the metabolism of purines, pyrimidines, and nucleotides
6. Disorders of the metabolism of sterols
7. Disorders of porphyrin and heme metabolism
8. Disorders of lipid and lipoprotein metabolism
9. Congenital disorders of glycosylation and other disorders of protein modification
10. Lysosomal disorders
11. Peroxisomal disorders
12. Disorders of neurotransmitter metabolism
13. Disorders in the metabolism of vitamins and (non-protein) cofactors
14. Disorders in the metabolism of trace elements and metals
15. Disorders and variants in the metabolism of xenobiotics

The overall incidence has been reported to be as 1 in 1000. More than 500 clinical conditions have been described and approximately 25% of them give signs in the neonatal period. Diagnosis of those diseases is based on a wide range of clinical signs and laboratory findings such as specific tests, biochemical analyses, and histologic and genetic studies. Among them very few present with dysmorphic features as shown below;

1. Lysosomal disorders (Mucopolysaccharidoses, Sphingolipidoses)
2. Peroxisomal disorders (Zellweger disease, Chondrodysplasia punctata, adrenoleukodystrophy)
3. Cholesterol synthesis disorders (Smith-Lemli-Opitz syndrome, Antley-Bixler syndrome)
4. Sulfation disorders (Diastrophic Dysplasia)
5. Organic acidemias (Glutaric Aciduria)
6. Pyruvate dehydrogenase deficiency
7. Congenital disorders of glycosylation

IS-008

Brain volume differences in Huntington disease using MRI

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Huntington's disease (HD) is an autosomal dominant degenerative disease that results from an expanded CAG repeat in the *IT15* gene. Recent neuroimaging advances have contributed to the improved definition of brain regions where neural alterations occur in patients with HD. Early research on HD focused on volumetric changes in brain gray matter (GM), mostly involving the basal ganglia and cortex. We enrolled 4 gene-positive subjects for the study. VolBrain was used for data analysis of all structural T1-weighted images. Brain tissues were segmented with a fully automated with Volbrain. For this MRI study, total intracranial volume and GM, WM, and cerebrospinal fluid (CSF) volume were calculated. The total brain volumes and total cortical grey and white matter volume of the HD patients were reduced by compared with matched controls.

IS-009

Nephrotic Syndrome and Genetics

Guven Toksoy

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Nephrotic syndrome (NS) is a serious disease with chronic glomerular disorders leading to leakage of high level (> 3 g of protein/day) of protein into the urine, lipiduria, low serum albumin and oedema. It is more common in pediatric age group than adult. Clinical diagnosis includes medical history, physical examination, serologic testing and renal biopsy. Prognosis and treatment varies depending on the pathological causes. Clinically, NS can be "primary", when kidneys are the only effected organ, or "secondary ", if other biological systems are influenced due to drug uses, immunological effectuates, metabolic, systemic or neoplastic reasons. NS with unknown pathogenesis, classified under "idiopathic NS", is the most common glomerular disease of the childhood. From the therapeutic point of view, NS is evaluated as steroid sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS) depending on the response to the therapeutic agents. Presently, more than 50 recessive or dominant genes are reported with association to monogenic forms of NS. In this presentation, genetic association of patients referred with NS to the Department of Medical Genetics of Istanbul Medical Faculty will be discussed within the scope of recent literature.

IS-010

Genetics of eye

Derya Ercal

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Malformations of the eye are among the most common causes of visual impairment in newborns. Recognization of pathogenic mutations in transcription factors has widened the understanding human eye development and some unusual inheritance characteristics of these disorders. The identification of these genes also has led to recognize the relation of consistent extraocular malformations in affected individuals. Clinical genetics and basic developmental biology provided our understanding of many critical developmental processes in human embryogenesis. The vertebrate eye consist tissues from different embryonic origins. The lens and the cornea are derived from the surface ectoderm. The retina and the epithelial layers of the iris and ciliary body originate from the anterior neural plate. On time activation of transcription factors induce signals to ensure the correct development of the different eye components. A single eye field forms centrally within the anterior neural plate during gastrulation. On the molecular basis, the expression of "eye-field transcription factors" are the main actors. This single eye field is separated into two, the optic vesicle and the optic cup consecutively. The lens develops from the lens placode under influence of the underlying optic vesicle. Master control gene is PAX6 which acts in this phase and genes encoding cytoskeletal proteins, structural proteins, or membrane proteins are activated also. As the cornea forms from the surface ectoderm, cells from the periocular mesenchyme migrate into the cornea giving rise for the corneal stroma. The iris and ciliary body develop from the optic cup. Outer layer of the optic cup becomes the retinal pigmented epithelium, and the main part of the inner layer of the optic cup forms later the neural retina with six different types of cells including the photoreceptors. The retinal ganglion cells migrate and grow toward the optic stalk forming the optic nerve. In this presentation the major molecular actors and cellular processes during eye development and the examples of genomic changes as causes of eye malformations in children are discussed which is needed for genetic counselling and prenatal diagnosis.

IS-011

Huntington's disease; patient and family

Hatice Ilgin Ruhi

Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Turkey

Huntington's disease (HD) is a progressive autosomal dominant neurodegenerative disorder caused by CAG-repeat expansions (polyglutamine) in the huntingtin protein gene (*HTT*). CAG-repeat length in the *HTT* gene is inversely correlated with age of onset. The characteristic findings of the disease are the development of movement disorders, cognitive decline and behavioural disturbances. Although the disease symptoms usually start after 35 years of age, juvenile onset is observed in 5-10% of cases. Pediatricians who are not familiar with this disease, may cause to delays in diagnosis. Diagnosis of juvenile onset cases and predictive testing issues are among the most common challenges of HD. Predictive testing is generally not recommended for those under 18. However, exceptions can be made because of suspicious clinical findings in childhood and adolescence. In this presentation, these two difficulties were discussed through case examples.

IS-012

Role of whole exome sequencing in diagnostic approach of neuroferritinopathies: A new family with *C19Orf12* gene deficiency

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Neurodegeneration with brain iron accumulation (NBIA) comprises a clinically and genetically heterogeneous group of disorders caused by *REPS*, *CRA*, *COASY*, *C19orf12*, *FTL*, *PANK2*, *PLA2G6* and *WDR45* genes. MPAN tipIV (NBIA4), caused by C19Orf12 is a very rare type characterized by iron deposition in globus pallidus and substantia nigra and progressive neurodegeneration. The aim of this study is to present the clinical and molecular features of two cases of the same family with *C19Orf12* gene defect. A 16-year-old male patient with first-degree cousin marriage between parents was admitted to our hospital at the age of 7 years with hyperactivity and learning disabilities. Brain MRI revealed lesions consistent with iron accumulation at the level of bilateral globus pallidus and sunstantia nigra. No pathogenic variant was detected in *PANK2*, *WDR45*, *PLA2G6* genes. The pathogenic c.204_214delCGGGGGGCTGT variant was detected homozygously on *C19orf12* gene by whole exome sequencing (WES) analysis. The same mutation was found to be homozygously in his brothers who has similar symptoms and heterozygously in each parent. Neuroferritinopathies are a rare group of genetic heterogeneous diseases that result iron accumulation and cognitive impairment in basal ganglia. Although there is no definitive treatment, in some patients, iron chelators can improve clinical and radiological findings, Therefore, early diagnosis is important. *C19Orf12* is one of the rarest causes. Up to now 38 different mutations have been identified in the *C19Orf12* gene. WES is an option to reduce the cost and time loss in the diagnosis of neuroferritinopathies which has genetic heterogeneity.

IS-013

Epidermolysis bullosa: Clinical phenotypes and genetics

C. Nur Semerci Gunduz

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Epidermolysis bullosa (EB) is a highly heterogeneous group of skin diseases with an autosomal dominant and recessive form characterized by skin fragility, blisters and erosion in the skin and mucous membranes by minor mechanical trauma. Mutations in genes that encode proteins involved in the cell-cell adhesion, and cell matrix structural components of epidermis, dermo-epidermal junction, and dermis of the skeleton are responsible for the etiology. Epidermolysis bullosa is divided into 4 types according to morphological characteristics by electron microscopy and immunofluorescence examination:

1. Epidermolysis bullosa simplex
2. Junctional epidermolysis bullosa
3. Dystrophic epidermolysis bullosa
4. Kindler syndrome

Mutations in *KRT4*, *KRT15*, *PLEC*, *KLHL24*, *DST*, *EXPH5*, *CD151*, *TGM5*, *PKP1*, *DSP*, *JUP* genes caused EB simplex subtypes; *LAMA3*, *LAMB3*, *LAMC2*, *COL17A1*, *LAM3A*, *ITGA6*, *ITGB4*, *ITGA3* gene mutations caused Junctional epidermolysis bullosa; and the mutants of the *COL7A1* gene caused dystrophic epidermolysis bullosa and mutations in the *FERMT1* gene cause the Kindler syndrome. Treatment of EB is carried out by supportive methods such as maintenance of ulcers and erosions, protection from trauma, and eating habits. Genetic counseling for these families due to their hereditary nature; and prenatal and preimplantation diagnosis because of mutations in known genes are important for the prevention of disease. New emerging molecular genetic techniques such as next-generation sequencing will contribute to the elucidation of the etiology of the disease and the development of new treatment modalities.

IS-014

Predictive testing approach in Huntington disease

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Huntington disease (HD) is a progressive autosomal dominant neurodegenerative disorder characterised by chorea, cognitive decline and behavioural disturbances. Predictive testing for HD became available in 1986 and the first recommendations concerning predictive test were published in 1989 and 1990. These recommendations were revised in 1994 after the identification of the responsible gene and the mutation, and the next revision of this guideline was published in 2013. These guidelines set minimum standards for predictive test process to provide maximum support to the applicant in decision-making process and to cope with the test result. A multidisciplinary approach including a clinical geneticist, neurologist and psychiatrist, and a multistep counseling session -pre-test, test and post-test- is recommended for this purpose. In the pre-test stage of the process, neurological and psychological evaluation is recommended for the baseline assessment of the applicant. It is also recommended that there should be a minimum interval of one month between the pre-test counseling

and the final decision of the applicant to take or not to take the test. Post-test counseling is also an important stage of the predictive testing process. The guiding principles in developing recommendations for predictive testing for HD are autonomy, beneficence, informed decision and confidentiality, and therefore, each applicant should be evaluated in this manner by a multidisciplinary team.

IS-015

Epigenetic factors and prenatal development

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Epigenetic, is defined as mitotically and/or meiotically heritable changes in genes function that cannot be explained by changes in DNA sequence. The change in gene expression without alteration of the DNA sequence takes place by covalent modifications such as DNA methylation, methylation and acetylation of histone tails, and posttranslational mechanisms with non-coding RNAs. DNA methylation, one of the most studied epigenetic mechanisms, is generally associated with silencing of the gene of interest, while demethylation is associated with expression of the gene of interest. As a result of histone methylation from the modifications of the tails of the histones in which the DNA chain is wound, the DNA helix is wrapped more tightly into the histone proteins, so that the transcription factors cannot be bound and the transcription of the gene of interest is suppressed. As a result of histone acetylation, which is another histone modification, the DNA helix is opened, and transcriptional activation takes place. However, this may have different results on gene expression, depending on which histone protein is acetylated or methylated. It is known that DNA methylation markers are important in prenatal period and epigenetic signals are effective in every step of development during fetal programming. DNA methylation and histone modifications have various effects in the fetal period by changing with the effects of nutrients, toxic substances and various environmental factors in prenatal period. However, it is no longer possible to think that epigenetic signs only affect the individual itself. Although the deletion of epigenetic marks in the sperm and egg during the period of embryonic development is thought to erase the epigenetic marks from the previous generation and create a pluripotent state from the previous generation, epigenetic signals from previous generations have been transferred to other generations in recent years, and in some cases there are publications showing intergenerational epigenetic transition. This situation has begun to show that many diseases known today as multifactorial may occur as a result of different expression of the genes that are affected by the passage of epigenetic signals from generation to generation.

IS-016

Molecular cytogenetic markers in hematological malignancies

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Hematological malignancies are important group of neoplastic diseases originating from hematopoietic and lymphoid tissues, namely leukemia, lymphoma and myeloma. They constitute approximately 10% of all cancers diagnosed per year. Their incidence rates are consistently increasing, however significant decline in mortality has been observed due to rapid advancements in their diagnosis and management over the last 30 years. Many of these advancements have been achieved by the help of genetic technology. Besides conventional cytogenetics, remarkable progress has occurred in the field of molecular cytogenetics. The application of relevant genetic tests have led to the establishment of novel biological markers as diagnostic and prognostic indexes, as guiding for the localization of genes that are responsible for the development of these malignancies. Today, geneticists are providing not only diagnostic tests but also giving the key knowledge of leukomogenesis and cancer which guide the specialist in a more favorable position to make the exact diagnosis, assess prognosis, select the most appropriate therapy and monitor the response to treatment. Therefore, it is noteworthy for every specialist working in the field of hematooncology to have sufficient knowledge of cancer genetics in order to transfer this information for patient care. The present talk will focus on the role of molecular cytogenetics in hematological malignancies. Most significant markers in acute and chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, myelodysplastic syndrome, multiple myeloma and lymphomas will be discussed and their role will be clarified with up to date literature and guidelines.

IS-017

Dissecting the molecular mechanisms of complex diseases through a pathway and network oriented analysis of -omics data

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The tremendous boost in the next generation sequencing (NGS) technologies and in the “omics” technologies makes it possible to look for the coordinated behavior among different levels of biochemical activity. In contrast to isolated molecules,

network and pathway oriented analyses are thought to better capture pathological perturbations and hence, better explain predisposition to disease. Especially in complex diseases, which are intrinsicly multifactorial, there are no strong associations for a single factor. In this regard, we have recently proposed a methodology (PANOGA) to analyze the -omics data in a network related context to identify pathways that are involved in disease development mechanisms. PANOGA can also help us to identify disease-associated pathway markers across different populations and these pathway markers can help us to understand individual disease development mechanisms in terms of the determination of individual targets for treatments, and hence bridging the gap between the -omics data and personalized medicine. Although PANOGA is originally developed to identify disease-associated pathways via further analyzing Genome-wide Association Study (GWAS) data, later it is shown to work well on different -omics datasets including transcriptomics, proteomics, and epigenomics studies. Using different –omics datasets, our group is currently working on the development of methodologies to extend this approach to individual level to identify specific modifications occurring on the genes within these identified pathways. Dissecting the individual disease development mechanisms will provide a valuable insight for discovering individualized therapy targets and will pave the way towards precision medicine applications.

IS-018

Precision medicine and genetics

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Omics data obtained from contemporary molecular analysis methods has enabled a new approach in understanding the interindividual differences in the molecular pathogenesis of the disease. Not for long ago, biological knowledge has been used to classify disease patterns and treatment regimens have been developed to the classifed group of disease disregarding the individual differences. As a result, a new taxonomy of human diseases has become available to provide better diagnosis, treatment and prevention strategies. The term precision medicine was first defined in 2011 to define "the best available care for each individual". Variability in genes, environment, lifestyle are the factors in the new classification of diseases. Data from genomics, transcriptomics, proteomics, and metabolomics provide the data to help this classification enabling the scientists to evaluate the expression of genetic variances as well as changes in their interactions in the organism in health and disease. With this new perspective, tailored treatment regimens have become available. There are two terms precision and personalized medicine with a fundamental difference; in personalized medicine, personalized treatment should be uniquely formulated for each individual. But in precision medicine, the approach should focus on to identify interindividual differences and find out the most effective treatment for a well-defined group of people. Precision medicine has been mostly investigated and its effects illuminated in cancer, pharmacogenomics, and Mendelian disorders. Tumor genotyping enabled a molecular genetic classification of tumors and every day a new molecule for targeted therapy of tumors is approved. Pharmacogenomics also is one of the areas in which precision medicine is important. For the physicians to decide the best treatment for a patient a simple molecular genetic analysis of genes coding drug metabolizing proteins is usually enough. As a result of this, the use of precision medicine in disease treatment provided many benefits such as trial and error prescriptions in treatment, drug side effects in patients and the healthcare system to control health care costs. Mendelian disorders are also affected by precision medicine approaches for both diagnosis and treatment. Improvements in sequencing technology provided the chance for diagnosis for many people suffering from certain genetic disorders. Below are the advantages of precision medicine during routine practice:

1. Preventive medicine rather than reactive interventions has become available after developments in sequencing and data analysis
2. Patient based optimal therapy regimens can be provided after analysis instead of using the same prescription for everyone
3. Drug metabolism is different between individuals and for best results to avoid adverse reactions individualized drug prescription is essential
4. Patients use daily doses regularly when they do not need to tackle with side effects
5. If the patient has the personalized treatment regimen, health quality increases, i.e. targeted drugs instead of classic chemotherapy regimens or polypharmacy planning according to the individual results of the patient improve quality of life in patients
6. As the researchers analyze a wide spectrum of patients some drugs have been added new indications after genetic analysis of diseases since the same drug target (mutation) can be observed in different clinical conditions
7. After all, the total cost of healthcare can easily be under control as individualized therapy regimens prevent treatment changes

The new sequencing technologies reduced the cost of sequencing an individual genome. By this way, genetic analysis has become an affordable tool for precision medicine. However, there is a need for standardization of analysis and data interpretation to enable the results carried from the lab to the bedside as the data obtained is complex and physicians other than geneticists hardly ever can comment on the results. The patients also want to know about the tests, analyses performed and the results. This is why genetic counseling and interpretation of data to the patient as well as the physician is essential. All tests should be performed after informed consent is taken from the patient and counseling should be given in two sessions before and after testing.

IS-019

Epilepsy genetics: Clinical and molecular diagnostic algorithms

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Epilepsy is the most common cause of chronic neurological diseases. Although metabolic, immune and structural brain anomalies, infectious and idiopathic causes are found in the aetiology of epilepsy, 75% of the causes are genetic. Idiopathic epilepsies are multifactorial disorders and the role of genetic factors in familial cases is more relevant. Epileptic encephalopathy or developmental encephalopathy terms are used in epilepsy cases with mental retardation, developmental delay or cortical malformations. In order to determine the genetic aetiology in epilepsy patients and decide which test to perform, it is necessary to consider a comprehensive clinical evaluation including prenatal-natal-postnatal history, family history, physical examination, laboratory and imaging findings. And a pedigree containing at least 3 generations is essential to estimate inheritance pattern. Each patient presenting with epilepsy should first undergo conventional karyotyping for chromosomal mutations. If a specific single gene disease or microdeletion syndrome is considered based on some dysmorphic findings, the target gene may be sequenced or the locus-specific FISH may be performed. Molecular karyotyping is the next method used in the detection of submicroscopic deletions/duplications that are one of the important causes of epilepsy. Multi-gene panels make a significant contribution to the diagnosis in early infantile epilepsies that are based on deficiencies in vitamins/cofactors or ion channels dysfunctions, in which the diagnosis at early stages could let to direct treatment selection. It is understood that de novo mutations that are thought to occur in the early embryonic stages are responsible for epileptic/developmental encephalopathies. In recent years, whole exome sequencing is increasingly being used for the diagnosis of epileptic encephalopathies and rare epilepsy syndromes. Pre and post-test genetic counselling should be given to families about the prenatal and preimplantation genetic diagnosis. Mentioning the recurrence risk in idiopathic familial epilepsies should not been forgotten. It should be kept in mind to explain the risk of germ-line mosaicism in case of de novo diagnosis. However, the aetiology of epilepsy has begun to be enlightened day by day with developing technologies, it still has a great dark side because epilepsy is a disease with complex mechanisms and interests to all systems.

IS-020

Ribosomopathies

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Ribosomopathies are a group of disorders commonly caused by defects in ribosome biogenesis. The eukaryotic ribosome is composed of 40S and 60S subunits, which associate to form the translationally active 80S ribosome. This process requires synthesis of rRNAs, approximately 80 core rbosomal proteins, more than 150 associated proteins and approximately 70 small nuclolar RNAs (snoRNAs). Assembly of rRNA, ribosomal proteins along with associated proteins and snoRNAs occurs in nucleolus to form pre-60S and pre-40S prerbosomal particles. These particles are exported to cytoplasm for further maturation. Nuclear trasport system is an important element of ribosome biogenesis and function. Transport of proteins and RNA between the nucleus and cytoplasm is accomplished by soluble transport factors through numerous pores embedded in the nuclear envelope. Failure of any steps of this complex procedure concludes severe human disorders. Bone marrow failure and various degree skeletal malformations are major outcomes of ribosomopathies. Trecher Collins syndrome, Roberts syndrome, Postaxial Acrofacial Dysostosis (Miller syndrome), Cartilage Hair Hypoplasia, Bowen_Conradi Syndromes are well known ribosomopaties with severe skeletal malformations. 5q syndrome and T Cell ALL, Relaps KLL consist of another group ribosomopathies with hematologic outcome. On the other hand, both hematologic and skeletal malformations are commonly associated in another large ribosomopathy group such as Diamond-Blackfan Anemia, Diskeratosis Congenita, Shwachman-Diamond syndrome, Cartilage hair hypoplasia syndrome. Nevertheless, new disorders due to impaired ribosome biogenesis and function are frequently being reported and the scope of this list is getting enlarged. In the talk, a simplified overview of complex ribosome biology and function as well as disease mechanisms behind diverse ribosomopathy phenotypes will be presented.

IS-021

Approach to dysmorphic patient

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'Congenital anomalies' represent all structural deviations of human body from normal anatomic structure. Dysmorphology is the branch of medicine studying anomalies. Anomalies are classified as major (malformations) or minor (dysmorphic features). Major anomalies are those that disrupt function. They affect 4-6% of children. Minor anomalies affect 15% of the population. Most frequent major anomalies are cardiac malformations, cleft lip/palate, neural tube defects and some limb

anomalies. Some etiological factors have been described for each of these malformations, and constitute (sub)microscopic chromosomal anomalies, single gene disorders, teratogenic agents and multifactorial conditions. Minor anomalies may constitute a recognizable pattern leading to diagnosis or may signal presence of major anomalies. First step in approach to anomalies is a thorough physical examination and correct definition of anomalies. Printed and electronic references should be used for correct definitions. All anomalies should be detected using imaging modalities. Following these investigations, single anomalies are classified into malformations, deformations, disruptions and dysplasias, and multiple anomalies are classified into syndromes, sequences, developmental field defects, and associations. Anomalies caused by metabolic diseases may also be classified into these subgroups, according to the underlying etiology. Estimation of embryologic timing of the defects and family history frequently help detection of the underlying cause. Well-structured approach to anomalies leads to correct application of diagnostic tests and accurate diagnosis. Etiological diagnosis of anomalies allows counseling on disease course, prognosis, treatment options, recurrence risks, available modalities of prevention, and relative risks of other family members.

IS-022

Heritable connective tissue disorders and accompanying cardiovascular abnormalities

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Heritable connective tissue disorders include syndromic conditions such as Marfan syndrome, Loeys-Dietz syndrome, Autosomal Recessive Cutis Laxa Type I, Arterial tortuosity syndrome and Ehlers-Danlos syndromes as well as non-syndromic conditions such as isolated thoracic/abdominal aortic aneurysm and dissection. Although individually rare, these disorders together reflect a significant proportion of human genetic diseases. They affect mainly the skin, the eyes, and the musculoskeletal, cardiovascular, and pulmonary systems. This group of disorders are genetically heterogenous and encompass a wide range of clinical presentation. Abnormalities in the structure of the connective tissue leads a risk for aneurysm formation and dissection of the aorta. Genetic defects in the connective tissue related pathways and genes affect connective tissue proper proteins. Significant progress in sequencing technology help us to understand the pathogenesis of these disorders in detail. This might lead to the development of new therapeutic interventions Which can decrease the risk of accompanying cardiac abnormalities. Recent studies showed that the use of the angiotensin-II receptor blockers like Losartan, significantly slowed the progressive aortic-root dilatation in MFS, Loeys Dietz Syndrome cases by antagonizing TGF-β signaling pathway. Genetics of these connective tissue disorders and therapeutic options will be discussed with our unique case cohort.

IS-023

cf-DNA test applications

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cf-DNA testing is the most sensitive and specific noninvasive prenatal screening test for trisomy 21 (T21). However, the test performance for other common aneuploidies and microdeletion/duplications is lower when compared to T21. The false positive and negative results of this test are associated with technical limitations and biological factors. Today, the cost of cf-DNA testing is more expensive than the classical screening and diagnostic tests. Therefore, the result of cf-DNA test confirmation studies should be evaluated and the most efficient algorithm for Turkey must be determined. The cytogenetic findings of 233 pregnancies including 9 twins followed by cf-DNA testing, revealed that the false positive rate was 14,4% for T21, 37,5% for T18, 80% for T13, 66,7% for rare autosomal trisomies, 61,9% for monosomy X and 70% for microdeletion/duplication anomalies in singleton pregnancies. Three false negative T21, each one of T18 and T13, and also one wrong gender have been observed. In the whole series, there were 74 false positive and 6 false negative cases. The most frequently observed biological factor was confined placental or true mosaicism, causative to discordant results. Low fetal fraction was also observed related to the discordant results. Certainly, there are also other technical limitations, which could not be handled by the users. However, we could investigate the placentas cytogenetically following the termination/delivery, to determine the role of mosaicism in discordant cases. There are different strategies used in the application of cf-DNA testing in European countries. According to these strategies Turkish data has been analyzed hypothetically and the findings of cost-benefit results will be open for discussion.

IS-024

Genetic approach to the hearing loss

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Hearing loss is the most common sensorial disorder that affects approximately one per 1200 live births with genetic causes accounting for approximately 50% of cases, other half is due to environmental factors. In addition to the infectious diseases during the mother's pregnancy, drug use (such as ototoxic antibiotics and diuretics), prematurity, hypoxia, various infectious diseases in the postnatal period, and trauma history can be considered as environmental factors. Genetic-based hearing loss is examined under two headings as syndromic and non-

syndromic. Approximately 20-30% of patients with genetically based hearing loss are syndromic patients. About 70% of people with hearing loss do not have any additional pathology. Studies with this group, which is considered as non-syndromic hearing loss, are difficult for various reasons. Hundreds of different proteins are involved in the complex structure of the inner ear. Some of the genes have been associated with both autosomal recessive and autosomal dominant hearing loss, and some genes cause both syndromic and non-syndromic hearing loss. Many different genetic problems are reflected only in the clinic with hearing loss and it is difficult to classify non-syndromic hearing loss families into phenotypic groups. When evaluating patients with hearing loss, family history, family tree, ethnicity and hearing status should be considered. The hereditary pattern of hearing loss, the audiometric features of the family members, the age, progression, degree and type of the hearing loss should be determined. A detailed physical examination should be performed to distinguish between syndromic and non-syndromic patients, and patients should be consulted with other branches if necessary and should be evaluated with a multidisciplinary approach. In some cases, hearing loss may be the first sign of a syndrome in which critical medical intervention is required (Jervell and Lange-Nielsan syndrome) or may have a significant impact on habilitation strategies (Usher syndrome). In people with age-related, noise-related or increased risk of drug-induced hearing loss, genetic diagnosis helps to avoid environmental causes of hearing loss. It is important to identify new mutations in order to clarify their clinical importance, and to suggest either prenatal diagnosis or preimplantation genetic diagnosis to the effected families. In recent years, with the spread of new generation sequencing systems, it is possible to investigate more than one gene in a short time. Several centers evaluate patients with panel studies that includes common genes following the evaluation of *GJB2* gene mutations. Although there are too many genes that cause hearing loss, several studies indicate that *SLC26A4*, *MYO7A*, *MYO15A*, *OTOF*, *CDH23*, the *TMIE*, *TECTA*, *PCDH15*, *TMC1*, *TMPRSS3* gene mutations are common among patients with nonsyndromic hearing loss. After these kinds of studies, all exon sequencing and all genome studies can be performed in cases where the etiology cannot be clarified. And also, whole exome / genome sequencing, should be supported by functional studies. Various expression studies and transgenic animal models are frequently used for these purposes. In addition, new studies have been carried out in the treatment of hearing loss. CRISPR-Cas9 gene regulation protein is a novel approach in the treatment of genetic diseases besides hearing loss treatment. The main objectives of all these studies are primarily the elucidation of the complex mechanism of hearing and the development of new treatment strategies.

IS-025

Amino acid biosynthesis disorders

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Amino acid synthesis disorders are very rare inborn errors of metabolism that have been described in recent years due to the introduction of advanced DNA sequencing methods. Until now four inborn errors of metabolism related to amino acid synthesis are reported, these are serine, glutamine, asparagine, and proline synthesis defect. Classically, pathophysiology in inborn errors of metabolism of amino acid is related to toxic effect of metabolic accumulation due to enzyme deficiency, on the other hand clinical phenotype develop due to low levels of tissue in amino acid biosynthesis defects. Here, four clinical and laboratory findings of four described amino acid biosynthesis defect are described, some treatment options related to subjects are also being discussed.

ORAL PRESENTATION ABSTRACTS (OP)

OP-21-001

A novel mutation, 8414dupT, on *BRCA2* gene of two siblings

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Breast cancer is the most commonly occurring cancer among women. A family history of breast cancer is one of the main risk factors for developing the disease. It is currently estimated that approximately 5–10% of breast cancers are due to an inherited predisposition, and approximately 20–25% of this risk is explained by two high-penetrance susceptibility genes: *BRCA1* (17q21) (MIM no. 113705) and *BRCA2* (13q12–13) (MIM no. 600185). The NGS analysis of the *BRCA* genes is described as follows. The sequencing data were analyzed with bioinformatics software: The Sophia DDM® software version 4.3.1 (Sophia Genetics SA, Saint Sulpice, Switzerland) was used to confirm point mutations and is also used to identify copy number variants (CNVs). Proband has found to carry heterozygous 8414dupT mutation which is a frameshift mutation that causes protein termination at codon 2811 as a result of NGS analysis. Therefore, as proband was carrying mutation other brothers were also screened for carrying 8414dupT mutation due to having a family history of prostate cancers. Mutation is also confirmed by sanger sequencing. In addition, 4 non-related breast cancer patients were found to have the same mutation. They were taken to family screening. Although this mutation was described as a pathogenic mutation in the silico database, it was first detected in a breast cancer case in our literature review. By analysis of more cases, maybe there could be found any relation between this mutation and disease in near future and could be added to databases.

OP-21-002

Does *BRCA* gene mutation affect comorbidity in patients with breast cancer?

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Pathogenic germline variants in *BRCA1* and *BRCA2* genes are related with increased risk of female breast and ovarian cancers, but they have also been associated with increased risks of several additional types of cancer including colon, liver, endometrium, cervix, fallopian tubes, peritoneum, melanoma, gallbladder and biliary ductus malignancies. However, there is no study in the literature on whether the *BRCA* genes mutation leads to an increase in comorbid diseases that may accompany breast cancer. In this study, 72 patients diagnosed with breast cancer between the years of 2016-2018 in Kayseri Training and Research Hospital were examined. Next Generation Sequencing was performed to detect *BRCA1* and *BRCA2* genes variants. The patients with and without pathogenic variants in the *BRCA* genes were compared. There was no significant difference between ages of the groups (p=0.673). Further, concomitant comorbidity was evaluated. All patients were examined for diabetes, hypertension, heart disease, asthma, neuropathy, chronic pain, osteoporosis, anxiety disorder, anemia, functional dyspepsia and thyroid diseases. The presence of asthma in the *BRCA* genes mutation group was relatively more frequent than non-mutation group (p=0.025). There was no significant difference was found in terms of other comorbid diseases. It is thought that BRCA gene mutation in breast cancer patients may be related to asthma. The genetic etiology and familial tendency of asthma supports this outcome. Further and larger studies are needed.

OP-21-003

The effects of nobiletin through *TLR9* signaling pathway in prostate cancer

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We investigated the effects of dietary polymethoxylated citrus flavonoid nobiletin (NOB) through TLR9 signaling pathway on PC-3 (hormone-independent) and LNCaP (hormone-dependent) human metastatic prostate cancer and HUVEC control cell lines. In order to determine the cytotoxic effects of NOB (5,10,20,40,80,160 μM) and CpG-ODN (1,5,10 μM), a ligand for TLR9, for 6, 24 and 48 hours, WST-1 analysis was performed. Additionally, the effects of NOB on TLR9 signaling pathway were determined by *TLR9* gene expression, TLR9 and IRF7 protein levels and IFN-α and IFN-β cytokine levels. The potential metastatic effects of NOB on these cell were analyzed by gelatin zymography of the MMP-2 and MMP-9. Our results showed that NOB had an significant inhibitory effect on the viability of PC-3 (40 μM), LNCaP and HUVEC cells (20 μM) ($p<0.05$). Besides, *TLR9* gene expression and TLR9 and IRF7 protein levels were significantly decreased in PC-3 cells while increased in

LNCaP cells due to different profile (p<0.05). After NOB treatment, the cytokine levels considerably decreased in LNCaP cells and increased in PC-3 and HUVEC cells (p<0.05). It was found that NOB decreased MMP-2 and MMP-9 activities in PC-3 cells, but increased in LNCaP cells (p<0.05). In conclusion, NOB act as an agonist in PC-3 cells but not in LNCaP cells and NOB had a hormone-independent metastatic effect on metastatic prostate cancer via TLR9 pathway. This study suggests that TLR9 signaling pathway may be regulated by NOB and thus, NOB may be valuable as a new therapeutic approach in metastatic prostate cancer *in vitro*.

OP-21-004

Cornelia de Lange syndrome with a novel *NIPBL* mutation and a 10q11.22-q11.23 deletion

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Cornelia de Lange syndrome (CdLS) can be inherited as an autosomal dominant condition or an X-linked condition. The aim of this case report is to contribute to the literature with the first report of 10q11.22-q11.23 microdeletion which has previously been reported in the *NIPBL* gene with the unreported heterozygous mutation and coincidentally. A 12-year-old girl who was referred to our outpatient clinic because of short stature was the child who was born with a primary cousin consanguineous marriage. Head circumference (4p), height (<3p) and body weight (10p) were measured at presentation. Her physical examination revealed a large forehead, arched eyebrows that grow together (synophrys), long curly eyelashes, anteverted nares, and clinodactyly of the fifth fingers. Echocardiography showed minimal MRI and varus deformity on foot radiograph. array CGH and *NIPBL* gene sequence analysis were studied. In microarray analysis, the deletion of 10q11.22q11.23 and p.Asn82Ser (c.245 A>G) heterozygous mutation in the *NIPBL* gene were identified and indicated as possible disease cause according to in silico databases. It has been shown that the region of repetitive deletion of 10q11.21q11.23 is the region of the fracture region. When the patients in the literature were evaluated in terms of clinical findings, varus deformity was observed in our patient in addition to the features in the database. Most affected individuals have an abnormal gene as a result of a new gene mutation and do not have an affected parent. Other genes may be found to be associated with CdLS in the future.

OP-21-005

The role of angiogenesis related *Rheb*, *HIF-1 alpha*, *CA9* and *TSP-1* genes in kidney cancer

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Renal cancer is one of the cancer types which display high tumor angiogenesis. The aim of this study is to search the role of angiogenesis related *Rheb*, *HIF-1α*, *CA9* and *TSP-1* genes amplification in kidney cancer. Patient samples were obtained from the Department of Urology of Istanbul Faculty of Medicine. The analyses were performed in the Department of Basic Oncology. *Rheb*, *HIF-1α*, *CA9* and *TSP1* gene expression levels were determined by Quantitative Real Time PCR in tumor and normal tissue samples of 63 patients with kidney cancer. Gene expression levels were calculated compared to *G6PDH* copy numbers. Our results were evaluated by SPSS programmer which has included Mann-Whitney U, z, 2-tailed test. *CA9* expression levels were significantly higher in the tumors compared with the normal tissue samples in our study (p=0,013). *HIF-1α* gene expression level was significantly higher than that of *G6PDH* in cancer tissue (p=0.035). *Rheb* gene expression levels were not found significantly higher than *h-G6PDH* gene expression levels (p=0,09) in patients with kidney cancer. In tumor samples positive correlation was found between *Rheb*, *HIF-1α* and *CA9* gene expression levels (p<0.001, p=0,018, p=0,020, respectively). No significant difference was encountered in terms of *TSP-1* gene expression level between tumoral and normal tissues except 2 patients in Stage 4 disease (p=0.026, p=0,3). A negative correlation was detected between *TSP-1* and *Rheb*, *HIF-1α*, *CA9* (p<0.001, p<0.001, p=0,028, respectively). Our findings are consistent with the fact that *HIF-1α* and *CA9* gene products are involved in the pathogenesis of renal cell cancer.

OP-21-006

The role of *SEPTIN 9* (*SEPT9*) gene DNA methylation on bladder cancer

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The *SEPTIN 9* gene (*SEPT9*) codes for a GTP-binding protein

associated with filamentous structures and cytoskeleton formation. *SEPT9* plays a role in multiple cancers as either an oncogene or a tumor suppressor gene. DNA methylation of *SEPT9* gene is often observed in a wide variety of cancers in fact, hypermethylation of the gene was recently introduced as a biomarker in some cancers. But methylation of *SEPT9* and its effect on protein expression is unclear in bladder cancer. Therefore, aim of this study was to determine firstly *SEPT9* DNA methylation profiles and secondly the effect of its methylation on Septin 9 protein expressions in bladder cancer. Methylation pattern of *SEPT9* gene was analyzed by pyrosequencing. Protein level of Septin 9 was determinated by western blot in 40 bladder tumors relative to 5 normal bladder controls. Sequencing analysis revealed significantly lower methylation frequencies in bladder tumor samples relative to normal samples ($p<0.01$). On the contrary, an increase in protein level was observed in almost half of samples. The reason for this condition may be post transcriptional regulation. As a result, *SEPT9* may be playing a role as oncogene and suggesting a need for further investigation on the explanation of oncogenic role on bladder cancers. Hypomethylation of *SEPT9* can be used novel candidate prognostic markers for bladder cancer.

OP-21-007

Our experience in BRCA-associated hereditary breast and ovarian cancer syndrome

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BRCA1- and *BRCA2*-associated hereditary breast and ovarian cancer syndrome (HBOC) is characterized by an increased risk for mainly female and male breast cancer and ovarian cancer. 80% of pathogenic variants in *BRCA1* and *BRCA2* are detected by sequence analysis and approximately 10% by deletion/duplication analysis. In our center, the results obtained by studying the whole gene sequence analysis of *BRCA1* and 2 with NGS (Next Generation Sequencing) method were compiled. Pathogenic variant was detected in 5 of 30 patients and VUS was detected in 2 patients. Four of the pathogenic variants are located in *BRCA1*; one was detected in *BRCA2*. Three of the pathogenic variants were frameshift (*BRCA1*:c.2215_2216insCT, *BRCA1*:c.2131_2132delAA, *BRCA1*:c.2952delT) and 2 were nonsense mutations (*BRCA1*: c.1059G>A and *BRCA2*:c.469A>T). Also, *BRCA1*:c.9976A>T variant which causes stop codon formation is classified as benign. *BRCA1* and *BRCA2* mutations were detected in 16.6% of patients with breast and ovarian cancer. This frequency can be considered slightly higher compared to the literature.

OP-21-008

Targeted gene panel sequencing for hereditary kidney diseases: Efficiently detects candidate pathogenic variants related with these disorders

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Hereditary kidney diseases like Polycystic Kidney Disease (PKD) is a heterogenous form kidney disease which multiple genes have been found to be implicated in disease etiopathogenesis. Genetic diagnosis is highly important for hereditary kidney diseases in order to ensure the etiology of the condition and counsel the patients properly. Twenty-one patients who admitted to our clinic with PKD and/or other nephropathy syndromes were screened for 44 genes related with kidney disorders. The exons/exon-intron boundaries were amplified by using Nephropathies Solution kit in MiSeq instrument. Sophia DDM platform and Sophia Genetics' MOKA were used in variant analysis and annotation. Variant Classification was performed according to HGMD Professional, CentoMd and other available in-silico tools and ACMG variant pathogenicity classification. Several pathogenic (P)\likely pathogenic (LP)\VUS variants were found in 32 genes included in our gene panel. Twelve cases had 16 novel variants in the *CLCNKB*, *DSTYK*, *PKD1*, *PKD2*, *PKHD1*, *SLC12A1*, *SLC4A1* and *TTC21B* genes. Six cases had 5 P variants in PKD1 and CYP24A1 gene and three cases had a LP variant in the BSND and PKD1 genes. One frameshift novel deletion was identified in a case whose family and her previous generation were affected with PKD. In addition, 6 cases had also CNVs in *HNF1B*, *CEP290*, *CLCNKB*, *PKHD1* genes. Our study affirms that genetic screening of patients with PKD and other nephropathy syndromes by using targeted gene panel not only eases the diagnosis but also help counseling the patients and their family members for the risk of developing the disease.

OP-21-009

Combination treatment of usnic acid and sorafenib on hepatocellular carcinoma

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Sorafenib (SOR) is the only drug approved for the treatment of hepatocellular carcinoma (HCC). However, SOR can cause significant toxicity in patients and thus, it is necessary to develop new treatment strategies directed at toxicity reduction and higher efficacy. For this purpose, for the first time we investigated combined therapeutic effect of usnic acid (UA), a lichen metabolite, and SOR. SOR and UA were treated with UA (12.5 µM and 25 µM) and SOR (0.1 and 0.5 µM) for 12, 24 and 48 hours, and cytotoxic effects were determined by WST-1 assay in HepG2 and SNU-449 HCC cell lines. Furthermore, we performed Annexin V and cell cycle analysis to investigate the apoptotic effects of the combination treatment. As a result, the cell viability of the HepG2 and SNU-449 cells significantly reduced to 26.0% and 18.0% at in combination treatment 25 µM UA+0.5 µM SOR, respectively for 48 h ($p<0.01$). The combination treatment induced more apoptotic cell death in HCC cells than SOR and UA alone. We found that the percentage of total apoptotic cells increased to 75.9% and 83.4% in HepG2, SNU-449, respectively at 25 µM UA+0.5 µM SOR. Additionally, combination treatment of 25 µM UA+0.5 µM SOR induced a considerable increase from 38.7% and 65.6% in control cells to 92.0% and 73.2% in G0/G1 phase for HepG2 and SNU-449 cells, respectively. In conclusion, combine treatment with SOR and UA exhibited a strong synergistic interaction (CI<1) and inhibited HCC cell proliferation by apoptotic death.

OP-21-010

The role of NGS method in the diagnosis of periodic fever syndrome

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Periodic fever syndromes are a group of autoinflammatory diseases and characterised by recurrent episodes of fever and systemic inflammation occur in the absence of autoantibody production or identifiable infection. The most responsible genes in this group are MEFV, MVK, NLRP3 and TNFRSF1A. We examined the variants in aforementioned genes detected in 30 patients with NGS (next-generation sequencing). We were able to explain the clinic of 11 patients with MEFV analysis. Although pathogenic variants were detected in the MVK gene in two patients, it did not support the clinic due to its heterozygous form. 3 likely pathogenic variants and one VUS (variant of unknown significance) were detected in the NLRP3 gene. In the TNFRS1A gene, 2 likely pathogenic and 4 VUS were detected. As a result, with these results, we aimed to emphasize the importance of NGS method in the diagnosis of periodic fever syndrome.

OP-21-011

A case of early onset breast cancer with pathogenic variation in *STK11* gene

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Peutz-Jeghers Syndrome (PJS) is an inherited autosomal dominant disorder consisting of characteristic gastrointestinal (GI) hamartomas, mucocutaneous pigmentations and predisposition to GI, breast and other cancers. In this study, we aimed to present a common mutation in *STK11* gene in PJS case with early onset breast cancer. Our case is a 34-year-old woman. She was referred us because of the early onset recurrent breast cancer by oncology clinic. Pathology results were invasive ductal carcinoma and in situ multifocal solid papillary carcinoma on left breast. After adjuvant chemotherapy, hamartomatous polyp was detected in her colonoscopy following rectal bleeding. She had a history of left oophorectomy for benign reasons. We detected pigmentations on lower lip mucosa, a brown papule on nose and a brown macula at left palmar region. In her family history, it was learned that her mother was operated nasal polyp excision three times and aunt's daughter had a 45-year-old breast cancer diagnosis and her 28-year-old sisters had black spots on lips developed in childhood. Similar skin lesions were present when the patient was a child. Next generation sequencing analysis for Hereditary Cancer Risk Panel was studied for PJS genetic diagnosis. It detected nonsense, heterozygous, c.250A>T pathogenic variation (rs137853076) on the exon 1 of *STK11* gene (ENST00000326873). In conclusion, physical examination is indispensable for the diagnosis of hereditary cancer syndromes. Molecular diagnosis of hereditary cancer syndromes give patient's relatives the opportunity to early diagnose and also risk reducing measures can prevent cancer formation.

OP-21-012

Zoledronic acid effectiveness and estrogen receptor status

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Zoledronic acid (ZOL), a bisphosphonate, has potent anti-tumor efficacy in breast cancer in the pre-clinical and clinical studies. However, the of an optimal exposure time and concentration are not understood clearly. In the present study, we investigated the cytotoxic and apoptotic effects of ZOL on MCF-7 estrogen positive breast cancer cells compared with MDA-MB-231 triple negative breast cancer cells by WST-1, Annexin V and cell cycle analysis. For this purpose, MCF-7 and MDA-MB-231 cells were treated with different concentration of ZOL (10-100 µM) for 24 and 48 hours. The viability of MCF-7 cells was significantly decreased in a time and dose-dependent manner ($p<0.01$). Compared with MDA-MB-231 cells, MCF-7 cells were less sensitive to ZOL treatment. The viability of MCF-7 cells reduced to 77.5% and 67.1% at 25 and 100 µM ZOL, respectively for 48 hours ($p<0.01$). However, there was a considerable increase in the percentage of late apoptotic cells (11.2% and 28.4%) after treatment with 25 and 100 µM ZOL, respectively in MCF-7 cells for 48 hours ($p<0.01$). Additionally, treatment with 25 and 100 µM of ZOL caused a significantly increased accumulation of MCF-7 cells in the G0/G1 phase arrest (80.5% and 84.5%, respectively) for 48 hours compared with control cells (70.0%). Consequently, ZOL exerts potential therapeutic effects on MCF-7 cells. However, MDA-MB-231 cells were more sensitive to ZOL than MCF-7 cells due to the molecular features and morphological characteristics of each subtype. Thus, the underlying mechanisms of therapeutic effects of ZOL are further investigated.

OP-21-013

Chrysin, a natural flavonoid found in apple peel, induces mitochondrial reactive oxygen species with accompanying apoptosis in colon cancer cells

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Cancer is among the costliest diseases of our modern age. Complex nature of cancer development renders treatment options somehow limited; yet prevention has gained utmost importance in the last decades among other approaches. Colorectal cancer is a slowly developing cancer type but is accountable for 694,000 deaths/year, making it responsible from 9% of all cancer deaths, and unfortunately these figures tends to increase worldwide. By its nature, colon cancer is the most suitable form of cancer for prevention approaches since this slow development time and all-time interaction with food constituents colon as a perfect locus for cancer chemoprevention approaches Epidemiological studies suggest that over 75% of all colorectal are preventable by means of a diet rich in vegetable fibers, fruits, antioxidants and vitamins and poor in animal fat. Flavonoids are group of compounds that found in various fruits and plants. Chrysin is a flavonoid commonly found in honey propolis and fruit skin. The aim of our study was to evaluate the effect of chrysin in colon cancer cells. In this study, we evaluated cellular toxicity via WST-8 method and flow cytometry, then measured intracellular and mitochondrial reactive oxygen species via flow cytometry in SW480- human colon adenocarcinoma cell lines *in vitro*. As a result, we found that chrysin induced apoptosis with accompanying intracellular and mitochondrial ROS that cannot be blocked by traditional ROS scavengers such as n-acetyl cysteine. These data might be used as a clue to incorporate chrysin into combination treatment regimens in the future.

OP-21-014

DNAJC10 (ERDJ5) is a novel biomarker candidate in breast cancer

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DNAJC10 is a member of DNAJ (HSP40) family of Heat Shock Proteins and its apoptosis promoting function has been previously reported in neuroblastoma, prostate and colon cancers. In this study, we evaluated the role of the *DNAJC10* gene in breast carcinogenesis by analyzing its *in vitro/in vivo* expression and its genetic/epigenetic alterations. We analysed a microarray dataset (GSE36133), containing gene expression data of 56 breast cancer cell lines, by means of R Bioconductor program. DNAJC10 expression was found to be relatively lower in basal-like cell lines (15/25) compared to HER2+ (5/13) and luminal cell lines (7/18). Q-RT-PCR results showed that DNAJC10expression was reduced in 3 out of 4 breast cancer cell lines compared to the nontumorigenic mammary epithelial cell line (MCF 10A). Immunohistochemical analysis revealed that *DNAJC10* expression was significantly less frequent in invasive ductal carcinoma samples (n=121) compared with adjacent normal breast tissues (n=32) ($P<0.0001$). According to Sanger-Cosmic database (v87), point mutations and copy number variations of DNAJC10 were very rare in breast cancer samples (0.47% and 0.13%, respectively). Methylation Specific PCR results showed that CpG islands found in in-silico predicted promoter regions are not frequently methylated in breast cell lines. Our results support the

idea that DNAJC10 is a potential biomarker and tumor suppressor candidate for breast cancer. Epigenetic factors other than promoter methylation could contribute to the downregulation of DNAJC10 expression. Functional, epigenomic and clinical studies are needed to ascertain the contribution of *DNAJC10* gene in breast carcinogenesis.

OP-21-015

Retrospective evaluation of pathogenic copy number variations detected via chromosomal microarray analysis

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Chromosome segment variations involving more than 50 bases are called Copy Number Variations (CNV). Chromosomal microarray method is used to detect CNVs in routine practice. Chromosomal microarray analysis (CMA) is a first-tier test in the evaluation of individuals with intellectual disability and developmental delay with the diagnostic yield ranging from 5 to 20% varying based on population examined. The International Standard for the Consortium of Cytogenomic Array recommended CMA as a first-stage cytogenetic diagnostic test for patients with CA and ID / GDD. Our study was carried out with retrospective evaluation of 300 patients with CMA with different indications with Affimetrix Cytoscan Optima chips in the Ankara Ataturk Research and Education Hospital. In the standard analysis method, 43 CNVs was detected at 298 patients. The length of 24 of the CNVs were below 5-Mb and they could not be detected with conventional karyotyping. The length of 14 of the CNVs were between 10 and 20-Mb. Standard analysis method could not detect 3 pathogenic CNVs which were below 100-Kb. Chromosomal microarray analysis can detect well-known microdeletion syndromes. It also contributes to the identification of genes that are responsible for the phenotypes in the new copy number variations. Based on our findings, we suggest that CMA should be used as a first-step test for the identification of new loci and the expansion of known phenotypes.

OP-21-016

Investigation of cfDNA in volatile condensate

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Breath Condensate is a non-invasive method of collecting fluid samples, which are representatives of airway lining fluid. cfDNA research in plasma samples of non-small cell lung cancer (NSCLC) cases is widely used and led to new insights and emerging of liquid biopsy, but there is limited number of cfDNA investigation in volatile condensate samples. By this study, we are aiming to identify if volatile condensate is appropriate source for cfDNA by using house keeping genes specific primer probes and quantitative real time polymerase chain reaction (RT-PCR) in healthy subjects. Four house keeping genes are on distinct chromosomes studied. The results and limitations are discussed.

OP-21-017

Molecular findings in prenatal array karyotyping: Clues and implications for reporting

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Prenatal array karyotyping has been widely used with the suggestion of guidelines prepared various internationally accepted communities. Routinely, array karyotyping is indicated in the presence of pathologic ultrasound findings and presented as an option to every pregnant woman who undergo invasive procedure. The SNP array methodology enables the detection of copy number variations (CNVs) at the molecular level, including various morbid genes of clinical importance. For this reason, a number of "coincidental" findings are also detected not so rarely, for which effective genetic counseling becomes challenging. In this study, additional molecular findings of 183 pregnant women who underwent prenatal array karyotyping were documented. A filtering algorithm was applied stepwise. In the final step, after screening for submicroscopic chromosome aberrations, the detection of CNVs with high marker counts involving morbid OMIM genes were investigated for single gene disorders. In addition, mosaic findings, absence of heterozygosity stretches, and in trio analysis, uniparental disomy scans were performed with mendelian error check options. It was observed that at least one molecular level finding was observed in more than %10 of the analyzes. In order to be reported following

criteria were considered: Only CNVs which were definitely or likely pathogenic (benign, likely benign and variants of uncertain significance were eliminated), genes those were leading to diseases with serious morbidity and mortality. Additional tests (such as point mutation screening on the other allele for recessive diseases for those heterozygote variants were detected) and confirmatory analysis were recommended.

OP-21-018

Testing for genetic causes of infertility: NGS based infertility panels

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Infertility is a complex multifactorial pathological condition and a significant proportion of infertility cases are due to genetic defects. Genetic factors account for at least 15% of male infertility. Female infertility is a heterogeneous condition and it is difficult to define a single genetic cause. Here, we present the development of an NGS panel for the detection of genetic variants with male and female infertility. We developed a next-generation sequencing (NGS) gene panel consisting of 36 genes known to be associated with female infertility and 41 genes associated with male infertility. Genes were included based on OMIM and literature data. Patients with sex chromosome aneuploidies, sex chromosome abnormalities and Y microdeletions were not included. Genomic DNA was isolated from peripheral blood samples Sequencing was performed on a MiSeq (Illumina). VCF files were analyzed and sequence variant classification was done according to ACMG Standards and Guidelines. 53 infertile females and 41 infertile males included in this study. 22 of infertile females and 11 of infertile males have no genetic variants. Totally 28 different gene variants were detected in females and 31 different gene variants were detected in males. Determining genetic causes of infertility has an important implication for the reproductive health and the general health of the patient. In addition, identification of genetic variants is likely to help in choosing the best therapeutic approaches for the patient. NGS panel will ensure to detect multiple disease-causing variants simultaneously though the costs and turnaround time will decrease.

OP-21-019

The effects of human chorionic gonadotropin-based hormonal therapy on the expression levels of proliferating cell nuclear antigen

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Nonobstructive azoospermia is a common cause of infertility in males. Proliferating Cell Nuclear Antigen (PCNA) is associated with spermatogonial DNA synthesis and proliferation. A higher expression of spermatogonial PCNA is correlated with higher germ cell maturation and sperm output and has positive effects on spermatogenesis. On the other hand, decreased expression of spermatogonial PCNA is correlated with impaired spermatogenesis in men. In this study, we aimed to understand the effects of human chorionic gonadotropin (HCG)-based hormonal therapy on the expression levels of PCNA, which interacts with a meiosis specific RecA homologues, LIM15/DMC1, and proteomic markers ESM1 and TEX101 in men with nonobstructive azoospermia. Forty-five patients who failed sperm retrieval procedures using microdissection testicular sperm extraction (micro-TESE) were enrolled in HCG-based hormonal therapy prior to a second micro-TESE. The expression levels of *PCNA*, *LIM15*, *ESX1* and *TET101* were assessed using RT-PCR analysis. PCNA RNA levels were significantly increased after the hormonal therapy, but the change in *LIM15* RNA levels was not consistent, and the change in *ESX1* and *TET101* RNA levels were not observed. In these patients who received hormonal therapy following an unsuccessful micro-TESE, the most important clinical problem is to choose the correct timing for second micro-TESE. The patients with increased *PCNA* RNA levels have better success rates for second micro-TESE. In this ongoing study, we are increasing our number of patients, in order to show significance on the expression levels of *LIM15/DMC1*, *ESM1* and *TEX101*, and correlate them with intratesticular testosterone levels, sperm counts and spermatogonial FISH results.

OP-21-020

A patient with a balanced inversion of chromosome 11 and unbalanced inversion of chromosome 2

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Inversions are structural chromosomal abnormalities in which, chromosome has two breakpoints and the segment in between rotates 180° and reinserts. Unbalanced genomic arrangements may occur if inversion results in a deletion/duplication of segments or breakpoint encompasses genes. Here we report an interesting case, a 7-year-old female patient who has both balanced and unbalanced inversions on two different chromosomes. The patient was examined for dysmorphic features and developmental delay at our clinic. She was large for gestational age and she had congenital hypothyroidism. Her gross motor development was compatible with her peers, but she had significant delay on language skills. She was suffered from recurrent urinary tract infections due to vesicoureteral reflux. At the physical examination; hypertelorism, strabismus, anteverted nares, bifid uvula, low-set ears, hypertrichosis, accessory nipple, 2-3 toe syndactyly and a cafe au lait spot on her leg was noted. A paracentric inversion at 2q12q14.3 and a pericentric inversion at 11p11.2q13.5 were detected at karyotype analysis. Microarray analysis performed to detect possible CNVs. 6,741.652 kb loss at 2q12.3q14.1 (108313177-115054828) region and a 1,411.035 kb loss at 2q36.1 (222294101-223705135) region of chromosome 2 were detected but chromosome 11 was intact. Cytogenetic analysis of the family members were normal and we have concluded that inversions were de novo. 2q12.3q14.1 deletions reported in the literature were associated with neurodevelopmental delay and dysmorphic features similar to our patient. This interesting case would be enlightening for future diagnosis of patients with similar region deletions.

OP-21-021

Autism and genetic testing

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Autism spectrum disorder (ASD) is one of the most important neuropsychiatric disorders of childhood in terms of prevalence, morbidity and disease burden. Autism spectrum disorder is characterized with repetitive movements and disruption in social interaction and communication. It is a lifelong neurodevelopmental disorder with childhood onset. Its prevalence is around 1% and the incidence is rising in the population. Although etiology is not fully understood, it is thought that environmental and genetic factors play role in the development of autistic behaviors. Due to variation in etiology, underlying cause can only clearly be identified 15-25% of the cases. Detailed genetic studies performed in ASD indicated that a chromosomal or Mendelian disease can cause or predispose in 15-40% of patients. The most common genetic cause is copy number variations in the genome (10-35%). The aim of this presentation is to summarize the current genetic testing approaches in ASD. The use of molecular karyotyping as a first-tier test has been performed in patients with mental retardation / multiple congenital anomalies, autism spectrum disorders around the world. Also, recent advances in whole exome sequencing allow rapid identification of variants associated with ASD. Finding out the underlying genetic reason of the autism provides more specific genetic counseling and identifies medical risks associated with ASD. Also, it contributes to precision medicine.

OP-21-022

A primary ovarian failure case with de novo t(X;10) translocation

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Premature ovarian failure defined as loss of normal function of ovaries before age 40. Chromosomal translocations are one of the most important causes of primary ovarian failure in adolescents and young individuals. Although, X-autosome translocations are frequently associated with streak gonads and clinical feature of Turner Syndrome, some of the X-autosome translocations can lead various clinical manifestations. In this case, we describe 19-year-old woman with secondary amenorrhea. She had her first period when she was 13-year-old. After 2 years later she suffers from amenorrhea and hormone replacement treatment was started. She has mild intellectual disability. She had history of supraventricular tachycardia episodes and surgery because of bilateral lacrimal duct stenosis. Initial investigations revealed hypergonadotropic hypogonadism (FSH=76.5 mIU/mL (N: 4-9mIU/mL), LH: 38.74 (N: 2-10mIU/mL) mIU/mL, estradiol = 23 pg/mL (N: 107-139pg/mL), progesterone= 0.69). On ultrasound examination of pelvis, ovaries were not visualised and thin endometrial line were noted. Cytogenetic study, performed according to routine procedures, revealed balanced translocation involving the short arm of chromosome 10 and long arm of the X chromosome in all the cells with the following karyotype: 46,X,t(X;10)(q22;p11.2). We conclude that t(X;10) may related with premature ovarian failure.

OP-21-024

The utility of reverse phenotyping with Whole-Exome Sequencing in an undiagnosed infant with neurological symptoms

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Whole-exome sequencing (WES) is one of the increasingly used next-gene sequencing methods to diagnose complex rare diseases. The purpose of this study is to determine the contribution of reverse phenotyping to diagnose diseases with blended phenotypes. A 22-month-old girl was referred to our clinic with convulsion, developmental delay, hypotonia and vomiting. She had intrauterine growth retardation and hypotonia. She was the first child of consanguineous parents. On physical examination she had growth retardation, hypotonia and dysmorphic facial features. Her laboratory tests were normal. She had white matter hypomyelination on brain MRI. A specific diagnosis could not be established via clinical features and laboratory tests and WES revealed homozygous mutations in three different genes. The variant c.3412_3418del(p.Val1138Metfs*25) in *CNTNAP1* gene classified as likely pathogenic, c.1090G>A(p.Val364Met) variant in DPYS gene was classified as variant of uncertain significance (VOUS), and c.2480G>A(p.Arg827Gln), in *ATP7B* gene classified as VOUS in accordance with ACMG 2015 criteria. The parents were found to be heterozygous for the same mutations. Following WES results, clinical compatibility was investigated. Developmental delay and hypomyelination in the patient were compatible with Congenital Hypomiyelinating Neuropathy caused by *CNTNAP1* mutations. Persistent vomiting is one of the symptoms of DPYS mutations due to Dihydropriminidase deficiency. A decreased ceruloplasmin level of the patient may be considered as the first sign for Wilson's disease caused by *ATP7B* mutations. Reverse phenotyping using WES shortens the diagnostic process, identifies the additional diseases in patients with blended phenotypes accompanied by consanguineous marriages and improves the quality of genetic counseling.

OP-21-025

Whole and clinical exome sequencing analysis for diagnosis of epidermolysis bullosa

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Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous skin fragility disorder. It is identified by mechanical tenderness, blisters and erosions both skin and mucosa. EB is classified into four main types, based on the depth, or level of blister formation. Most common type is Epidermolysis Bullosa Simplex (EBS) and other types are Dystrophic Epidermolysis Bullosa (DEB), Junctional Epidermolysis Bullosa (JEB) and Kindler Syndrome. For twenty seven patients with clinical EB subtypes, we made whole exome sequencing and clinical exome sequencing analysis using Illumina Next Seq 500 sequencer with Agilent SureSelect Human All Exon V5 and Sophia Genetics - Clinical Exome Solution kit. All single nucleotide variations (SNV) and also copy number variations (CNV) have analyzed by Sophia DDM® Software with filtering EB related following genes: *ATP2C1, CD151, CDSN, CHST8, COL17A1, COL7A1, CSTA, DSG1, DSG2, DSG4, DSP, DST, EXPH5, FERMT1, GRIP1, ITGA3, ITGA6, ITGB4, JUP, KRT1, KRT10, KRT14, KRT5, LAMA3, LAMB3, LAMC2, MMP1, PKP1, PLEC, TGM5, EDAR, KLHL24, AREI, PSS4, STF1, STFA.* We found mostly novel mutations. Most prevalent mutated gene is COL7A1. There are two recurrent mutations *COL17A1* c.1141+5G>A and *COL7A1* exon 13-24 homozygous novel deletion. We will have better understanding of the Turkish EB patients mutation spectrum with our findings.

OP-21-026

Do functional variants of *MIF* and *MBL* genes influence outcome in patients underwent autologous stem cell transplantation for multiple myeloma?

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Multiple myeloma (MM) is a plasma cell malignancy, with wide survival range and multiple risk factors and staging systems linked to survival. Macrophage migration inhibitory factor (MIF) is a potent proinflammatory cytokine. Mannose-binding lectin (MBL) enhances opsonization and activates complement. This analysis was performed to evaluate the relationships of MIF -173G/C and MBL codon 54 variants with clinical features and susceptibility in patients underwent Autologous stem cell transplantation (ASCT) for MM. A total of 155 patients (Female/Male: 74/81) who underwent ASCT and 200 healthy subjects (Female/Male: 99/101) were included. The median follow-up period was 36 months. Genotyping of these variants was determined by PCR-RFLP. Genotype and allele frequencies were compared between the study groups using χ^2-test. Kaplan-Meier curves for Progression-free survival (PFS) and Overall survival (OS) were compared using a log-rank test. The median age at diagnosis is 55 years for patients. In all, median OS was 79 months in patients. OS showed that 16.1% patients died. PFS was associated with gender (p=0.049, 95% Cl: 0.258-0.998). Individuals with BB genotype showed a significant association with 10.607-fold increased risk of MM (p=0.001). The genetic analysis association with survival was performed under a recessive genetic model (CC vs. GG/CG). *MIF* GC/GG genotype was significantly associated with longer OS (median 5 years) compared to CC genotypes (p=0.016). Our study indicated that the *MBL* codon 54 functional variant might contribute to MM susceptibility in Turkish population. Also, our results imply that the OS in MM patients is associated with the -173G/C variant of *MIF* gene.

OP-22-001

The first Turkish patient with Pierpont syndrome and *TBL1XR1* mutation

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Pierpont syndrome is a rare autosomal dominant disorder characterized by mental retardation, hypotonia, characteristic facial features and short stature. The facial features of this syndrome are high forehead, hypertelorism, deep-set eyes, narrow palpebral fissures, full cheeks, broad philtrum and large ears. Other prominent features are deep creases on palms and on soles. *TBL1XR1* gene is responsible for this syndrome. Until today only ten affected patients have been reported. 1,5 years old boy was reffered to us for developmental delay. He was the second child of consanguineous (second cousin) Turkish parents. There was no delay in motor development of the patient. His height was 77 cm (3-10th centile), weight 9500g (3-10th centile). Physical examination, microcephaly, high forehead, upslanting palpebral fissures, strabismus, bifid nose, fleshy ears, gum hypertrophy, pectus excavatus, single palmar crease, deep grooves on soles and hypotonia were noted. Asymmetric septal hypertrophy was detected by echocardiography. Chromosomal microarray analysis was normal. On the basis of the observed clinical findings, he was diagnosed as Pierpont Syndrome. De-novo heterozygous c.1337 A>G (p.Tyr466Cys) mutation of *TBL1XR1* was detected in the patient. In conclusion this patient is the first Turkish patient with Pierpont Syndrome and he had asymmetric septal hypertrophy which has not been reported in this syndrome.

OP-22-002

A case with a rare genetic syndrome: Marshall Smith syndrome

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Marshall Smith syndrome is a rare autosomal dominant genetic disorder characterized by accelerated skeletal maturation, dysmorphic features, intellectual disability and failure to thrive. The only known gene for this syndrome is *NFIX* gene. We present a 19 month girl who was the second child of a nonconsanguineous parents. Physical examination demonstrated long

face, prominent forehead, prominent eyes, exophthalmos, long eyelashes, blue sclera and retrognathia. She gained head control at 7 months and started to sit at 11 months of age. Bone age at 1,5 year of age was approximately 5 years. Clinical diagnosis was compatible with Marshall Smith syndrome on the basis of these typical manifestations and *NFIX* gene sequencing revealed a novel heterozygous c.1287delC (p.G430Vfs*34) mutation. Consequently, we aimed to present a rare case with Marshall-Smith syndrome who had a novel mutation in NFIX gene.

OP-22-003

A case of complex mosaic Turner: cytogenetic/ array comparative genomic hypridisation (aCGH) discrepancy

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Array comparative genomic hybridization (aCGH) has the ability to detect deletions and duplications of DNA segments that can be too small (approximately less than 1 to 2Mb) to be detected by cytogenetic analysis. However, use of aCGH is hindered in detecting mosaicism. An apparent female, who was clinically diagnosed as Turner syndrome, was referred for genetic analysis. The proband was 16 years of age at the time of the referral. Cytogenetic analysis was performed following a short cell culture protocol by G-banding. Blood sample was also obtained from the mother of the proband for cytogenetic analysis. Peripheral blood was also obtained for aCGH analysis. DNA sample obtained from the blood sample was analysed using the Agilent oligonucleotide microarray with 8*60K coverage. The results were analyzed using the Agilent CytoGenomic edition 5.0.0.38 analysis program. The cytogenetic investigation showed that the proband was mosaic; in such the karyotype of the proband was reported to be 46,X,i(X)(q10)[26]/46,X,del(X)(q11.2)[11]/45,X[8]/46,XX[5]. The karyotype of the mother was 46,XX. The aCGH result revealed that the proband has a deletion of 57,252kb of Xp22.33-p11.21 region. The karyotyping result of the proband is in concordance with Variant Turner syndrome. Although aCGH analysis detected a deletion, the mosaicism could not be detected. Generally, if more than 50% of the cells have different chromosome complement, aCGH could detect the mosaicism. However, as shown with this case as well, although the resolution of the aCGH is higher, the cytogenetic investigation is still the first in line to detect mosaicism.

OP-22-004

De novo t(X;5) in a patient with premature ovarian failure and recurrent vertebrae fractures

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Premature ovarian failure (POF) is characterized as hypergonadotrophic amenorrhea before the age of 40 and it is confirmed by detecting elevated serum FSH levels (above 40 mUI/L) twice. Cytogenetic abnormalities predominantly concerning X chromosome including Turner syndrome variants such as monosomy X, isochromosomes, deletions and X-autosome translocations are the main genetic aberrations leading POF. Our case is a 30-years-old female patient with a history of early menapause and multiple fractures of the vertebrae. She was referred to our clinics with a prediagnosis of POF. She had a history of recurrent compression fractures of L1-L5 vertebrae. The pedigree analysis revealed that there was a first degree cousine marriage between the parents. Karyotype analysis was performed initially and reported as 46,X,t(X;5)(q24;p13.2). Molecular cytogenetic analysis were performed to detect the breakpoints and reported as 46,X,t(X;5)(q24;p13.2)[20].isht(X;5)(D5S23+,D5S721+;D5S23-,D5S721-)[10]. Microarray analysis was performed for further investigation and a 597,016 kb loss containing 2 OMIM genes including *AGTR2* and *PLS3* were detected in the long arm of the X chromosome. De novo translocations between chromosome X and autosomal chromosomes are rare but several cases have been reported in the literature. Molecular mechanisms underlying X chromosome aberrations and POF is believed to be due to gene dosage and position effects. Deleted Xq23 region in our patient is a well known critical regions associated with proper ovarian function in women. Moreover, *PLS3* gene located in Xq23 is involved in the process of bone modeling and remodeling therefore it is one of the susceptibility genes of XLD osteoporosis.

OP-22-005

Molecular pathological evaluation of Alport syndrome

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Alport Syndrome (AS) is a hereditary kidney disease. AS is caused by mutations in *COL4A3*, *COL4A4* and *COL4A5* genes, which express α3, α4, α5 chains of Type IV collagen. These mutations lead to hematuria, proteinuria, interstitial nephritis and kidney failure. The disease has different forms like dominant depending on X, autosomal dominant and autosomal recessive. Mutations mostly occur in the *COL4A5* gene. For genetic diagnosis of AS, DNA was isolated from blood samples and coding regions sequenced by next-generation sequencing (NGS) technology with multiplicom kit. Bioinformatics analysis was performed with Sophia DDM. The aim of this study was to evaluate the pathologic assessment of patients diagnosed with AS. In this study, 23 variants were identified in 48 patients prediagnosed with AS, 21 males and 27 females. After bioinformatics analysis, pathogenic variants were observed in 5 patients, likely pathogenic variants in 4 patients and uncertain significance variants in 14 patients. In addition, 6 novel variants were found in the *COL4A3* gene and in the *COL4A5* gene. Due to the high number exons of genes related to molecular diagnosis of AS, evolution of AS with Sanger sequencing will be more difficult and expensive. Therefore, it is more effective to analyze related genes with NGS methods. As a result of this study, with the decreasing costs of NGS and widespread use, the idea that NGS can be used with high accuracy especially in the prediagnosis and possible treatment of other hereditary diseases is supported.

OP-22-006

Osteogenesis imperfecta type I caused by a novel mutation of the *COL1A1* gene in Turkish family

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Osteogenesis imperfecta (OI) consists of heterogeneous group of disorders characterized by susceptibility to bone fractures and decreased bone density. There is significant variability in range of severity from perinatal death to a subtle increase in fracture frequency. In this case, we aimed to present a patient with novel variant in *COL1A1* gene that may be associated with OI pathogenesis. Twenty-seven-year-old female patient admitted to medical genetics clinic with compound proximal ulnar fracture without significant trauma. Further physical examination revealed blue sclera, normal stature, absence of dentinogenesis imperfecta, no bony deformity, no limitation of mobility. This was the first fracture history present. Family history revealed that mother also had a fracture history of forearm, knee and phalanges with no significant trauma. Sequence analysis for osteogenesis imperfecta was ordered for index case. Analysis was done with next generation sequencing (NGS) for *COL1A1* (ENST00000225964), *COL1A2* (ENST00000297268) genes. In fourth exon of *COL1A1* gene frameshift causing, novel, heterozygous c.344dupG variant was found. Parental analysis revealed maternal inheritance of the variant. Genetic analysis was also offered for the patient's daughter who have blue sclera and also developed a fracture in right femur at the time of analysis. Same genetic variant was also demonstrated in the daughter. This is the first delineation of a novel heterozygous mutation in the exon 4 of *COL1A1* causing OI Type I. Novel mutations in patients could reveal new insights to pathogenesis and treatment of the disease.

OP-22-007

A case with a de novo heterozygote *ACTG1* variant: Genotype-phenotype correlation

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ACTG1 gene provides a role for gamma actin protein which is a subtype of actin protein family. Mutations in this gene associated with deafness, eye coloboma and Baraitser-Winter syndrome type 2. This rare genetic disease is characterized by variable facial features, anomalies of skeleton system, heart defects and neurologic problems. Autosomal dominant is a genetic pattern of the disease, most of the cases have de novo changes. We present a female propositus referred to the clinic with neuromotor development delay, deafness and epilepsy. Physical exam showed dismorphic facial features including triangular face, high arched eyebrows, posteriorly rotated ears, epicanthus, high palate, microcephaly and wide root of noose, additionally she had increased lombar lordosis. MRI studies showed trigonocephaly, enlargement in the central areas of cerebrospinal fluid, mild lissencephaly near to bilateral frontal lobes and sylvian fissures, increased signal in putamen and caudate nucleus, corpus callosum agenesis and anomalies of migration in the brain matter. Conventional and Molecular (aCGH) cytogenetic studies were normal. Clinical Exom Sequencing revealed the presence of novel heterozygous c.193C>G variation, this variant leads to

a p. Leu65Val change in *ACTG1* gene. Sanger sequencing confirmed the heterozygous variant in the propositus. This variant was neither found in ExAC nor 1000G databases and regarded as variant of unknown significance and damaging based on the in-silico prediction tools (DANN, dbNSFP.FATHMM, MetaLR, MetaSVM, MutationAssessor and MutationTaster). Our case has some features matching with Baraitser-Winter syndrome 2, genotype-phenotype correlation will be discussed.

OP-22-009

Clinical and molecular findings of neurofibromatosis type 1: Identification of three novel mutations of the *NF1* gene

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Neurofibromatosis Type1 (NF1) is a common autosomal dominant neurogenetic disorder with an incidence of 1 in 2500-3000 individuals. Café-au-lait spots, neurofibromas, axillar and inguinal freckling, lish nodules and skeletal abnormalities are main clinical features. It is caused by mutations of the *NF1* gene, located on chromosome 17q11.2 that encodes the protein neurofibromin. *NF1* is one of the largest known genes and more than 2600 mutations have been identified in the Human Gene Mutation Database. The aim of this study was to define clinical and molecular characteristics of NF1 patients. During the last one year (January 2018-january 2019), we analysed 14 patients (12 unrelated and 2 from one family). All patients were shown café-au-lait spots in 14 (100%), axillary and/or inguinal freckling in 13 (93%), neurofibromas in 6 (43%), lish nodules in 4 (29%), scoliosis in 3 (22%) and glial tumor in 1 (7%). 10 *NF1* mutations (9 different mutations) were detected in our patients. *NF1* mutation detection rate was 72%. Three of the 10 mutations detected in our patients were not identified until now. No mutational hotspots within the *NF1* gene were detected. We think that analysis of *NF1* gene by NGS metod is important for both early diagnosis and genetic counselling.

OP-22-010

A novel mutation in *HECW2* gene resulting neurodevelopmental disorder with hypotonia, seizures, and absent language

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Heterozygous mutations in the *HECW2* gene were recently found to be associated with severe developmental delay, absent speech, epilepsy, encephalopathy, hypotonia, dystonia/dyskinesia, microcephaly, and structural brain anomalies. Here we present a novel de novo heterozygous mutation in the *HECW2* gene in a male patient with growth retardation and severe developmental delay along with epileptic encephalopathy and structural brain anomalies. The height, weight and head circumference of the case at the age of 7 were less than 3 percentiles. He had severely delayed psychomotor development besides absent language and feeding difficulty. His first seizure was seen when he was 2-year old. Motor tonic seizures was stated to continue daily and generalized epileptic changes were seen in his EEG. Cranial MRI showed progressive cerebral, cerebellar and brainstem atrophy. A novel heterozygous mutation of c.G4484A (p.R1495K) was found in the 27th exon of the *HECW2* gene (NM_001348768) in the proband-based WES analysis. The parental study showed that this mutation was de novo. Mutations in *HECW2* gene cause "Neurodevelopmental Disorder with Hypotonia, Seizures, and Absent Language; NDHSAL" (#617268). Feeding difficulties, growth retardation, autism, and osteopenia are other clinical features that can be seen in this disease. To the best of our knowledge, only four mutations have been identified in ten patients in the literature. The patient with a novel *HECW2* variant is presented in here since the number of reported cases is low, and the new mutations are still needed to totally illuminate the genetic background of the disease.

OP-22-011

A rare *HNF1A* gene mutation in a Turkish family with maturity-onset diabetes of the young (MODY)

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Maturity-onset diabetes of the young (MODY) is a hereditary form of Diabetes Mellitus (DM) and different gene mutations are associated with the disease. *HNF1A* (Hepatocyte Nuclear Factor 1-alpha) on chromosome 12 is one of the most frequent mutated genes in the disease which its mutation increases disease susceptibility. In adults, HNF1A protein is important in the expression of beta cell genes, like insulin gene and glucose transporter Glut2. The mutation c.814 C>T, R272C in exon 4 of the *HNF1A* gene causes the loss of DNA-binding activity of the HNF1A protein *in vitro* and dominant negative effect *in vivo*. This mutation is very rare in Turkish population and to our knowledge has not been reported up to now. Patients who were diagnosed with Maturity-onset diabetes of the young (MODY) have been referred to our department for HNF1A gene mutation analysis. Genomic DNA is isolated from 10ml peripheral blood. Then, DNA is sequenced using sanger sequencing method and *HNF1A* gene is screened for any possible mutation. Among the referred patients the c.814 C>T, R272C rare mutation in *HNF1A* gene was observed in two members of a Turkish family. Mother was diagnosed with Diabetes Mellitus at 26 and her son was diagnosed with the disease at 24. This mutation is a rare mutation in Turkish population and can cause MODY type of Diabetes Mellitus.

OP-22-012

Glutaric aciduria type 2: A case report

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Glutaric aciduria type II (GAII, OMIM#231680) is a rare autosomal recessive metabolic disease caused by mutations in the *ETF* or *ETFDH* genes. Symptoms and presentation age of late-onset GAII are highly variable. GAII is a treatable disease, but it may be difficult to diagnose because of this clinical heterogeneity. Muscle biopsy with the characteristic acylcarnitine and urine organic acid levels may confirm the diagnosis of GAII but in some cases, the absence of these biochemical profile can cause misdiagnosis. We aim to present the relationship between compound heterozygote *ETFDH* gene mutation and clinical findings in the light of the literature. Seven years old female patient referred to our clinic in order to genetic diagnosis for glutaric aciduria. When the patient was 9 months old she had muscle weakness and Tandem MS with multiple acyl carnitine elevation. And she had diagnosed as glutaric aciduria with lipid droplets in muscle biopsy. Her treatment was started. Afterwards she had only two hypoglycemia attacks. She weighed 19 kg (2p), her height was 122 cm (15p). There was no dysmorphism, parental consanguinity and family history. In next generation sequencing analysis (NGS), we detected pathogenic, heterozygote, frameshift c.1198_1201delACTC and in "trans" position pathogenic heterozygote c.1130T>C (L377P) mutation on the *ETFDH* gene (ENST00000354232). Parents' *ETFDH* gene analysis is planned to confirm compound heterozygote status as revealed by next generation sequence analysis. In conclusion glutaric aciduria should be considered as a diagnosis of muscle weakness and genetic testing may prevent more invasive diagnostic testing such as muscle biopsy.

OP-22-013

Genetic fitness: True story

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The Circassians were driven away from their mainland during 19th Century and forced to migrate to land of Ottoman Empire. An estimated population of 2346 Circassian was deported from Istanbul to Cyprus. Many of the passengers however died at sea due to Malaria and unknown causes. Only, 1351 Circassians arrived to Cyprus and many of them had faced Malaria again. Malaria was endemic to Cyprus. Moreover, Thalassemia, well characteristics autosomal recessive genetic disorder, was the second most serious public health condition on the island after malaria. It is well known that thalassemia mutation traits are resistant to Malaria. In this report, we studied one large Cypriot family whose grandparents were in that ship journey. The sequence analysis of *HBB* gene revealed heterozygous c.316-106C>G (IVS- II-745) (II-745) mutation. The collection of this data was used to conclude that a typical natural selection scenario. The single mutation in this case did not limit survival; it in fact enhanced the survival changes of them to form new colonization and the transfer of the mutation to their offspring.

OP-22-014

Fifteen year story of a balanced translocation t(2;7)(p21;p15): Unraveling the phenotype of Saethre-Chotzen/Robinow-Sarouf syndrome or still undiagnosed skeletal dysplasia after next generation sequencing?

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Recent developments in genomic analyses have facilitated the precise mapping of translocation breakpoints associated with Mendelian disorders to decipher if the rearrangement is likely to contribute to the observed phenotype. We evaluated the phenotypic consequences of an apparently balanced translocation in a family affected by craniosynostosis and limb malformations presenting with a dominant inheritance pattern and variable expressivity. We applied large-insert jumping libraries to localize the breakpoints and confirmed these results with Sanger sequencing to characterize breakpoints of a t(2;7)(p21;p15), followed by gene expression studies to explore the functional impact of the rearrangement. Sequencing revealed five breakpoints, disrupting two genes, *HDAC9* and *MACC1*. We discovered altered expression of *TWIST1* located downstream of *HDAC9*. Our results suggest that an inversion in the HDAC9-TWIST region in 7p21.1 affects regulation of *TWIST*, thereby producing a skeletal dysplasia with intrafamilial variable expressivity. These analyses suggest that the mechanism of this rearrangement might involve alteration of regulatory sequences located at a distance in cis that dysregulate *TWIST* and insinuate *HDAC9* as a new disease locus producing craniosynostosis.

OP-22-015

CHST3-related multiple dislocations and severe short stature in 3 families

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Chondrodysplasias with multiple dislocations is a heterogeneous group of skeletal dysplasia which consist of different nearly 10 diseases. Clinical and radiological findings are effective sings for differential diagnosis, but several researches showed the difficulty of distinction of these diseases. *CHST3*-related skeletal dysplasia (#143095) is characterized by severe short stature and multiple dislocations of large joints. To date nearly 50 cases have been reported and the other most frequent clinical and radiological findings are rhizomelia, short metacarpal bones, brachydactyly, camptodactyly, kyphoscoliosis, club feet, small epiphyses, irregular end plates of the vertebral bodies, narrowed intervertebral space. Fusion of vertebras and distal bifurcation of humeri were only noted in a few patients. Six patients from unrelated 3 families were referred with severe short stature and multiple dislocations. All of the patients had vertebral changes and most of them had knee, elbow, and hip dysplasia. We performed clinical exome sequencing (CES) to illuminate the responsible mutations. Homozygous missense c.776T>G mutation in two families and compound heterozygous c.740G>C, and c.881T>C mutations in *CHST3* gene were detected. c.776T>G mutation is most frequent mutation and have been reported predominantly in Turkish patients. It is suggested that it may be accepted as a hot point in *CHST3* gene for Turkish patients with multiple dislocations, severe short stature and vertebral changes. Other two mutations are previously unreported novel mutations. Our study provides new 6 cases with two novel mutations and prospective genotype-ethnicity correlation for *CHST3*-related skeletal dysplasias.

OP-22-016

Characterization of a novel frameshift mutation in the *TRPS1* gene as a cause of Trichorhinophalengeal syndrome type 1 in a Cypriot Heritage Family

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Trichorhinophalangeal syndrome type I (TRPSI, MIM190350) is an extremely rare autosomal dominant multisystem disorder characterized by craniofacial and skeletal abnormalities. The TRPS1 gene, localized on chromosome 8q24, which encodes a zinc finger transcriptional repressor GATA binding protein involved in hair development and chondrocyte modulation. TRPSI is presented by a distinctive facial appearance that includes sparse scalp hair, a rounded nose, a long flat area between the nose and philtrum, and a thin upper lip. Individuals with this condition also have skeletal abnormalities such as cone-shaped epiphyses in their fingers and toes and short stature. The current family-study represents affected patients from three generations who presented with short and sparse scalp hair, most pronounced in the temporal area and in a unique triangular shape in the mid occipital scalp. Additional findings included beaked nose with a long philtrum, widened proximal interphalangeal joints, short toes and onycholysis of finger- and toenails. Sequence analysis of the *TRPS1* gene revealed a novel c.2854_2858del (p.Asn952Argfs*2) frameshift mutation leading to a premature stop. Interestingly, one of the affected family member also has Turner's syndrome from a consanguineous marriage. Clearly, two rare genetic conditions in a patient are extremely rare and this combination is the first presented case so far. To the best of our knowledge, the c. 2854_2858del frameshift mutation was not previously reported. Therefore, this study contributes one more mutation to the growing list of reported mutations for this syndrome. The present results can enhance our knowledge on this complicated, rare and severe genetic disorder.

OP-22-017

Rare and extremely unusual presentation of glutaric aciduria type I in a 35-year-old woman

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Glutaric Aciduria type-I (GA-I, MIM 231670) is a treatable autosomal recessively inherited disorder that is represented by irregular excretion of glutaric acid due to a defect in amino acid or fatty acid metabolism pathways. Glutaryl-CoA dehidrogenase (GCDH) enzyme is a key enzyme in the catabolic pathways of the amino acids tryptophan, lysine and hydroxylysine and its deficiency causes GA-I. Presentation and progression of disease shows variable ranging from asymptomatic carrier state to catastrophic encephalopathy. GA-I usually presents before age 18-months with mild or severe acute encephalopathy, striatal degeneration, and movement disorder, most often acute dystonia. Here we report a case of 35-year-old female with very late-onset GA-I. The patient was admitted to neurology policlinic with the complaints of headache and forgetfulness. The neurologic examination and neurocognitive tests including trial making test and visuospatial abilities were in normal limits except accompanying anxiety and depression. The cranial MRI showed many ependymal lesions, white matter lesions, cerebellar atrophy. She is the second child of a consanguineous marriage and has a sister with congenital malformation as well as epilepsy. Sequence analysis revealed a pathogenic homozygous variant within the *GCDH* (MIM608801) gene, c.1204C>T, p.(Arg402Trp), already reported as associated with GA-I. The reported patient is the first case with a known genotype causing a different and unusual phenotypic feature for GA-I. Therefore, this study widens the phenotype-genotype spectrum of GA-I increasing our knowledge on this complicated and severe genetic disorder.

OP-22-018

Detection of Duchenne Muscular Dystrophy carriers with quantitative fluorescent polymerase chain reaction

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Duchenne and Becker muscular dystrophies (DMD/BMD) are most common X linked neuromuscular diseases. DMD is progressive, lethal, affecting 1/3300 live-born males. BMD is milder, allelic form of DMD. Both of them result from mutations in Dystrophin gene at Xp21.2. Partial gene deletions responsible for up to %60-65 DMD cases and %5-10 of cases result from gene duplications which are cluster in 2 "Hot-spot" regions. Mutations are either inherited from female carriers (2/3) or occur de novo (1/3). In affected males, deletions can be easily detected using multiplex PCR. But determining female carrier status is difficult. In this study we aimed to optimize gene dosage method based on quantitative fluorescent PCR (QF-PCR). We used fluorescently labeled primers for amplification and automated detection of amplicons. Tests designed in multiplex format and 18 exons which located at "Hot-spot" regions included. The same time, promoter region and STR markers also included the test as internal control and for linkage analysis. Followed by PCR genetic analyzer used for detection of PCR products. Twenty-four families included the study, which they had previously diagnosed member. We found the same results, which previously reported, in 20 patients, whereas 3 patients have an extra exon deletion and in 1 patient has less exon deletion than previously reported. In 19 families mothers were carrier, in 5 families mothers were not carrier. As a result, we conclude that quantitative florescent PCR is a fast, reproducible and robust for detection of deletions of DMD/BMD patients and useful method for carrier screening.

OP-22-019

Comparison of expression levels of *PER1, PER2* and *PER3* genes at insomnia diagnosed individuals and night shift working health care personnel

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Sleep is one of the most basic living conditions for all creatures, from the beginning of life till the end. All creatures possess an innate mechanism that regulates the cycle of dormant and waking states. The most fundamental mechanism for the dormancy-wakefulness cycle is the circadian rhythm. The circadian rhythm consists of *PERIOD, CRY, BMAL* and *CLOCK* genes' suppression cycle and it has been known and researched since the 18th century. The day-and-night cycle must be consistent with our biological clock. The most common cause of health problems in case of unusual working hours is that the biological clock is incompatible with the working hours. While healthy individuals' tendency to sleep increases or decreases in connection with day-night cycles, differences are observed in individuals experiencing sleep disorders. Difficulties in sleeping, ensuring sleep continuity and terminating sleep is defined as insomnia. In this study, the expression levels of *PER1, PER2* and *PER3* genes, which have an impact on metabolism and behaviour in the circadian rhythm of locomotor activity, are evaluated in individuals diagnosed with insomnia and healthcare personnel working at night shifts. RNA isolation was performed from the peripheral blood from the volunteers, followed by cDNA synthesis and the expression levels of these genes were obtained in Real-Time PCR. As a result, there was a statistically significant difference in the expression levels of the *PER1, PER2* and *PER3* genes of the individuals who were diagnosed with insomnia and the health personnel working on the night shift.

OP-22-020

The role of a rare variant in Canavan disease: An in silico follow-up

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Deficiency of the enzyme aspartoacylase (ASPA) causes progressive leukodystrophy called Canavan disease (CD), which is inherited in an autosomal-recessive pattern. The ASPA gene is located on chromosome 17 (17p13ter) and is responsible for the hydrolysis of N-acetyl-L-aspartate (NAA) into acetate and free aspartate. The most common form of the disease is infantile CD with an age of onset between 3–6 months of age. The clinical symptoms of the disease show varying severities and include symptoms like macrocephaly, hypotonia, and irritability. Over 100 mutations have been reported in the ASPA gene to date. CD could be observed more commonly in the Ashkenazi Jewish population, with some mutations being almost exclusively seen in this population. Here, we present a 6-month-old female patient with infantile CD from the Turkish Cypriot population. The patient was normocephalic with developmental delay together with delayed myelinization at the corpus callosum. A prominent NAA peak was demonstrated by magnetic resonance spectroscopy. The patient was homozygous for the c.79G>A (p.Gly27Arg) mutation that has only been reported very rarely in a few populations and once in the Turkish population. Protein–ligand interaction calculations based on the in-silico-mutagenized and energy-minimized ASPA model suggested that Arg-27 distorted the productive orientation of a stable tetrahedral intermediate analogous to the natural catalytic intermediate at the active site of the enzyme. Overall, our study provides new insights into the molecular consequences of the identified mutation and allows for the rational design of further *in vitro* or ex vivo research studies.

OP-22-021

Homozygous terminal deletion on 4q35.2 in a child with developmental disability and healthy parents with heterozygous deletion in the same region

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Terminal deletions in the long arm of chromosome 4 is an uncommon event with a worldwide incidence of approximately 0.001%. Majority of these deletions occur as de novo. Based on the deletion region in chromosome 4q, there are two types of deletion: i) interstitial, from centromere to 4q28.3 and ii) terminal, from 4q31.1 to 4qter. Interstitial and terminal deletion have a broad phenotypic manifestations. Terminal deletion cases have more commonly craniofacial and skeletal abnormalities, ulnar deficiency, cleft lip and palate, congenital heart defects, autism spectrum disorder, and intellectual disability. Herein we described a girl born in 2017 with 3,950g weight as a fourth children of consanguineous marriage. Her parents referred to the pediatric clinic of Akdeniz University Medical Faculty due to the walk and speech inability. Her parents stated that their first three children were healthy. In the detailed information taken from her parents, there were other family members having walk and speech delay. In our case, numerical and structural chromosomal abnormalities were not observed after conventional cytogenetic analysis. However, homozygous deletion was determined in the 4q35.2 region when subtelomeric fluorescent in situ hybridization (FISH) method was applied. To explain this phenomena subtelomeric FISH analysis was applied to her parents and heterozygous deletion observed in 4q35.2 region in both of them. Hereby, we report a case with homozygous deletion in the 4q terminal region as a first. Single nucleotide polymorphism (SNP) array analysis will be performed for the index case and for the other family members having walk and speech delay.

OP-22-022

Is it 21pstk? A case of a hidden trisomy 20p arisen from the balanced translocations

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Unbalanced translocations are one of the important causes of developmental delay and are responsible for 1% of cases. Usually, they arise from the balanced translocations. As with all chromosome segments, translocations can be associated with the short arms of acrocentric chromosomes and its evaluation may be complicated. We present a case of der(21) which was arisen by this way. A 4-year-old male patient, born in nonconsanguineous parents, was admitted with the indication of developmental delay. His mother had 2 miscarriages and a son with difficulty in speaking and walking, spasticity, and swallowing difficulties of solid foods by the age of 6 years and he died by the age of 16 years. The patient had developmental delay and stereotypic and autistic movements. He had no seizures. He had hyperphagia. At 9 years of age, the patient's autistic movements decreased. All measurements>97p. He had plump nasal root, marked ears, high palate arc, and retrognathia. The testes were hypoplasic. Clinical findings are partially compatible with trisomy 20p. Karyotype analysis revealed 21 pstk. Array-CGH analysis showed a 13.7 Mb duplication of 20p13-p12.1. FISH analysis with the mixture of 20p subtelomeric FISH probes + LSI21 probes revealed an additional 20p signal on the tip of the chromosome 21p. Mother of patient showed balanced t(20;21) and the karyotype of the patient was evaluated as 46,XY,der(21)t(20;21)(p12;p11.2)mat. Polymorphisms of acrocentric chromosomes are quite common and this may mask the translocations. So, pstks should be examined carefully and further evaluations should be done carefully.

OP-22-023

A case with 5q microdeletion: Features overlaps with DiGeorge syndrome

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Microdeletions of the 5q11.2 region are very rare syndrome; in the literature only six patients with a deletion in this region have been reported so far. 5q11.2 deletion syndrome shows a phenotypic spectrum that overlaps with CHARGE and 22q11.2 deletion syndrome including choanal atresia, developmental delay, heart defects, external ear abnormalities, and short stature. We report on a 13 year-old boy with facial dysmorphic features, neuromotor retardation and cardiac findings. aCGH was planned to rule out any microdeletion syndrome. As a result of arrayCGH analysis using 180K CGH + SNP oligoarray, size of 11900 kb copy number loss (68 gene) was detected in chromosome 5q11.1-q12.1 region. High resolution chromosome banding analysis of the case revealed 46, XY, del (5) (q11.1q12.1) karyotype. In order to determine if this CNV is inherited or de nova, aCGH analysis was performed to the parents and found as normal. In addition to the aCGH, to rule out any possible balanced translocation carrier involving 5q region in parents, cytogenetic analysis was performed and found as normal karyotype. Genetic counseling was given to the patient's family after evaluating the patient's physical findings with array-CGH results.

OP-22-024

Pyruvate kinase deficiency in four children with two unpublished mutations

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Pyruvate kinase is a key enzyme of anaerobic glycolysis which helps keeping the energy level of red blood cells and their viability in circulation. The genetic heterogeneity of pyruvate kinase deficiency (PKD) is high and, to this day, over 250 different mutations have been identified. We aimed to emphasize the importance of genetic testing in patients with unexplained non-immune hemolytic anemia. Four patients who had been followed because of non-spherocytic hemolytic anemia and in whom no causative enzyme deficiencies were identified were referred for targeted next-generation sequencing using the Oxford Red Cell Panel, a 50-gene panel for inherited anemias. We studied four patients (2 females, and 2 males) with evidence of chronic hemolytic anemia aged between 4 years and 24 years. Three of the four patients had jaundice, pallor and hepatosplenomegaly, while one patient had growth retardation and hypotonicity. One patient had gallstones and also undergone splenectomy at the age of two. While homozygous mutation was detected in three of four patients, only one patient had a compound heterozygous mutations (c.602G>A, c.1675C>G). The five identified mutations are single nucleotide gene changes. Two of the five mutations (c.602G>A, and c.172C>T) are previously unpublished. The clinical presentation of PKD ranges from frequent transfusion in neonates to mild jaundice in adulthood. Total pyruvate kinase in liver and red cell (*PKLR*) gene sequencing is necessary for the characterization of all patients with PKD and for genetic counselling. We also report two previously unpublished mutations in *PKLR*.

OP-22-025

A case report with 18q deletion syndrome characterized by severe skin findings

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18q deletion syndrome is a contiguous gene deletion syndrome characterized by hypotonia, mental retardation, crap-like mount, tapered digits and hearing loss. Clinical findings vary according to the size of affected region. We present a case with 18q deletion syndrome with severe skin findings. A 5-day-old male patient was admitted with the indication of dysmorphism and polydactyly. His birth weight was 4,300 g. The patient's anthropometric measurements were in normal ranges (25-75p). He had dysmorphic facial findings including hypertelorism, crap-like mouth, thin eyebrows and hair and bilateral postaxial polydactyly. Contractures of the interphalangeal joints, skin dryness and peeling was remarkable findings. He had also PDA and ASD. The karyotype analysis revealed 46,XY,der(18)t(15;18)(q24.3;q21.13)pat. Fine-mapping and breakpoint analyses were performed with Array-CGH. Our patient's clinical findings were compatible with 18q deletion syndrome. He had structural heart anomalies, renal ectasia, polydactyly and joint contractures. Dermatological findings of our patient were severe and he had recurrent skin infections and dehydration. ECTD8 and SERPINB8 genes located in the deleted region, are associated with 'ectodermal dysplasia' and 'peeling skin syndrome' respectively. The patient's severe skin and hair findings could be explained with the deletion of these two genes. Advance technologies like array-CGH are useful to determine the exact deletion size and establish true phenotype-genotype correlation.

OP-22-026

The importance of dysmorphology in genetic diagnosis-a case report with index finger anomaly

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A 22-year-old primigravida patient was referred to us at 32-week gestation for genetic counseling for fetal skeletal anomaly. There is consanguinity between parents and there is no family history of congenital anomaly. The ultrasonographic evaluation showed polyhydramnios, IUGR, bilateral pes equinovarus and bilateral

joint contractures of upper extremities. Genetic counseling was given to parents about prognosis and fibroblast culture from skin biopsy and autopsy was offered after termination. Autopsy revealed a significant index finger anomaly. This finding was helpful to make a diagnosis as Catel-manzke syndrome. Because the DNA could not be isolated from fibroblasts, we planned to perform *TGDS* sequence analysis to parents. Medical geneticists are particularly interested in rare diseases. There are more than 7000 known rare diseases and the diagnosis is often wrong when diagnose rapidly in rare diseases. Approximately, 2.5% of newborns have malformations that are responsible for 20–30% of neonatal and 30–50% of infantile deaths. Recently, the use of online databases has replaced dysmorphology textbooks.The most commonly used site Face2gene and when we use these databases we can diagnose earlier and don't have to perform more genetic tests. One of limitations of these databases is that it is very difficult to collect information on very rare diseases. Despite the developments in both databases and sequencing technologies, dysmorphological examination and clinicians' gestalt are still very important in syndromic diagnosis.

OP-22-027

CYP4F22 gene mutations in patients with autosomal recessive congenital ichthyosis: Identification of three novel mutations

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Autosomal recessive congenital ichthyosis (ARCI) is a genetically heterogenous keratinisation disorder which is clinically classified in five main forms: lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), harlequin ichthyosis (HI), self-healing collodion baby (SHCB), bathing suit ichthyosis (BSI). Mutations in *TGM1, ABCA12, ALOX12B, ALOXE3, NIPAL4, CYP4F22, PNPLA1, LIPN* and *CERS3* genes have been described in patients with ARCI. However, in 20% of the ARCI patients the genetic defect remains unknown. The aim of this study is to investigate the mutations in the *CYP4F22* gene in ARCI patients who don't have mutations in two common ARCI genes, *NIPAL4* and *TGM1*. Twenty-two patients diagnosed as ARCI and having no mutations in *TGM1* and *NIPAL4* genes were included in the study. Their *CYP4F22* genes were sequenced using Sanger sequencing method. In 5 of 22 (22,7%) ARCI patients 4 different mutations, of which one was previously reported, were found in *CYP4F22* gene. In the study three novel mutations (c.727C>T, c.976C>T, c.1189C>T) were detected. In silico prediction tools and segregation analyses supported the evidence for pathogenicity of mutations. Two of our cases were carrying c.1303C>T mutation which was reported previously. In this study the clinical and histopathologic features of the patients were discussed and evaluated for the genotype- phenotype correlation. This study expands the *CYP4F22* mutation spectrum and provides more accurate genetic counseling for patients at risk.

OP-22-028

Werner syndrome: Two siblings with a novel splicing mutation in *WRN* gene

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Werner syndrome is a rare autosomal recessive progeroid disorder. Symptoms of Werner syndrome are short stature, early cataract, scleroderma-like skin, characteristic bird-like face and premature graying of the hair. It is caused by pathogenic variants of the *WRN* gene that encodes RecQ DNA helicase. It has a 1:1,000,000–1:10,000,000 overall incidence and because of founder mutations Japan and the region of Sardinia in Italy are countries with the highest frequencies of Werner syndrome. In this study, two siblings with Werner syndrome with a novel mutation in the *WRN* gene is presented. Two male siblings at age 40 and 45 years whom parents from same village. Both have short stature, scleroderma-like skin (especially facial skin), premature cataract, beak nose, characteristic facial features and gray hair. In the third decade they followed by endocrinology department for fatty liver and diabetes mellitus. Older patient referred to our clinic for early retirement. Taking into consideration the clinical features, they were diagnosed to have Werner syndrome. Molecular analysis revealed a novel homozygous mutation in the patients: a splicing mutation c.2967+1G>C. Parents haven't been analysis yet. In conclusion, a novel mutation defined in this study may help to make phenotype genotype correlation in patients with Werner syndrome.

OP-22-029

A case with mutation in the *TNFRSF1A* gene

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Tumor necrosis factor (TNF) receptor-associated periodic syn-

drome (TRAPS) is a rare autosomal dominant hereditary disease of the group of recurrent autoinflammatory syndromes. The prognosis is generally good; the main risk is the development of amyloidosis. Corticosteroid therapy is usually administered during attacks. Severe cases require treatment with biological agents. In this study, DNA fragment analysis and next generation sequencing methods were applied to elucidate the patient with recurrent fever and joint pain. A six-year-old girl with recurrent fever and joint pain was referred to a medical genetics clinic for a etiologic study on the consideration of autoinflammatory disease. On physical examination, there was no feature except bilateral swelling in the knee. Echocardiography and knee magnetic resonance examination were unremarkable. The superficial tissue ultrasonographic examination of the bilateral knee region was observed fluid accumulation 30 mm on the left and 15mm on the right in the thickest site, at the suprapatellar level. Fluid was observed in the joint range. In the sample from the joint fluid, the white blood cell was 74000/m^3. In the analysis of the peripheral blood, white blood cell count was 17.7x10^3/µL, CRP: 31 mg/L, fibrinogen: 4.6g/L, sedimentation: 25 mm/h. The 24-hour urine protein/creatinine was 0.27 mg/mg. FMF fragment analysis revealed no mutation and the diagnosis of FMF was excluded. The next generation sequence analysis revealed a likely pathogenic, heterozygous c.362G>A(R121Q; rs4149584) alteration of the *TNFRSF1A* gene (ENST00000162749). Then the segregation analysis was planned. In this study, we pointed out the *TNFRSF1A* mutation in periodic fever syndrome cases. Early diagnosis by genetic testing can prevent amyloidosis.

OP-23-001

The clinical significance of *HOTAIR/miR-217* axis on renal cell carcinoma

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Renal cell carcinoma (RCC) originates from the accumulation of many genetic and epigenetic changes leading to the activation of proto-oncogenes and / or inactivation of tumor suppressor genes. Long non-coding RNAs (lncRNA) are associated with many pathological processes, such as proliferation, metastasis, apoptosis and drug resistance. *HOTAIR*, a lncRNA, is known to be targeted by *miR-217* in patients with RCC, and it shows competing endogenous RNA (ceRNA) activity for this miRNA. In light of this information, we aimed to investigate the relationship of *HOTAIR/miR-217* axis with clinical parameters of RCC. In this study, miR-217 and *HOTAIR* expression levels were analyzed in commercially available cDNA panel suitable for RCC patient profile. This panel contains cDNA samples of the tumor and surrounding healthy tissue of 19 RCC patients. *HOTAIR/miR-217* expression level ratio was associated with the clinical parameters of RCC. As a result of the study, increased expression level of *HOTAIR* was significantly associated with decreasing expression level of miR-217 in patients with RCC (p=0.041). *HOTAIR/miR-217* ratio was found to be higher in females than males and also in the age group of 35-44 than over 65 (p=0.027 and p=0.011, respectively). In addition, high *HOTAIR/miR-217* ratio was significantly associated with increased neutrophil / lymphocyte ratio (NLR), a worse overall survival marker in RCC patients (p=0.044). Altogether, *HOTAIR/miR-217* is a useful prognostic biomarker for RCC in terms of clinically significant parameters in RCC development.

OP-23-002

A rare *AMH* variant in a case with persistent Mullerian Duct syndrome

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Persistent Mullerian Duct Syndrome (PMDS) is a rare form of sexual development disorders in which Mullerian duct residues are observed in males with 46, XY karyotype. Cases with PMDS have normal male genitals and also have a uterus and fallopian tubes. PMDS is often caused by the mutations in the anti-Mullerian hormone (*AMH*) gene and shows an autosomal recessive inheritance. We report the clinical findings and genetic testing results of a 15-month-old child diagnosed with PMDS. The case was brought to the emergency department of our hospital by his family with the complaint of scrotal swelling and redness. The patient was phenotypically male and bilateral undescended testis and strangulated inguinal hernia was found. When the case was operated for inguinal hernia, the well-formed uterus was detected situated alongside the bladder and extending into the inguinal canal. In addition, both testes were found to be in the same inguinal canal (transverse testicular ectopia). The patient was referred to medical genetics department after surgery. The karyotype of the case was 46, XY. The next generation sequencing was performed to evaluate the *AMH* gene. A rare c.343_344delCT (p.Leu115ThrfsTer58) homozygous variant was detected in exon 1 of *AMH* gene. Inguinal hernia and undescended testes may be an isolated finding or may be a characteristic feature of a syndrome. In similar cases, getting the opinion of the geneticist is important for the confirmation of the diagnosis and for genetic counselling.

OP-23-003

Two diseases associated with chromosome 19 in an infertile male patient

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Myotonic dystrophy type 1 is caused by mutations in the *DMPK* gene. Cytogenetic location of this gene is 19q13.32. Mutations in the *NOTCH3* gene cause Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Its cytogenetic location is 19p13.12. A 40-year-old male patient was referred to our department with the diagnosis of infertility. Spermiogram analysis was reported as azoospermia and he had high levels of FSH, LH and prolactin. Chromosome and Y chromosome microdeletion analysis of the patients were normal. At the same time, there were prolonged contractions in the patient's lower and upper extremities. He had extensive muscle weakness especially in his hands and face. After the Triplet Repeat Primed PCR, fragment analysis was performed for *DMPK* gene. CTG repeats were found to be increased and we diagnosed this patient as myotonic dystrophy type 1 (DM1). Oligospermia and azoospermia were reported in approximately 73% of DM1 cases in literature. On the other hand, the patient had a history of migraine, cognitive impairment, transient ischemic attack and numbness in his arms and legs. His cranial MRI showed hyperintensities in bilateral temporal subcortical white matter. Radiological imaging was typically compatible with CADASIL syndrome. *NOTCH3* gene was analyzed by using Next-Generation Sequencing method and we detected c.5668-11C>T heterozygous mutation. It was a novel mutation. The patient suffered from both myotonic dystrophy and CADASIL syndrome due to the mutations of different genes on the same chromosome (chromosome 19).

OP-23-004

Investigation of *LC3* gene expression in patients with coronary artery disease

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Despite the advances in the treatment of cardiovascular diseases, these diseases are the leading cause of death in the world and these patients considerably had limited the quality of life. Autophagy is the decomposition of damaged or degraded organelles and long-lived proteins in the cell and it disassembles them back into the building blocks. The role of the pathways associated with autophagy in pathogenic mechanisms that leading to coronary artery disease has not been fully understood. The *LC3* gene is the main marker of autophagy. The aim of this study was to demonstrate the association of *LC3* gene expression and coronary artery disease. During the coronary bypass operation 2 myocardial tissue samples were obtained before stopping the heart and after making it work again from 20 CAD patients (15 Males, 5 Females). Total RNA was isolated from these tissues by the Trizol method. Expression of *LC3* gene was determined by Real-Time PCR. There was a statistically significant difference in the expression of *LC3* gene in the tissue samples ($p=0.0055$). *LC3* gene expression was found to be decreased in postoperative tissues. A decrease in *LC3* expression after surgery indicates a decrease in the efficacy of autophagy when stress in the coronary artery is eliminated. We believe that the repetition of this study with larger patient samples and also the expression of other genes associated with autophagy may be more useful in clarifying the relationship between autophagy and CAD.

OP-23-005

Predicting the molecular phenotype of familial amyotrophic lateral sclerosis: Computational studies of the rare SOD1 A4T mutant protein

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Copper–zinc superoxide dismutase (SOD1) is a highly conserved enzyme whose fundamental function is to scavenge superoxide anions in the cytoplasm of cells. It is a soluble dimer composed of two identical subunits, each of which folds into an eight-stranded "Greek key" β-barrel. Autosomal-dominant mutations in the gene for SOD1 are linked to familial amyotrophic lateral sclerosis (FALS), a fatal neurodegenerative disease that affects motor neurons. This study presents the clinical case of a female patient with rapidly progressive FALS in the largest kindred with FALS described to date and aims at predicting the structural consequences of the rare alanine-to-threonine substitution at position four (A4T) in the mature SOD1 protein in an in silico setting. The results of biomolecular modeling and residue–residue interaction profiling suggest that although the polar side chain of threonine-4 fails to engage in hydrophobic interactions with the neighboring non-polar residues in the final SOD1A4T model, the characteristic overall fold of the predicted mutant remains intact after in silico mutagenesis and energy minimization. Also, Gibbs free energy calculations suggest a destabilizing role for the threonine-4 allele in SOD1 folding. Accordingly, a systematic study of both the crystallographic architecture of position four mutants, including SOD1 A4T, and their dynamic behavior in solution should prove interesting and useful to any researcher who intends to translate this group of *SOD1* gene variants into (F)ALS phenotypes.

OP-23-006

Features of electroencephalography in Huntington disease: Evaluation of genotype and electrophysiology of one family

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Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder. It is caused by an abnormal expansion of a CAG repeat and it can be identified before clinical onset by predictive genetic testing. Clinical features of HD has progressive motor dysfunction, cognitive decline, and psychiatric disturbance. Abnormal electroencephalography (EEG) findings have been reported in HD patients. These are reduction of the EEG amplitude and reduction of the alpha frequency band. Also, modification in the alpha-theta border related EEG alterations in premanifest HD individuals may be related to the course of the pathological process. We present genotype and EEG findings of a family in this paper. The family consist of eight persons. The parents are healthy mother and father with HD (CAG: 50). There are six children. Three children had HD and their CAG repeat was found respectively 55, 69, 52. One person is premanifest HD (CAG: 55 and normal neurologic examination). EEG assessment of symptomatic both individuals showed suppression of alpha waves and rapid beta waves. Also, the premanifest person's EEG showed irregular basal rhythm, rare slow teta and increased prefrontal delta wave activity. These findings suggested that in HD, EEG disturbances can be seen affected patients even in premanifest.

OP-23-007

A population based study: Genetics of smoking

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The psychoactive substances are the most dangerous social problems world-wide. Studies demonstrated that using psychoactive substances affect human health both physically and mentally. One of the psychoactive substances is nicotine. It is well known environmental and genetic factors affect nicotine

dependence. The neurotransmitter serotonin has a wide range of central nervous system activities. Recent studies showed the role of the polymorphic serotonin transporter gene which effects nicotine dependence as well as associated with psychological traits. The serotonin transporter-linked polymorphic gene region has a variable number of tandem repeats. These tandem repeats are believed to alter the transcriptional efficiency of the *5-HTT* gene. Here, we aimed to investigate the association between this polymorphic sites and smoking behavior in Turkish Cypriot population. A total of 100 smokers and 100 non-smokers Turkish Cypriots were enrolled in the present study. Peripheral blood samples are collected and genomic DNA was extracted. The PCR-RFLP was used to determine the 5-HTTVNTR2 polymorphism. The allelic frequency and genotype distribution results showed a statistically strong association (P<0.0001) between smokers and non-smokers in the studied population. This study is the first association study that investigated the allelic frequencies of 5-HTTVNTR2 polymorphisms linking with smoking behavior. To conclude, immediate genome wide association strategies should be designed for preventative and precise medicine in the Turkish Cypriot population.

OP-23-008

The role of cytokines in the pathophysiology of chronic tonsillitis

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Chronic tonsillitis is characterized by recurrent and persistent infections of palatine tonsils. Tonsillar hypertrophy is a process characterized by the palatine tonsil hypertrophy, which is not always accompanied by the infective process. These two diseases are developed by different pathophysiological mechanisms at the same tissue. Many different chemokines' role was studied in the chronic tonsillitis. We aimed to show the expressions of *IL-1 α* and *β, IL-6, IL-8, IL-15* and *TNF α* in the chronic inflamed tonsil tissue. The study was conducted at Baskent University Departments of Otorhinolaryngology and Medical Genetics. Total 45 samples obtained from tonsillectomy due to chronic tonsillitis (17) or tonsillar hypertrophy (28) were participated in the study. The expression levels of cytokines were determined via Real Time Polymerase Chain Reaction (RT-PCR) technique and comparison was made between the tissue groups. We only found statistically difference in the expression of IL-8. The mean expression level of *IL-8* was higher in hypertrophy group. It may be related to increased number of germinal centers in hypertrophy group. We did not find any statistically difference in the expression levels of *IL-1 α* and *β, IL-6, IL-15* and *TNF α*. New studies searching these or other cytokines may guide us to find the difference between hypertrophy and chronic inflammation.

OP-23-009

Gene expression research in children with attention deficit hyperactivity disorder

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Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder that affects usually children and adolescents. Besides it also effects also adults. Especially, twin and adoption studies show ADHD to be highly heritable. Therefore, in this study, we aimed to explore expression analysis of particular genes and effects of different alleles of selected gene on children with ADHD which are highly suspicious genes. Besides, different children with ADHD use different drugs which are used for ADHD treatment were researched to explore of this expression and allele analysis studies. This study was comprised of three groups as control group without ADHD, children with ADHD treated with methylphenidate and atomoxetine. Samples were collected both pre-treatment and posttreatment for children with *ADHD. SLC6A3, SLC6A4, SLC1A2, VMAT2, MAOA, COMT, GLYAT, GRM5, DRD4, TPH* and *ADRA2C* genes, which are suspicious genes associated with ADHD, were selected for expression analysis. Besides *CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6* and *CYP2D6*10* alleles were analyzed and corelated with treatment of patient children. As a conclusion, expression analysis showed us there were significant differences for ADHD and treatment caused return to normal of the expression of determined genes. However, there is no any significance correlations among analysis of *CYP2D6* alleles, cause of there was not enough sample for each combination of sample groups (pre-treated/post-treated ADHD samples with *MHP/ATX* and 5 different allele combinations). As further studies, larger group which include more patient children and children have more different allele group should be organized and studied to explain correlation between alleles, ADHD and treatment.

OP-23-010

Cytokine gene polymorphism frequencies in Turkish population with comparisons to other populations: A meta-analysis

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Differences in cytokine production are related to sequence variants in cytokine genes. Allelic variants in the promoter regions in for *TNF-α, INF-γ, IL-6, IL10* and *TGF-β* cytokine genes have been identified. In the present study, we examined eight single nucleotide polymorphisms (SNPs) in five cytokine genes in the Turkish population (n=300) using PCR-SSP method. The SNP data were tested for HWE equilibrium fit by calculating expected genotype frequencies and comparing them to the observed values using Arlequin software version 3.1. *TNF-α* (-308), *IL-6* (-174) and *IL-10* (-592,-1082,-819) data of the control groups from previous studies conducted on different populations were compared with the Turkish population of the present study. The genetic distances between the study group and other populations were calculated and a neighbor-joining tree was constructed by PHYLIP. The genotype data were compared with the data of 13 other ethnic groups and one Turkish population previously published. The genotypes of *TNF-α, IFN-γ* (+874), *TGF-β* (codon 10/25) of the study investigated population were not found to be different. However, there is a significant frequency difference in *IL6, IL10* genotypes between ethnic groups. The studied population was found to be genetically much closer to European populations. Difference observed between the study group and a previously reported Turkish population indicates the heterogeneity of the population living in Turkey. This study provided more reference values for these polymorphisms and generated a control group to be used in further association studies especially in autoimmune disease, malign disease, transplantation, GVHD and other human disease.

OP-23-011

A novel mutation in *WDR62* gene in a patient with autosomal recessive primary microcephaly

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Autosomal recessive primary microcephaly (MCPH) is defined by decreased head circumference and various degrees of intellectual disability. Until now, 24 loci (MCPH1-MCPH24) were reported in the diagnosis of the MCPH. It has been reported that *WDR62* is the second causative gene of autosomal recessive microcephaly (MCPH2) playing a significant role in spindle formation and the proliferation of neuronal progenitor cells. Mutations in *WDR62* gene were associated with malformations of cortical development in and primary microcephaly. Here, we report an 8-year-old girl, born to consanguineous parents. Our patient had decreased head circumference that was recognized at 26 weeks of pregnancy and brain abnormalities (schizencephaly). Parents of our patient had a previous pregnancy that was terminated due to hydrocephalus at 28th week. The next generation sequencing was performed for the diagnosis of the MCPH. We detected a novel homozygous frameshift mutation c.384_385delAG (N131Wfs*3) in exon 4 of *WDR62*, a gene already known to be related to MCPH. Segregation analysis showed heterozygous *WDR62* mutation in both parents. This study is broaden of clinical and molecular spectrum of MCPH2 and to contributes to a better characterization of the genotype-phenotype correlation.

OP-23-012

Design and analysis of an effective antigen against tetanus by in-silico method

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Tetanus neurotoxin (TeNT) is produced by Clostridium tetanus under anaerobic conditions, this toxin affects the human nervous system and makes lethal condition with painful and uncontrollable muscle spasms. This life-threatening illness in newborn babies and injured adult humans can now be controlled by protective approaches such as vaccination. There are a lot of disadvantages in the production and use of toxoid vaccine while the recombinant vaccine has many advantages over the toxoid vaccine. Therefore, in order to design a recombinant vaccine against tetanus, the amino

acid sequence of the toxin (TeNT) (causative of tetanus disease) was extracted from the NCBI and UniProtKB databases. Then the high-level immunogenic, antigenic and conserved regions of TeNT was determined using immunoinformatics programs. By combining the epitope rich parts of the toxin, a recombinant vaccine (T1LT2LB) was designed. In-silico analyzes was performed to gain information of the structural and immunogenicity properties of the target protein which is expected to be obtained as a result of joining different peptide fragments. The entire T1LT2LB peptide was comprised of a total of 496 amino acids including the amino acids added by His-tag and the restriction enzyme cleavage sites. In bioinformatics analysis, T1LT2LB peptide shows more immunogenicity than tetanus toxin (toxoid). The codon usage CAI value and GC content of the gene encoding T1LT2LB were as 0.66, 30.79% respectively. The value obtained from the Vaxigen of this protein was 0.48 and the value obtained from Kolaskar & Tongaonkar Antigenicity was 0.21.

POSTER PRESENTATION ABSTRACTS (PP)

PP-001

Neurofibromatosis type rare form: 17q11.2 microdeletion syndrome

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17q11 microdeletion syndrome is a rare severe form of neurofibromatosis type 1 characterized by mild facial dysmorphism, developmental delay, intellectual disability, increased risk of malignancies, and a large number of neurofibromas. A case with 17q11.2 microdeletion syndrome is presented in this report. A 17-year-old male patient, who had a tertiary degree of consanguinity relationship between his mother and father, was referred to us with a pre-diagnosis of Neurofibromatosis type 1 because of widespread cafe-au-lait spots in his body. The patient had learning disabilities and poor school performance. His Cranial MRI results revealed hamartomas in the right cerebellum and 2 T2 hyperintense focuses in the right parietal lobe. On physical examination, he had normal height and weight, had microcephalia (circumference was <3p), and had hypertelorism, down-slanting palpebral fissures, large nasal tip, multiple cafe-au-lait spots and pectus excavatum. NF1 whole gene sequence analysis of the patient yielded no mutations. Array CGH analysis was performed and 1409 kbp of deletion was detected in 17q11.2 region containing the *NF1* gene and reported as compatible with 17q11.2 deletion syndrome. There were no individuals with similar findings in his family tree. Array CGH test was also offered to his parents in genetic counselling sessions. The patient was diagnosed with 17q11.2 microdeletion syndrome according to his clinical findings and genetic test results. Patients should also be closely monitored due to malignancy such as optic glioma, retroperitoneal fibrosarcoma and medulloblastoma. Affected individuals have a 50% risk of transmitting the microdeletion, and prenatal and preimplantation genetic diagnosis is possible.

PP-002

Kleefstra syndrome (9q34.3 microdeletion syndrome): A case report

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Kleefstra syndrome is a rare autosomal dominant disease characterized by mental and speech retardation, facial dysmorphisms. In 75% of the cases, de-novo heterozygous deletions in the region of 9q34.3 which contains the *EHMT1* gene, can be observed. A 7-year-old girl with unconsangineous parents, was referred to us because of autism symptoms. The patient could not speak, had epilepsy and had been receiving special education for 2 years. She also had gait disturbance, frequent falls and night blindness. The cranial MRI results revealed that she had corpus callosum and splenium hypoplasia, but generalized spike waves 1-2 seconds were also detected in her EEG for. Height, weight, head circumference percentile values were found to be on average. On physical examination, hypertelorism, antevert nostrils, prognatism, pectus excavatum and brachydactyly were detected. *UBE3A* methylation test was performed on suspicion of Angelman syndrome due to epilepsy and inability to speak, however no abnormality was observed. Array CGH test was also performed and result was normal. In the region 9q34.3, a 531 kbp of deletion, which contains the *EHMT1* gene and overlapping with the critical region of Kleefstra syndrome, was detected. There are no similar findings in the family tree. In genetic counselling sessions, the patient's parents were also offered array CGH test. In conclusion, patient was diagnosed with Kleefstra syndrome according to clinical findings and genetic test results. In the differential diagnosis of Kleefstra syndrome, Smith-Magenis, Pitt-Hopkins, Rett syndrome, 2q37 deletion syndromes and autism cases should be eliminated.

PP-003

Orofaciodigital syndrome XVII: A rare case report

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We present two siblings with a very rare disease caused by a mutation in *INTU* gene. They are from consanguineous parents without a family history, a male 18 months old and a female who died 4 months old. The male patient had global developmental delay. In the examination of him, height 92 cm (=90p) and weight 7,5kg (<3p), broad nasal bridge, epicanthal folds, multiple nodules on the tongue, high palate, ankyloglossia, polydactyly were seen. He had central polydactyly with 6 fingers on his left, preaxial polydactyly with 6 toes on the left and pre- and postaxial polydactyly with 7 toes on the right foot. Echocardiography revealed atrioventricular septal defect, bicuspid aorta, persistent left superior vena cava, and pulmonary vein stenosis. He had two heart surgery and one surgery for the nodules of the tongue. Younger sister, deceased, had atrioventricular septal defect, frontal synostosis, an operated pelvic cyst, short duodenum, hydronephrosis, vaginal agenesis, and a mass in the heart. Whole exome analysis of the male showed a homozygous deleterious mutation c.64del p. (Ser22Hisfs*49) in *INTU* gene. Later testing revealed the same homozygosity for the deceased sister and heterozygosity for the parents. As the syndromes autosomal recessive nature were shown previously, siblings were diagnosed with Orofaciodigital Syndrome XVII. There is one previously reported case with the syndrome in the literature. And another patient with renal cysts with a mutated *INTU* gene. INTU is a core subunit of the CPLANE (ciliogenesis and planar polarity effector) complex, which plays an essential role in ciliogenesis.

PP-004

A case of Rubinstein Taybi syndrome with a very rare finding; Dandy Walker malformation

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Rubinstein taybi syndrome (RSTS) is a rare genetic disorder. It occurs in an estimated 1 in 100,000 to 125,000 newborns. This syndrome is characterized by intellectual disabilities, global developmental delays, distinctive facial features (down slanting palpepral fissures, beaked nose, malpositioned ears with abnormal helices), broad thumbs and first toes, short stature and other findings. Inheritance pattern of RSTS is autosomal dominant. De novo mutations are the most reported mutations with no family history. RSTS is caused by mutations in *CREBBP* (16p13.3, approximately 40-50% of cases) and *EP300* (22q13.2,approximately 3-10% of cases). 10%of RSTS cases have a microdeletion on chromosome 16p13.3. Many of cases have no mutations in these genes and the cause of the condition is unknown. We presented a 7 months-old girl who has atypical facial appearance such as down slanting palpebral fissures, prominent beaked nose, high-arched eyebrows, malformed ears with abnormal helices, broad nasal bridge, frontal bossing, capillary hemangioma, mild micrognathia, skeletal anomalies including broad great radial angulated thumbs and great halluces. The striking features on brain diffusion MRI were dandy walker malformation, focal thinning of the corpus callosum, focal pachygyria and polymicrogyria. Here, we reported a RSTS patient with very a rare finding; dandy walker malformation and a novel pathologic variant (*CREBBP* gene: NM_004380.2 c.1953_1960delTCACTTATinsC (p.His652Term) (p.H652) Heterozygous) is detected by molecular analysis according to in silico analysis.

PP-005

A case with 15q11-13 duplication syndrome

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15q11-q13 duplication syndrome is characterized by central hypotonia, developmental delay, mental disability, seizure and autism. The 15q11-q13 chromosome region, which contains several Low Copy Repeats (LCR) is known for its instability and is prone to genomic rearrangements. The 15q11-13 chromosomal region contains essential imprinted genes necessary for neuromotor development. A 2 year and 4 month-old girl was admitted in our clinic with history of delayed developmental milestone, mental retardation, broad-based gait with dysmorphic facial features. Our patient was the only child of a unrelated Turkish couple. Her parents had a history of mild mental retardation. Father also had behavioral abnormalities. Patient was delayed in all aspects of development. She had also severe learning disability. She had dysmorphism including wide forehead, deep set eyes, broad and depressed nasal bridge, and low set enlarged ears, there was no history of any epileptic seizures. Karyotype analysis was performed from the patient and was determined as 46, XX. Then, chromosomal microarray analysis was performed to determine the copy number variations in the patient. Microarray analysis showed duplication in the 15q11.2q13.1 and 8p11.21q11.1 region. Respectively, there are 24 and 4 OMIM genes in the 15q11.2q13.1 and 8p11.21q11.1 region. Changes in this region have been referred to in the literature as chromosome "15q11-q13 duplication syndrome". The clinical effect of the 8p11.21q11.1 region duplications is unknown. It is important to perform microarray analysis in the diagnosis and genetic counseling of microdeletion and microduplication syndromes which may be missed by routine karyotype analysis.

PP-006

Joubert Syndrome: A novel mutation of *TCTN3* gene

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Joubert Syndrome (JS) is a rare genetic disease that has multiple subtypes and is associated with 34 genes. JS is characterized by oculomotor findings, hypotonia, ataxia, respiratory findings, developmental retardation and neuropathologic abnormalities of cerebellum and brainstem. The prevalence of JS is less than 1 in 100,000. We report a case of Joubert Syndrome in a 5-year-7-month-old boy presented with severe developmental delay and failure to thrive and ataxic gait. Our patient was the only child of a consanguineous couple. There was no history of any neurological problems in the family. In clinical examination he had low muscle tonus in trunk and extremities. Cardiac and respiratory physical examination was normal. In ocular examinations, it was found that he could not follow the moving object and nystagmus was present. In the neuroradiological evaluation of the patient, there were classical features of Joubert Syndrome showed hypoplastic cerebellar vermis with hypoplasia of superior cerebellar peduncle similar to molar tooth sign in the middle of the brain. Whole exome sequencing analysis was performed. A homozygous new mutation c.1004G>A (p.Gly335Glu) of the *TCTN3* gene was detected. The pathogenic variants of *TCTN3* are caused by autosomal recessive Joubert Syndrome 18. It has been determined that this mutation is pathogenic according to the in silico prediction tools. This variant has not yet been published in the scientific literature. The current study further expands the *TCTN3* mutation spectrum.

PP-007

A case of Cri du Chat syndrome

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The Cri du Chat syndrome (CdCS) is a genetic disease resulting from a deletion of the short arm of chromosome 5 (5p-). The deletions can vary in size from involving only a single band 5p15.2 to the entire short arm. Most of cases are sporadic and approximately 12% result from unbalanced segregation of translocations or recombination involving a pericentric inversion in one of the parents. CdCS occurs in an estimated 1 in 20,000 to 50,000 newborns. Infants with this syndrome often have a high-pitched cry that sounds like that of a cat. The disorder is characterized by intellectual disability and delayed development, microcephaly, low birth weight, and hypotonia in infancy. Patents have distinctive facial features; hypertelorism, low-set ears, a small jaw, and a rounded face. We report a 6-month-old patient with round face, broad nasal root, hypertelorism, epicanthal fold, preauricular skin tag, thin upper lip, high pitched cry and hypotonia. She has secundum ASD on echocardiogram. Transfontanel USG and abdominal USG are normal. She has a partial loss of eyelashes on her right eyelid. Chromosome analysis showed that 46,XX,del(5)(p15.1) karyotype. FISH analysis confirmed 5p deletion. We diagnosed the patient with Cri du Chat syndrome precisely. This syndrome should be thought that a child with high pitched cry, distinctive facial features and developmental delay.

PP-008

A case of Wolf Hirschhorn syndrome accompanied by thrombocytopenia

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Wolf Hirschhorn Syndrome (WHS) is a congenital malformation characterized by partial deletion in the short arm of the chromosome 4. This syndrome is associated with typical facial appearance, minor/major congenital abnormalities, motor-mental retardation and convulsions. We aimed to present a case with WHS who had multiple system anomalies and developed rare thrombocytopenia during follow-up. Our case was a 9-month-old boy who was referred to our department because of various dysmorphic findings and developmental retardation. Physical examination revealed flat face, hypertelorism, slanting eyes, depressed nasal bridge, micrognathia and unilateral cryptorchidism. Echocardiography findings showed asymmetric septal hypertrophy and aberrant band in the left ventricle. Moderate sensorineural hearing loss was detected in the right ear. Chromosome analysis of patient's identified as 46,XY,del(4)(p15.3) supported the diagnosis of WHS. Karyotype analysis of the parents were normal. Additionally, thrombocytopenia was detected during the follow-up period. In addition to the typical findings, many system pathologies such as ophthalmological, immunological and hematologic features may accompany the disease. Follow-up of these patients with WHS is essential, hematological findings may show-up as thrombocytopenia occurred in our patient.

PP-009

An approach to amenorrhea with three cases

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Amenorrhea is the absence of menstrual cycles. Anatomic defects, dysfunction of the ovaries, systemic and endocrine pathologies are the main causes of amenorrhea. While primary amenorrhea is to failure to reach menarche, secondary amenorrhea is absence of periods in a woman who has been having normal menstrual cycles previously. Detailed history and physical examination, serum hormone levels, radiological findings, molecular and cytogenetic tests are used for diagnosis. We reported three cases of amenorrhea with different clinical features. A 16-year-old woman referred as primary amenorrhea, who had well developed breasts and axillary/pubic hair. Hormone levels were normal. MRI was revealed only a small right ovary and coccygeal hypoplasia, but uterus was not visualized. The karyotype was 46,XX; diagnosed with Mayer-Rokitansky-Kuster-Hauser syndrome type 2.Second patient was 17 year old woman and presented with secondary amenorrhea. The physical examination revealed Tanner stage 2 breast development and female type pubic hair distribution. Elevated FSH, LH and decreased estradiol level were reported. MRI examination revealed a hypoplastic uterus but both ovaries were not visualized. Karyotyping was 46,XY and SRY was detected. Diagnosed with 46,XY disorder of sex development. 22-year-old patient with elevated FSH, LH and decreased estradiol levels was referred to our clinic due to secondary amenorrhea. Her last menstrual bleeding was 2 years ago with medication. Radiological examinations showed that underdeveloped uterus-endometrium and absent of ovaries. Karyotyping was 46,XX and her diagnosis was gonadal dysgenesis. It is very important differential diagnosis of the amenorrhea because of the treatments depend on specific diagnosis.

PP-010

Coexistance of tetrasomy X and taurodontism: A case report

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Tetrasomy X is a rare sex chromosome aneuploidy which was first described in 1961. Up to date, approximately 100 cases have been reported. The clinical features of tetrasomy X are tall stature, midfacial hypoplasia, upslanted palpebral fissures, hypertelorism, epicanthus, small mandibula, clinodactyly, radioulnar synostosis and menstrual irregularities. All patients have variable IQ values ranging from 30 to 70. Taurodontism is a rare dental anomaly characterised by pulp chamber enlargement and apical displacement of the pulpal floor. Taurodontism can be seen together with various chromosomal anomalies. We presented a 8-year-old girl with tetrasomy X and taurodontism. The patient was the eldest of the three children of non-consanguineous parents. Physical examination revealed epicanthus, upslanted palpebral fissures, mild hypertelorism, broad nasal root, mid-face hypoplasia, mild prognathism, taurodontism, dental caries, malocclusion, clinodactyly of the fifth finger, microcephaly and short stature. The height, weight and head circumference of the patient was 131cm, 18kg and 46cm, respectively. She had breast development of Tanner stage I and infantile female genitalia. She had difficulty in speech. Pediatric psychiatric evaluation revealed mild mental retardation. Her bone age was compatible with chronological age. Cytogenetic analysis revealed a 48,XXXX karyotype. The karyotypes of parents and siblings were normal. Chromosomal abnormalities should be considered in dental disorders such as taurodontism. It is important that these cases are evaluated by a clinical geneticist in terms of diagnosis and appropriate genetic counseling.

PP-011

Two siblings with a rare diagnosis, Raymond type X-linked syndromic mental retardation

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Mutations in zinc finger DHHC-type containing 9 (*ZDHHC9*) gene are very rare and among the reasons for X-linked intellectual disability. In the firstly reported cases, Marfanoid habitus was presented as a sign of syndrome along with intellectual disability/developmental delay and behavioral problems. Even the latter studies described similar neurodevelopmental clinical findings, Marfanoid features were not underlined. Two male siblings, the age of 9 and 1 were evaluated due to their intellectual and motor delay, early hypotonia, and dysmorphic features. In the physical examination, increased height and weight, prominent ears, pectoral anomalies, genu valgus and pes planus were found in both patients. Whole exome sequencing (WES) analysis was performed only to older sibling since the neurodevelopmental clinic was more severe and the clinical findings were more established. A hemizygote splice site mutation [c.777+1G>A (NM_016032)] in *ZDHHC9* gene related with Raymond type X-linked syndromic mental retardation (OMIM#300799) and a heterozygote splice site mutation [c.1469+1G>T (NM_173653)] in *SLC9A9* gene related with autism susceptibility (OMIM#613410) were found in the WES analysis. Only the first mutation was

found in the other sibling. As the number of reported patients have been limited, there is not any consensus on the clinical findings of *ZDHHC9*-associated X-linked intellectual disability. The patients presented here are regarded to contribute to the identification of the clinical picture. This study shows the efficacy of WES analysis in the diagnostic of intellectual disability patients and its importance in terms of identifying the risk factors affecting the clinic as well as the main phenotype.

PP-012

A family with Symphalangism syndrome

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Multiple synostosis syndrome/symphalangism is an extremely rare disorder with autosomal dominant inheritance, course with multiple joint fusions and hearing loss due to stapes ankylosis. The features of three cases affected in the same family are presented here. A 5 years old male patient was born to a 25 years old mother by cesarean section with a birth weight of 3600 g at 42 weeks of gestation who was referred to pediatric genetics department because of limitation of neck movements, limited flexion of interphalangeal joints, inability to flex toes and waddling gait. Similar findings were observed in the 30-year-old mother and his 45-day-old brother whose parents are non-consanguineous. Neuromuscular examination showed limited flexion, extension and lateral bending of the neck, broad thumbs, bilaterally restricted flexion at 1-2. DIP and 4-5. PIP, absent interphalangeal creases at 4-5. PIP, limited extension of knees. In addition to that similar findings, the mother had flexion limitation in the right hip and hearing loss due to stapes ankylosis. Hand X-ray showed bilaterally fusion of proximal and middle phalangeal joints at 5th finger. Based on these findings patient was diagnosed with Multiple Synostosis Syndrome and *NOG* gene analysis was scheduled for the molecular diagnosis. There is a genetic heterogeneity in Multiple Synostosis Syndrome (OMIM # 186500). It is an OD skeletal dysplasia with an unknown prevalence which generally develops secondary to a heterozygous mutation of *NOG* gene. Although it is rare, it should not be forgotten that it is easily recognized by its typical dysmorphism and radiological findings.

PP-013

Investigation of the polymorphisms of deleted in azoospermia like (*DAZL*), 5-metylentetrahydrofolate reductase (*MTHFR*) and follicle stimulating hormone receptor (*FSHR*) genes in male infertility

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Male infertility is a genetically heterogeneous health condition and is difficult to identify due to the complexity of interactions between individuals and environmental factors. Researchers have detected several single nucleotide polymorphisms (SNPs) in *MTHFR, DAZL* and *FSHR* genes in patient groups, however, very few of them were related to male infertility. In this study, we investigated the polymorphisms including 677C/T (rs1801133) and 1298A/C (rs1801131) for *MTHFR* gene, 260A/G and 386A/G (rs121918346) for *DAZL* gene, -29G/A (rs1394205), 919A/G (rs6165) and 2039A/G (rs6166) for *FSHR* gene using PCR-RFLP technique in patients diagnosed with infertility and azoospermia. We aimed to determine the relationship between spermatogenesis and allele frequencies. In this study, we selected an infertile patient population diagnosed with normal karyotype, no deletion detected as a result of Y-deletion screening and no evidence of hormonal imbalances related to infertility and who has registered in between the years 2014 and 2016. Patients were grouped as azoospermia or oligospermia according to their spermiogram results. We investigated the association of *FSHR*, *MTHFR* and *DAZL* gene polymorphisms with male infertility in 156 azoospermic and oligospermic individuals. In this study, we did not detect any polymorphism that was statistically related to male infertility. We conclude that the *FSHR, MTHFR* and *DAZL* gene polymorphisms are not among the genetic factors that may cause male infertility.

PP-014

Microfluidic sperm sorting chip usage as an alternative method in recurrent IVF failure patients

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It is known that sperm preparation techniques in IVF are intended to select the best quality sperm. The aim of this study was to compare the density gradient method and the microfluidic chip method in recurrent IVF failure patients in terms of fertilization and pregnancy rates and also to evaluate these methods according to sperm morphology and sperm DNA fragmentation index. The study included 428 patients with unexplained infertility and recurrent IVF failure patients. Fertilization and pregnancy rates were compared in the first time IVF trial patients and in the recurrent IVF failure patients according to the methods. Morphology and DNA fragmentation index comparison of sperm samples taken from 30 randomly selected men from the group were evaluated by Toluidine Blue cytochemical staining method. There was no statistically significant difference between fertilization and pregnancy rates when compared with gradient and chip methods in first time IVF trial patients. However, in recurrent IVF failure patients there was a significant difference in fertilization rates but there was no statistically significant difference in pregnancy rates. In the study performed in 30 randomly selected patients from the group, the microchip method significantly decreased sperm DNA fragmentation index according to density gradient method. Both methods significantly increased the percentage of sperm with good morphology compared to the control group. Microchip method may be recommended in patients with recurrent unsuccessful in vitro trials. The sperm DNA fragmentation test prior to the treatment will be helpful in selecting the appropriate sperm washing method.

PP-015

A case report of Mosaic Turner's syndrome with 45,X/47,XXX karyotype

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Turner's Syndrome (TS) is an important cause of short stature and primary amenorrhea in young females. Turner syndrome, defined as a loss or abnormality of the second X chromosome, occurs in approximately 1/3000 live-born females. Approximately 45% of postnatal TS patients have a pure 45,X cell line without any detectable mosaicism. Other karyotypes that may be mosaic with 45,X most commonly include: 46,X,i(Xq), 46,XX, 47,XXX, 46,X,del(Xp), or 46,XY. Typically the isochromosome of the X, consisting of two long arms of X and designated 46,X,i(Xq), is the most frequent of the mosaic cell lines. The first case with the 47,XXX karyotype was described cytogenetically by Jacobs et al. in 1959. While the phenotypic characteristics of the 45,X have been widely described, reports on the specific the mosaicism are less frequent. The natural history of a few cases of mosaic chromosomal pattern 45X/47XXX has been described and different expressions of somatic stigmata of Turner's syndrome – mostly milder than that associated with 45X karyotype – have been reported. 45,X/47,XXX mosaicism is quite rare karyotype. In our clinic, we observed case of a 13-year-old girl with growth retardation who has mosaic 45,X/47,XXX karyotype. Giemsa-tyrpsin banding and karyotyping of prepared lymphocyte cultures (in metafase) were performed according to International System for Human Cytogenomic Nomenclature (ISCN) 1995. Chromosome analysis from peripheral blood cells revealed 45,X/47,XXX (85%-15%,respectively) karyotype. Fluorescence In Situ Hybridization (FISH) revealed a similar karyotype as 45,X (75%), 46,XX(3%), 47,XXX (22%).

PP-016

Genetic factors in male infertility

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Approximately 50% of infertile cases are due to a problem of male origin. Genetic causes of infertility can be classified as Y-chromosome microdeletions, cystic fibrosis gene mutations causing congenital vas deferens agenesis, numerical and structural chromosomal abnormalities and genetic syndromes one of the symptoms is infertility. Understanding the genetic causes of male infertility is important both for treatment approaches and for informing the patients about the risks that may be caused by their babies. On the Y chromosome there are genes involved in the determination of male sex, sperm formation and development. The region of these genes is known as AZF (Azoospermia factor) region and divided into 3 main groups (AZFa, AZFb and AZFc (AZFd)). The deletions in the AZF region are the most important causes of male infertility. Chromosomal abnormalities are much higher in infertile men (5.8%) compared to the normal population (0.5%). Cystic fibrosis (*CFTR*) gene mutation was defined in 85% of patients with congenital vas deferens agenesis, accounting for 1.4% of azoospermic cases. In 2018, 5 of the 150

male patients who applied to the medical genetics department due to infertile were found to have pathogenic, likely pathogenic and unrecognized variants in the *CFTR* gene analysis, which was studied with the new generation sequence method. In 6 patients, there was a deletion in the AZF region. Chromosomal anomaly was detected in 18 patients. In male infertility, 20% of patients are genetically diagnosed and it is recommended to perform array CGH for other male infertile cases.

PP-017

A case of neurofibromatosis with a new neurofibromin mutation: c.5392C>T

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Neurofibromatosis is a genetic disorder of the nervous system, it is considered to have an autosomal dominant inheritance and characterized by multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, iris Lisch nodules, and choroidal freckling. A 21-year-old clinically diagnosed male patient has been referred to the Department of Medical Genetics in Kirikkale University Faculty of Medicine. He presented with presternal perifollicular papules of 7 days duration. On examination, multiple subcutaneous soft swellings along with multiple café-au-lait spots were seen all over his body. He also had inguinal and axillary freckling. Lisch nodules on both irides were seen in his opthalmologic examination. Family history revealed similar skin lesions in his paternal grandfather, father,uncle, aunt, brother and sister. For molecular genetic diagnosis 2 ml of peripheral venous blood was taken, after DNA isolation multistep pathogenic variant detection protocol based on cDNA sequence analysis was performed. Heterozygous "class 1" c.5392C>T, p.Gln1798Ter mutation in exon 38 of *NF1* (neurofibromin1) gene has been detected with mutation surveyor programme. To our knowledge this is the first report of *NF1* gene c.5392C>T mutation.

PP-018

Molecular analysis of *SMN1* and *SMN2* genes with the patients pre-diagnosed with spinal muscular atrophy

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Spinal muscular atrophy (SMA) is an autosomal recessive inherited neurodegenerative disease characterised by degeneration of spinal cord motor neurons and atrophy of skeletal muscles. After cystic fibrosis (CF), SMA causes the most death in childhood. There are two copies of *SMN1* gene which are located on the human chromosome 5q11.2- q13.3. The *SMN2* gene is only 5 base pairs different from the *SMN1* gene and shows 99.9% homology. RFLP (Restriction Fragment Length Polymorphism) method was used in Medical Genetics Laboratory Erciyes University's Hospital, for analysis of SMA patients. The Ministry of Health has started to give medicines for SMA patients, but also demands for copy numbers in the report. Therefore, MLPA (Multiplex Ligation-Dependent Probe Amplification) method is began to used in our laboratory to show the number of copies. Peripheral blood was obtained from the patients and genomic DNA was isolated. Afterwards fragment analysis was performed by the MLPA method. The results were evaluated in the Coffalyser program. Homozygous deletion was detected in the 7th and 8th exons of the *SMN1* gene in 39 of 390 patients who were pre-diagnosed with SMA between 2015 and 2018. This study confirms that both deletion and duplication results and copy numbers can be given to the patients simultaneously with MLPA method. In conclusion, MLPA is the most widely used method in detecting deletion / duplication in terms of its accuracy, sensitivity and detailed information and provides relevant data for genetic counseling.

PP-019

JAK2 gene V617F mutation analysis in myeloproliferative diseases

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Polycythemia rubra vera (PCRV), essential thrombostopenia (ET), and agnagenic myeloid metaplasia (AMM) are clonal myeloproliferative diseases caused by multipotent progenitor cells. V617F point mutation was detected in the 12nd exon of the *JAK2* gene in patients with PCRV, ET and AMM. JAK2 is a tyrosine kinase enzyme that acts on the molecular signaling pathway to regulate the proliferation of hematopoietic cells. V617F mutation increased the phosphorylation activity of JAK2 and induced spontaneous cell growth and erythrocytosis. Cases diagnosed as myeloproliferative disease in the Department of Internal Medicine, Department of Internal Medicine, Erciyes University Medical Faculty, were evaluated for the *JAK2* gene V617F mutation. The patient DNA was isolated from the peripheral blood samples taken from the patients with QIAmp DNA Blood Mini Kit (Qiagen) and for the qt PCR JAK2 MutaQuant kit (Qiagen) were used. 50 ng genomic DNA, Quantitect probe PCR mix, nuclease free water, PPM, 5 µl per standard) were used. The results of the analysis performed in Erciyes University Medical Genetic Molecular Genetic Laboratory in 36 (10.31%) patients with 349 PCRV, in 14 (34.14%) of 41 patients with ET and in 5 (27.77%) of 18 AMM patients In total, 55 (11.45%) of the 408 cases had V617F mutations. As a result of our study; 1. The frequency of JAK2 mutations in patients with MPD in our region is similar to the literature. 2. V617F mutation screening in the *JAK2* gene has been evaluated as a method that facilitates the diagnosis and classification of myeloproliferative diseases.

PP-020

Determination of senescence susceptibilities of adipose tissue-originated mesenchymal stem cells from obese and non-obese mouse models

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Obesity one of today's major health problems, is the pathological excess of body fat the result of a continuous positive energy balance. By increasing the number of cell divisions in cell culture, telomeric function is impaired and / or DNA damage causes cells to enter the replicative senescence process. In this thesis study, adipose tissue derives mesenchymal stem cells (ADOMSCs) were obtained from C57BL6 strain mice fed with normal diet (NF) and C57BL6 strain mice fed with high fat diet (HFD). These obtained cells were determinated as senescence at the end of 14th (early culture) and 30th (late culture) days in culture. At the end of thesis study, body weight difference of HFD/obese mice compared to NF/control increased by least 10 grams. Glucose tolerance was observed at more severe level in the HFD compared to the NF. As a result of 30 days senescence tests, the number of β-gal positive cells (NF 12.33% and HFD 35.83%) and G2/M cells (NF 43.68% and HFD 87%) in HFD were found to be higher than the NF. The cell proliferation of the HFD group relative to the NF was found to be lower than that of the proliferation test using the MTT cytochemical staining method. According to the result of apoptosis test with annexin V, it was found that the number of apoptotic cells was higher in HFD (10.16%) than in NF (7.27%). As a result, obesity it thought to increase the susceptibility to senescence in ADOMSCs.

PP-021

Investigation of hematological malignancies with cytogenetic and fluorescent in situ hybridization methods

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Blood diseases can be divided into benign and malignant diseases. Malignant diseases are defined as abnormalities of blood cells and their failure to function as a result of excessive proliferation. Leukemias are classified as acute or chronic according to the course of the disease. Acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML). Lymphoma is the type of cancer seen in blood cells called lymphocytes. Multiple myeloma (MM) is a type of bone marrow cancer that originates from plasma cells that are normally cells in the bone marrow. Myelodysplastic syndrome (MDS) is a type of malignant disease that occurs with abnormal development of blood cells in the bone marrow. Blood samples were taken from the patients with hematological malignancy by heparin injector. G-banding method for cytogenetic examination, cytocell probes for fluorescence in situ hybridization were used. In one of the 35 patients who were studied in 2018, was positive for t(14;18) and t(11,14). For MDS, 6 of 180 patients were positive for 5qdel and 3 were positive for 7qdel. For MM, three of the 66 patients were positive for 17pdel. For CLL, three of 85 patients were positive for cep12, 13qdel for positive and 17 for 17pdel. FISH analysis was obtained in all cases. Metaphase could not be obtained in 32 of 366 patients. When two methods were compared, the FISH method was found to be more sensitive.

PP-022

A case with 45,X[34]/46,X,i(X)(q10)[5] karyotype

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One of the characteristic features of the Turner syndrome is short stature. A 6-year-old patient presented with a short stature complaint. Physical and gynecological examination; height was measured as 93 cm, body weight 13 kg. Uterus was normal. The ovaries were not in the normal location. The patient's lymphocyte culture was performed, metaphase chromosomes were obtained, and G-banding was performed. In karyotype analysis, 45,X [34]/46, X, i (X) (q10) [5] mosaic turner syndrome were detected. The patient did not have a history of chronic illness or family. In Turner syndrome, since clinical features differ according to age, chronological age should be considered when evaluating. Reduced growth rate in childhood, short stature, age-based growth rate below the 10th percentile, basal FSH level significantly higher, common otitis media, hearing loss, cubitus valgus, hyperconvex hypoplastic nails, multiple pigmented nevi, 4. metacarpal shortness, high arched palate and widely spaced nipples are seen. Because the genes related to the length are mostly in the short arm of the chromosome, the length of the patients with mosaic karyotype are longer than the cases with 45,X karyotype, but they are still shorter than normal. The somatic anomalies are less likely to develop. In Turner syndrome, although many organs and systems are affected by varying degrees, hypogonadism due to short stature and gonadal dysgenesis is major components. Turner syndrome should be considered in all girls with pubertal delay, especially in girls with short stature. The case is presented to contribute to the literature because of its rarity.

PP-023

A family with rare E167D mutation from Turkey with a total of four members clinically diagnosed as FMF

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FMF (Familial Mediterranean fever) is an autosomal recessive disease that mainly affects Armenian, Jewish, Turkish and Arab populations and characterized by recurrent and self-limited fever, peritonitis, arthritis, pleuritis and skin lesions such as erysipelas. The disease occurs as a result of mutations in the *MEFV* (Mediterranean fever) gene. This gene including 10 exon and placed on chromosome 16p13.3. *MEFV* gene-related mutations in the disease is very important in the diagnosis. A 18 years old female case applied due to abdominal pain and chest pain. (Deoxyribonucleic acid) was isolated from peripheral blood sample of cases and all exon sequencing analysis of *MEFV* gene was done. According to our results, a rare heterozygous E167D mutation was detected in our proband and her father but not detected in her brother and mother. Additionally heterozygous E148Q mutation was detected from our proband and her mother. Also heterozygous R202Q mutation was detected probands'father and brother. The age of onset was 10 years and

the frequency of attacks was 1 per month. The proband has family history of FMF, abdominal pain, chest pain and arthritis but has not erythema, appendectomy, fever and amyloidosis. The clinical data of family members were given in table 1. Because of the *MEFV* heterogenity in Turkish FMF patients, larger serial analyses using different methods are necessary to detect the distribution of *MEFV* mutations and to determine genotype--phenotype associations.

PP-024

A combined oxidative phosphorylation deficiency 10 case in a non-consanguineous family

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Combined oxidative phosphorylation deficiency 10 (COXPD10, OMIM: # 614702) is an autosomal recessive disorder caused by homozygous or compound heterozygous mutation in the mitochondrial translation optimization 1 (*MTO1*) gene resulting in variable defects of mitochondrial oxidative respiration. Affected individuals present in infancy with hypertrophic cardiomyopathy and lactic acidosis (LA). mild to severe global developmental delay/intellectual disability. The severity is variable, but can be fatal in the most severe cases. Healthy parents without consanguinity, but originated from the nearby districts, applied for the investigation of the etiology of their son died at the age of 4 months. The patient whose complaints started to obvious since postnatal 3rd day died with vomiting, blurring, dyspnea, and metabolic-lactic acidosis. It is learned from medical records that the increased Krebs metabolites and tyrosine metabolites in the evaluation of urine organic acids and also the elevated alanine levels in tandem MS analysis was present. The trio-WES analysis was performed from the DNA samples of the parents and the patient whose is isolated at another center. A known pathogenic mutation [c.1390C>T (p.Arg464Cys) (NM_012123.3)] in the *MTO1* gene related with COXPD10 was found in homozygous state in the patient and heterozygous state in the parents. The features of COXPD10 are not specific which can make accurate diagnosis difficult, often requiring exome sequencing or gene panel analysis. In patients with LA, developmental/cognitive delay and other features of the mitochondrial disease, physicians should consider this disease in the differential diagnosis.

PP-025

Identification and frequency of *CFTR* gene variants

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Cystic Fibrosis (CF) is a prominent autosomal recessive disease and caused by the pathogenic variants in Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene. This gene is responsible to encode a transmembrane protein that generates a cAMP-dependent chloride channel in the membranes of epithelial cells. The disease is substantially diagnosed by abnormal sweat chloride testing. For the molecular genetic testing of the disease, genomic DNA was isolated from blood specimens considering the manufacturer's protocol. Then, Next Generation Sequencing (NGS) was performed on an Illumina MiSeq NGS Platform. The bioinformatics analysis was performed in Sophia DDM software. In this study, we aimed to evaluate the frequency of variants detected in CF patients with the assessment of pathogenicity. For the clinical evaluation of the variants, the criteria created by the American College of Medical Genetics (ACMG) Standards was considered. Among these variants, the deletion of the Phenylalanine 508 (p.Phe508del or c.1521_1523delCTT) variant was the most observed variant in patients with CF with the percentage of 14.65% (n=23). For the assessment of pathogenicity, there are 42 pathogenic variants (26.75%), 50 likely-pathogenic variants (31.85%) and 92 variants with unclear clinical significance (57.96%) were found in 157 patients with CF. While the most frequent variants are found in CF patients on the exon 11 of *CFTR* gene as a delF508, also the other variants can be detected with a high-spectrum because of improvement on NGS technology. In this context, it would be possible to combine all the variants together associated with CF in a national database.

PP-026

Effect of metformin on multipotent stromal cells

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Cellular senescence is a degenerative process that stops cell division, causes loss of function in the cell, but in this process, the cells are metabolically active. Metformin is an active agent that is frequently used in Type-2 diabetes and helps regulate blood sugar by reducing the insulin resistance of cells. Metformin is also known to be involved in the activation of AMP-activated protein kinase (AMPK). AMPK activation suppresses mTOR, which is known to be linked to aging, cellular senescence and diseases related to aging. In this study, metformin was given to cultured MSHs and biological effects such as cellular cycle, proliferation and senescence on these cells were examined. According to the obtained findings, metformin-administered MSHs has shown decreased senescence, cell cycles continued longer, and proliferation continued for a longer time. Furthermore, expression of Klf4 stemness cell shown increased expression at the metformin given cells. This suggests metformin may be used for culture for therapeutic purposes and potentially usable against aging and aging related cancer and other degenerative diseases in order to ensure the life span of the organism.

PP-027

Spectrum of *PAH* gene variants in phenylketonuria patients

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Phenylketonuria (PKU) is an autosomal recessive inherited disease, caused of the most frequent innate errors of amino acid metabolism that impairs postnatal cognitive development. It leads to the changes in the gene encoding phenylalanine hydroxylase (PAH), an enzyme that transforms phenylalanine to the other compounds, causing phenylalanine (Phe) to the accumulation of neurotoxicological effects. *PAH* gene analysis is crucial for the differential diagnosis and accurate treatment for the disease. The frequency of various *PAH* variations varies according to the ethnicity. The aim of this study was to detect the *PAH* gene variants. The study included 225 patients and their families who were diagnosed with phenylketonuria. Each proband was pre-diagnosed clinically with phenylketonuria and directed to the Department of Medical Genetics at Erciyes University. After the isolation of DNA from the blood samples taken from the subjects, variants and exon and intron deletions in the PAH gene were sequenced by DNA sequencing. A scope of 68 distinctive *PAH* variants were identified. The variants were distributed throughout the 13 exons, 12 introns, 5'UTR and 3'UTR region. Those variants are evaluated as pathogenic of clinical effects on exon 2(n=11), 5(n=12), 6(n=16), 7(n=61), 8(n=9), 10(n=2), 11(n=21), 12(n=12) and intron 2(n=1), 4(n=5), 10(n=65), 11(n=11). As a result of this study, it is seen as a necessary step for the construction of national database for *PAH* gene variant. This will be important and fundamental for the foundation on genetic-based diagnoses, prenatal diagnoses and population viewing.

PP-028

Chronic tinnitus and *BDNF/GDNF* promoter methylations

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BDNF and GDNF are neurotrophic factors that play key roles in the auditory pathway. While the relationship between serum levels and polymorphisms of *BDNF/GDNF* and chronic tinnitus (CT) is emphasized in the literature, there is no study showing the link between the promoter methylations of these genes and tinnitus. For this purpose, the relationship between CT and *BDNF/GDNF* promoter methylations was investigated to identify their role in the pathophysiology of tinnitus. In this case-control study, we examined the possible effects of *BDNF/GDNF* methylations in the blood samples of patients with tinnitus complaints for more than 3 months. Sixty tinnitus subjects between the ages of 18-55 and 50 healthy control subjects in the same age group who were free of any otorhinolaryngology and systemic disease were selected for examination. Methylation of total 11 CpG sites in *BDNF* and *GDNF* promoter were determined by the bisulfite-pyrosequencing method. No statistically significant difference was found between *BDNF/GDNF* promoter methylations in the comparison of control group and the CT ($P>0.05$).

To our knowledge, this is the first study in the literature investigating the relationship between CT and *BDNF/GDNF* promoter methylations. Since this study is limited to blood tissue only, it may be necessary to confirm the results with a larger group of patients and tissues in which BDNF/GDNF originates.

PP-029

Investigation of *CYP2D6* variants in children with attention deficit and hyperactivity disorder

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ADHD is a chronic condition that is constantly marked with inattention, hyperactivity and sometimes impulsivity. Stimulants such as methylphenidate and nonstimulants such as atomoxetine are commonly used drugs in ADHD treatment. Cytochrome P450 2D6 (CYP2D6) plays a role in the metabolism of up to 25% of clinically used drugs. Polymorphisms in this gene cause significant changes in CYP2D6 enzyme activity and serve as biomarkers that guide drug therapy. Our aim is to determine the effect of variants of *CYP2D6* gene on the metabolism of drugs used in ADHD. For this purpose, Clinical Global Impression (CGI) scales of patients were evaluated. The severity of the disease (CGI-S) or the degree of improvement (CGI-I) was graded between 0 (not ill at all) and 7 (extremely ill). Forty-three children with ADHD and thirty-eight healthy children of similar age were included in the study. The patient group was divided into two according to drug use, thirty-five methylphenidate and eight atomoxetine users. DNA was isolated from 2ml of blood, which was collected from all the children in the study. The mutation analysis was performed by pyro-sequencing method to investigate the effect of five different *CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6* and *CYP2D6*10* alleles on disease and treatment processes. In our preliminary study, Pearson correlation analysis was conducted between *CYP2D6* variants and CGI scores of the patients and no statistically significant relationship was found ($p>0.05$). In order to fully demonstrate the association of *CYP2D6* gene with methylphenidate, atomoxetine therapy, there is a need for more patients and studies with different groups.

PP-030

Screening molecular markers in various hematological malignancies

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Leukemias are divided into two groups as acute and chronic according to maturation and survival characteristics. Acute Myeloid Leukemia (AML) is the clonal malignancy of hematopoietic stem cells. Acute lymphoblastic leukemia (ALL) is a type of leukemia that is common in children and causes death if untreated due to neoplastic transformation of hematopoietic stem cells. The Philadelphia chromosome (Ph) is a marker chromosome in 90% of CML patients and 20% of patients with acute leukemia (ALL). In this study, Erciyes University Hospitals Medical Genetics Laboratory between 2014-2017 Myeloproliferative neoplasm (MPD) t(9:22), ALL t(9:22), t(4:11), t(1:19), t(12: 21) and AML t(8:21), t(15:17), inv16, NPM1 tests sent to 5566 Q-PCR. 2053 of MPD, 2137 of AML, 1376 of ALL tests was studied. Of these patients, 8% of patients with a diagnosis of Myeloproliferative disease were diagnosed with CML (9:22). 4% were positive for AML and 4% were positive for ALL. In order to know the diagnosis in hematological malignancies, molecular markers should be examined together with other determinative tests. For this reason, quantitative measurement of molecular markers in hematological malignancies is important for initial diagnosis of disease and minimal residual follow-up after routine treatment.

PP-031

45,X and SRY positive male with infertility: A case report

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45,X karyotype is usually seen in women with turner syndrome. This karyotype is a rare phenomenon in male phenptype and happens due to SRY gene translocation to another chromosome. SRY autosomal chromosome translocation is a rare condition and is mostly seen with acrocentric chromosomes. In this case, 29 year's old male patient referred to our clinic because of seconder infertility. The spermiogram analysis revealed azoospermia. The patient had no significant signs of clinical ex-

amination. 45,X karyotype and excess band on q arm of chromosome 19 was detected in GTG-banding karyotype analysis. SRY positivity and AZFa, AZFb, AZFc gene deletions was revealed in PCR-RFLP analysis. Then confirmed that absence of Y chromosome and SRY bearing a chromosome of F group in metaphases FISH analysis. We recommended that analysing karyotype from father of patient for balanced carriage of chromosome Y/19 translocation. As a result, SRY gene positivity on chromosome 19 and AZF gene deletion describes the patient's male phenotype and azoospermia. İn the light of these findings, it is not possible for the patient is his child's biological father.

PP-032

Atypical case of Angelman syndrome in infant with 45,X,der(15)t(y;15)(q12;q10) karyotype

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Angelman syndrome (AS) is a rare genetic neurodevelopmental disorder characterized by intellectual disability, recurrent seizures, movement or balance disorder, behavioral abnormalities, serious speech and language delay. Prevalence of AS is estimated to be 1/10,000 to 1/20,000 worldwide. Onset is usually between 6 and 12 months of age. In approximately 70% of patients there is a de novo maternal deletion of 15q11.2-q13 region. 2% of cases are associated with paternal uniparental disomy, about 2-3% occur due to imprinting center defects. Pathogenic variants can be detected in sequence analysis of *UBEA3A* gene in about 11% of individuals. Less than 1% of patients have cytogenetically distinguishable chromosomal aberrations, such as translocations or inversions. In this presentation, we describe an atypical case of Angelman syndrome in a 5-month-old boy with hypotonia, feeding difficulties and dysmorphic features. This rare case of AS has occurred due to de novo unbalanced translocation t(y;15) and was associated with lethal outcomes.

PP-033

Distal 10p duplication at distal 18q deletion syndrome

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Distal 18q deletion syndrome is characterized by the loss of distal to 18q21 and its incidence is 1 / 40.000. Common characteristics of individuals are short stature (usually due to GH deficits), hypotonia, foot problems and learning disability. We present a rare change in the number of copies in order to contribute to genotype-phenotype studies. A 9-month-old male patient presented with complaints of inability to sit without support. He was born at term with NSVD as weight 3050g to unrelated healthy parents. He was being followed for sekundum atrial septal defect and mild pulmonary stenosis. There was no consanguinity between parents and his mother lost 4 siblings because of abortion. The karyotype was 46, XY. He had a history of shaking of the right leg 4-5 times a day during the awake period from birth to fourth month. EEG was normal and this complaint spontaneously regressed. On physical examination, he was 7 kg(<3p), 75 cm(5p) and his head circumference was 42 cm(<3p). In addition to central hypotonia, there were down slanting palpebral fissures, open mouth, micrognathia, long filtrum, low-lying columella and 2.-3. partial syndactyly in the toes(figure1). Cranial MRI revealed focal thinning of the corpus callosum trunk. TFT,CBC and biochemistry were normal. In the array-CGH, interstitial gain of 13 MB in the region of 10p15.3p13 and interstitial loss of 16.8 MB were detected in the region of 18q21.33q23. In our patient with short stature, hypotonia, developmental delay and microcephaly findings, there was no evidence of aural stenosis/hearing loss associated with deletion of 18q22.3. The history of tremor or suspected seizures was thought to be due to dysmyelinization.

PP-034

Partial trisomy 4q, case report of a rare chromosomal disorder

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Partial trisomy 4q is a very rare chrosomal aneuploidy which present different clinical features. In this paper, we present a 17 month-old girl with growth retardation showing recurrent febrile convulsions. Although in the fetal US examination, intrauterine thickened nuchal fold was seen, prenatal screening tests were normal. Karyotype analysis was performed because of

the presence of polydactyly and dysmorphic craniofacial appearance. The karyotype analysis is 46,XX,der(2)t(2;4)(q37.3;q32.2). The cause of partial trisomy was due to maternal balanced translocation. In this presentation, the clinical features of the case with partial trisomy 4q was discussed with the literature.

PP-035

A mosaic Klinefelter syndrome patient with 45,X/46,XY/47,XXY karyotype

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Klinefelter Syndrome (KS) classified as numerical chromosomal disorder. In this syndrome there is an extra X chromosome to a normal 46,XY male karyotype. This is the most frequent sex chromosomal disorder in males with 1/500 prevalence worldwide. Approximately 80% of patients have classic Klinefelter Syndrome with 47,XXY karyotype. Other 20% of cases have another numerical chromosomal abnormalities (e.g. 48,XXXY or 48,XXYY), mosaicisms (e.g. 46,XY/47XXY) or structural X chromosome abnormalities (e.g. 47, iXq,Y). Characteristic clinical features of KS patients are tall stature, eunuchoid body shape (decreased upper to lower segment ratio) small testes, gynecomastia, infertility and azo- or oligospermia. Generally psychosocial problems are present in these patients. Also adult patients have laboratory findings like low serum testosterone levels and high serum gonadotropin levels. Patient generally diagnosed while they are evaluated for infertility. About 11% of azoospermic men and 4% of infertile men diagnosed as KS. In this case, we present a mosaic KS patient with 45,X/46,XY/47XXY karyotype. Patient and his partner referred to our clinic because of two pregnancy losses and one termination of pregnancy due to anomalies of fetus. They have one healthy child also.

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