ERCİYES MEDICAL JOURNAL

Erciyes Medical Genetics Days 2018
7 – 10 March 2018, Erciyes University, Kayseri, Turkey

ERCİYES MEDICAL JOURNAL

Best Oral Presentation

First Place

Anti-inflammatory and apoptotic effects of quercetin and curcumin on chronic myeloid leukemia cancer cells.
Ergül Mutlu Altundağ

Second Place

Uncoupling protein 2 gene (UCP2)-866G /A variantis associated with Nicotine dependence and Schizophrenia
Ayşe Feyda Nursal

Genetic counselling challanges in panel testing of hereditary breast ovarian cancer susceptibility
Kanay Yararbas

Third Place

Diagnostic competence of let-7c-5p and mir-223-3p serum levels in differential diagnosis of prostate diseases and prostate cancer
Onur Eroğlu

Lysinuric protein intolerance and HOIP deficiency in a boy with homozygous missense mutation in the RNF31 gene and homozygous deletion of SLC7A7 gene
Lamia Aliyeva

Best Poster Presentation

First Place

A patient with two syndromes due to paternal uniparental disomy of chromosome 2 (pUPD2) related with homozygous novel mutations of the RAB3GAP1 and UNC80 genes
Ferda Perçin

Second Place

A rare 22q13.3 deletion (Phelan-McDermid) syndrome
Halil Özbaş

Third Place

10q26 deletion syndrome and 22q13 duplication syndrome, in two cases
Zeynep Esenler

CONTRIBUTION OF THE CLINICAL AND LABORATORY FINDINGS FOR CORRECT DIAGNOSIS

E. Ferda Perçin

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

It is important to repeat the clinical evaluation after both initial and laboratory results in order to be able to accurately diagnose the disease. Because of the diagnostic methods known as gold standard, there is an error in varying proportions. Undoubtedly, there is also the possibility of making mistakes in clinical diagnosis, and for this reason it needs to be supported / verified by laboratory analyzes. Clinical preliminary diagnosis / diagnosis should be based, even to decide which laboratory analysis should be selected to get to the diagnosis of the disease. Each method has its advantages and disadvantages due to its diagnostic competence and sensitivity differences. In other words, it is possible to select the appropriate method according to the type of change in genome by clinical diagnosis. In some very rare genetic diseases, the laboratory can achieve clinical diagnosis. Even in this case, however, it may be possible to recognize false positive and false negative in the laboratory results by evaluating the clinical findings and laboratory results of the patient again. New technologies in genetics are developing very rapidly and their use can shorten the diagnosis time of the disease. Nevertheless, it should not be forgotten that these methods do not have the potential to diagnose every disease.

MOLECULAR ASPECTS OF CONGENITAL HAND AND UPPER EXTREMITY ABNORMALITIES

C. Nur Semerci Gündüz

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

Congenital upper limb abnormalities cause functional deficit and psychological problem. The incidence of limb malformation is various in different population studies. While some of them 6/10.000 live birth and the incidence of upper limb abnormalities to be 3.4 per 10.000 live birth. Phenotypic manifestation show extremly heterogenity. These abnormalities occur isolated or as part of a syndrome. The study of animal model and elucidation of the molecular mechanisms of embryonic development have effected the classification of limb abnormalities. The limb buds formed by lateral plate mesoderm at 4th weeks after fertilisation. Formation of limd buds are regulated by three signal center which are AER (Apical Ectodermal Ridge) for proximodistal axis, ZPA (Zone of Polarizing Activity) for anterioposterior axis and, ectoderm for dorsoventral axis. Fgfs, Shh and Wnt are secreted molecules in this signal centers respectively. Many genes mediate and control this morphogenetic properties and later development: *FGFs, WNT7a, LMX1, GLI3, HOX* genes group, *LIMBR1* etc. In this presentation the congenital abnormalities of the hand and upper extremity, and the related genes are mentioned based on embryonic development.

ENVIRONMENTAL POLLUTION AND GENETICS

Özgür Çoğulu

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For millions of years, the relationship between living things and the environment has continued smoothly particularly due to the adaptive mechanisms. Up to the last century, the environment has played a very important role in the adaptation of living things. However, since the beginning of the last century, environmental conditions have begun to change rapidly due to the destruction caused by human beings.

This change unfortunately brings negative conditions for the vast majority of living things including human. This change, also referred to as environmental pollution, is not only limited to living things, but also affects the conditions of the world and the future. The greatest effects on living things are through genetic and epigenetic mechanisms. Agents that cause environmental pollution cause genetic mutations directly, but also lead to mutations and changes in gene functions through epigenetic mechanisms namely methylation, histone and chromatin modifications and microRNAs indirectly. On the other hand, these changes also lead to climate change, and they also have an evolutionary effect on living things indirectly as well.

Here, changes on the basis of living and non-living relationships on earth will be explained with examples of the most often used chemicals that cause environmental pollution and how they threaten our health by affecting genetic and epigenetic mechanisms.

PRENATAL DIAGNOSIS vs PREIMPLANTATION GENETIC DIAGNOSIS

Volkan Baltacı

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Genetic disorders are generally incurable diseases. Preimplantation diagnosis techniques have been one of the most effective tools we have that prevent the occurance of genetic diseases. Prenatal applications have provided us with several advantages especially within the last few years. However, the biggest disadvantage of prenatal genetic diagnosis applications is that when a disease is detected, the risks of medical termination of the pregnancy will have effect on the mother. Yet, PGD has a great advantage which is that it protects the mother from medical abortion as well as decreasing time necessary for having a healthy baby. It provides diagnosis of single gene disorders and controls the qualitative and quantitative features of chromosomes. One of the limitations of PGD is that since the DNA is obtained from one or a few cells, so, there aren't enough DNA samples to work with, which causes problems during diagnosis and increases the possibility the test neglecting certain aspects that may cause it to give inaccurate results. One of these aspects is called ADO, 'Allel Drop Out'. This basically means that either the maternal or the paternal allel is excluded from the test. If we were to consider the same aspect in prenatal diagnosis, the most significant problem is maternal contamination and placental mosaicism. 0.23% of the mosaicism occurring in the placenta (after CVS procedure) was detected in the fetus as well. Mosaicity in embryonic level changes between 15-80%.

NEW GENETIC MARKERS IN INFERTILITY

Zerrin Yılmaz Çelik

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Infertility is a highly complex disorder. Genetic status of couples might have an important determinative role in having children. The genetic causes of infertility are also complex and which are including chromosomal abnormalities, DNA copy number variations, single gene mutations, multifactorial conditions and epigenetic disorders. Genetic abnormality can exist in female or male. Male infertility factor is almost always identified by the finding of an abnormal semen analysis. Findings for female infertility include irregular or absent menstrual periods and primary ovarian insufficiency. Unknown genetic causes and genetic risk factors in couples have been identified current genetic analyzing technologies. Some of these genetic tests are using for research purposes and can be introduced in clinical practice in future. This presentation includes current data coming from research on the genetic basis of infertility dealing with disorders of gender-specific or both sexes.

PRENATAL DIAGNOSIS AND SCREENING OF 22q11.2 MICRODELETION

Seher Başaran

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22q11.2 microdeletion is characterized by congenital heart defects, hypocalcemic hypoparathyroidism, T-cell mediated immune deficiency, palate abnormalities, and intellectual disability. This microdeletion is the most common microdeletion in live born in human (1:4000-1:6000). The frequency of the deletion is higher in spontaneous miscarriages (1:1500). Although *de novo* mutations occur mostly on maternal chromosome, no significant relationship between maternal age and presence of a fetal 22q11.2 deletion has been observed.

About 90% of the deletions are 2-3 Mb in size, 7% of the deletions are smaller than 2 Mb but covered the critical region of the deletion and 3% are outside this region. Classical cytogenetic investigations can be uninformative depending on the size of deletion and the resolution of the karyotyping. Therefore, in the presence of the typical clinical findings, fluorescence in situ hybridization (FISH) technique should always be applied for the diagnosis. If the results are found normal, microarray study is indicated.

Except the known cases of deletion carrier parents, prenatal diagnosis of the 22q11.2 microdeletion is possible only in the presence of typical ultrasound findings, such as conotruncal heart defects, ventricular septal defect, cleft lip-palate, thymus hypo/aplasia. The demographic, ultrasound, cytogenetic and molecular cytogenetic results of the cases with 22q11.2 microdeletion will be presented at the session.

Today, cell free DNA testing is offered for the screening of some microdeletions including 22q11.2. The presentation will cover also the prenatal diagnostic outcomes in cases of screen positive test results.

CONSTITUTIONAL MISMATCH REPAIR DEFECT SYNDROME

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The DNA mismatch repair (MMR) system, which corrects single base-base mismatches and small insertion/deletion loops that emerge during DNA replication, plays an essential role in maintaining genome integrity. The MMR proteins are also involved in a number of other cellular functions including G1 and G2 checkpoint regulation, apoptosis, and immunoglobulin recombination.

Heterozygous germline mutations in one of the mismatch repair (MMR) genes including *MLH1*, *MSH2*, *MSH3*, *MSH6* or *PMS2* cause the dominant inherited adult cancer syndrome termed Lynch syndrome characterized by early onset of colorectal cancer and endometrial cancer in women as well as predisposition to urinary tract, stomach, small bowel and brain tumours.

However, homozygous germline loss of function mutations in any of these MMR genes result in the rare "Constitutional Mismatch Repair Deficiency Syndrome (CMMRDS)" which is characterized by the development hematologic, central nervous system, colorectal, and/or other malignancies early in childhood.

Apart from the lack of awareness for this rare cancer predisposition syndrome among physicians, other factors that may play a role in delayed diagnosis include the lack of clearly disease-specific clinical features and the overlap with neurofibromatosis type 1 (NF1). The majority of these patients also possess clinical findings reminiscent of neurofibromatosis type 1, mainly the presence of café-au-lait spots, but no germline *NF1* mutations.

Determination of the causative mutation in patients with CMMRDS has significant clinical significance as it would facilitate timely identification and surveillance of heterozygous and homozygous individuals who are at risk for developing malignancies.

EPIGENETIC MEMORY

Sacide Pehlivan

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The mechanism that determines when, where, and how long genes will work, in other words, the changes that occur in the emergence of genetic information encoded in DNA without any change in the structure or sequence of DNA is defined as "epigenetic", which means "genetic over genetics". The work of the genes is similar to an orchestra, put it differently, this mechanism constitutes the language of conversation between the cells. The first article about epigenetics came out in 1970, the second article in 2002 (X inactivation, total of 6). Seventy articles were published in 2003 and 4237 in 2016. Between January 1, 2018 and February 12, 2018, 1298 articles appeared in Pubmed.

Epigenetics is one of the fastest growing areas in biological research. The developments in technology have provided genome-wide epigenetic research, such as mapping DNA methylation in the human genome. It has shown that a number of functional but non-protein-coding RNA (npcRNA) and even RNA groups are present thanks to high-yielding, high-resolution technologies related to DNA, RNA and protein analysis. It is suggested that these RNAs which do not code protein but has a functional role are important in epigenetics and that even the most commonly studied miRNAs can act as a communication language (ceRNAs hypothesis).

In summary, this speech wil include the examples of studies showing that various epigenetic markers can not only participate in the regulation of cellular processes, but also act as intracellular "communication language" and exchange extensive information within the cell.

AUTOINFLAMMATORY DISEASES AND GENETICS

Ahmet Dursun

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The term "auto-inflammatory" appeared on 1999 to describe an emerging family of clinical disorder. Diseases apparently different from auto-immune syndromes were characterised by unprovoked inflammation, due to dysregulation of the innate immune system without auto reactive T lymphocytes and auto antibodies. Although initially autoinflammatory diseases did not have a deserved clinical interest, curiosity of the immunopathogenesis have been investigated by many researchers in the last decade. This interest has been mainly related to diseases' metabolic, chronic degenerative, neoplastic and inflammatory nature. Atherosclerosis, diabetes, neurodegenerative syndromes and osteoporosis are significant examples of common diseases in which the well known inflammatory substrate shares many similarities with the typical autoinflammatory state. In addition, aging, characterised by chronic inflammatory status as well as the onset of age-related diseases have been under investigation. The terms "immunosenescence" and "inflammaging" has been used as a result of these researches.

Autoinflammatory diseases are a group genetically diverse but clinically similar disease characterised by recurrent fever associated with rash, serositis, lymphadenopathy and musculoskeletal involvement. One of the main mechanism of this clinical status is the unprovoked inflammation triggered by the molecule called "inflammasome" which is a stoplasmic protein complex containing sensor molecule, adaptor protein (ASC) and caspace 1. Inflammasome is formed after the recognition of intracellular danger-associated molecular patterns (DAMPS) by NOD-like receptor (NLR) especially the NLRP3 and it plays a crucial role in production and secretion of pro-inflammatory cytokines such as interleukin-1 (IL-1).

A NEW METHOD FOR ANALYSIS OF EXOME SEQUENCING DATA DEPENDING ON VARIANT PRIORITIZATION

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After the first genome had been sequenced in 2003 with an international project, Human Genome Project, the 1000 Genomes Project also revealed the analysis of 1092 and 2504 genomes respectively. By the initiation of 1.000.000 genome project, powerful databases are needed. Whole exome sequencing of human samples was reported to detect approximately 20,000–30,000 SNV and indel calls on average. So, it is very important to choose the best tool that suits the related study. With the help of this new in-house method for variant prioritization of exome data without using in-silico methods, the annotated data have been decreased by 7.4–13.8 times (mean=10.9). As a result, this in-house workflow can easily be used for simplifying the annotated data without using any in-silico methods.

RARE DISEASES IN TURKEY

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Rare diseases are life-threatening and chronically debilitating diseases. A rare disease is defined by the European Union and many other countries as one that affects less than 5 in 10,000 of the general population. There are between 6,000 and 8,000 known rare diseases and around five new rare diseases are described in medical literature each week. These groups of diseases are very heterogeneous and able to affect multiple systems usually. Eighty percent of rare diseases have a genetic component and the remaining 20% are due to environmental factors or idiopathic.Often rare diseases are chronic and life-threatening. Rare diseases can be single gene, multifactorial, chromosomal or non-genetic. Although rare diseases show different epidemiological characteristics between the countries, they constitute an important public health issue and cause multiple problems to diagnosis with special characteristics, treatment and follow-up. Especially in countries like Turkey where consanguineous marriages are common, risk of higher incidence in autosomal recessive diseases are increased. There have been difficulties in diagnosis, starting to treatment and prevention because of low incidence, delayed departure of patients to right research center/hospital busy with the disease and limited number of the available hospital.

We have established Acibadem University (ACU) Rare Disease and Orphan Drug Research and Application Center (ACURARE) by corporate support of ACU Center for Health Policies, School of Medicine and Faculty of Pharmacy in 2016. The Center's mission is to integrate academic knowledge and practice in the field of RD and OD for research and policy development in Turkey. The Center has existing national and International relationships with experts and institutions to achieve this mission. First of its kind in Turkey, as a multi-departmental center, ACU-RARE gathers researchers, academics, patient organizations and policy makers under its umbrella. The hub like structure of ACU-RARE gives capacity to facilitate networking, training, demonstration and dissemination activities and services.

GENETICS OF VALVULAR HEART DISEASES

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Altough many Valvular Heart Diseases (VHD) are acquired during adult life time, familial clustering and heritability have been noted for common heart valve defects, such as bicuspid aortic valve and myxomateus mitral valve prolapse, denoting an underlying genetic basis. Over the past decade, advances have been made understanding in gene network and molecular mechanisms regulating normal valve development. Linkage analyses of large families, transgenic animal models, *In vitro* studies, micro RNA, transkriptomic assesment of tissues gave important progress which lead the improvement of current therapeutic strategies as well as guiding the management of family members at risk. Because of complex genetic and phenotypic heterogeneity, incomplete penetrance and contribution of genetic modifier loci, it is always not clear to identify causal genes. It is also difficult to translate the findings of *in vitro* studies and transgenic animal models to humans.

Improved understanding of the genetic basis, in the pathogenesis of valvular heart diseases(VHD) as other developmental issues in human will create great opportunities for the development of pharmacological treatment and prevention. The increasing availability of next generation sequencing (NGS)will help to determine key genes and elusive pathways in VHD. These pathways will be keys for tissue engineering.

In this presentation; formation of the embriyonic heart tube, endocardial cushion morphogenesis, genes affecting early and late developmental stages, signaling pathways and spesifically, genes which affect the commonly seen bicuspid aortic valve development and genetical approach to clinical folow-up will be discussed.

GENETICS OF MOVEMENT DISORDERS

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So many articles about the genetics of movement disorders has been published every year. Moreover, the contribution of genes to etiology is very variable for different movement disorders. In this case sometimesit can be caused difficulties for clinicians to recognize.

Because the genetics of movement disorders are very complex, genetic testing results determining the clinical diagnosis can only be suggested for genes that are unequivocally disease causing. It is presented a reviwev of genetics of movement disorders such as dystonia, atypical parkinsonism, chorea, myoclonus and tremor with brief case videos in this presentation.

THE CLINICAL UTILITY OF LIQUID BIOPSY AND THE VALIDATION OF NEXT-GENERATION-SEQUENCING

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The genomic based precision medicine has led to many advances in the molecular characterization of many tumor types. Since the next-generation-sequencing (NGS) developments in the most recent years make it applicable in cancer diagnostics through mutational assessment, multi-gene panels have been designed by many genetic diseases diagnosis laboratory to select patients for different and novel treatment modalities. However, in patients without tissue availability or as in many cases have been diagnosed on small tissue samples that may be not always sufficient. Thus, the analysis of cell free DNA (cfDNA) derived from liquid biopsy samples, in particular from plasma, represent an established alternative to provide mutational testing for treatment decision making. More than that the performance of liquid biopsy analyses may be further improved by next-generation-sequencing.

While most tissue based NGS genotyping is well established in routine laboratory practice, the NGS application of liquid biopsy is still challenging, requiring an experienced laboratory management including an experienced medical geneticist for the clinical reporting and also a careful validation of the whole process, from blood collection to variant calling and reporting.

Within this presentation, this evolving field have been reviewed through our laboratory experience on large scale of liquid biopsy NGS studies of cancer patients. The methodological points that are crucial also have been highlighted via the multi-gene panels targeting lung cancer, colorectal cancer, hepatocellular carcinoma, neuroendocrine tumors and prostate cancer to accurately select patients for treatment administration by NGS on cfDNA.

PHARMACOGENETICS

Ayşe Gül Zamani

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Pharmacogenetics examines the differences in drug response resulting from genetic variations as a common area of two disciplines. Genetic variations that exist in human can change activation of prodrugs, interaction with receptors, rate of drug metabolism, excretion of metabolites and drug drug interactions

The goal of pharmacogenetics is to reduce the side effects(ADR), to improve the effectiveness of the treatment, to reduce the money spent on drugs and to prevent drug-related deaths by organizing the drug dose according to the individual. Genetic variations are single nucleotide differences, microsatellite repeats, deletion-insertions, and copy number changes. In the end, only a small proportion of patients(20-50%) benefit from treatment. Studies have shown that 70% of side effects are preventable. 50% of drug side effects are due to genetic reasons. 59% of the genetic causes are variations of the phase I metabolism enzymes.Drug metabolism is carried out by the phase I and II enzymes. These enzymes have a large number of alleles that vary according to the person and ethnic groups. The combination of these alleles leads to the monitoring of different metabolic phenotypes in drug pharmacokinetics. In this case, treatment failure is observed in patients due to drug toxicity or insufficient dose. Next generation sequencing and other developing genetic methods have increased the accuracy and applicability of pharmacogenetic studies. Future studies will further enhance the effectiveness of pharmacogenetic applications. This will lead to major improvements in patient care and overall health.

FROM DOWN SYNDROME TO ALZHEIMER'S DISEASE: NEW TARGETS FOR TREATMENT

Hatice Ilgın Ruhi

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Down syndrome (DS) is the most common complex chromosomal disorder associated with intellectual disability and characteristic physical anomalies including facial dysmorphism, congenital heart defects, problems in gastrointestinal, immune and endocrine systems, growth retardation and, susceptibility to leukemia. DS occurs 1 in 700-800 newborns globally. Down syndrome is also a neurodegenerative disease. The majority of individuals with Down syndrome develop early onset Alzheimer's like disease. However, the phenotype in DS vary widely from one individual to another, and variable penetrance is observed.

The human chromosome 21 contains 300-400 genes. The overexpression of the genes on chr 21 plays an important role in determining the DS phenotype. Besides, dosage imbalance between trisomic and disomic genes, mitochondrial dysfunction and enviromental factors have effects on variable penetrance. All of these constitute research topics as potential pharmacological targets for the treatment of Down syndrome.

Nowadays, with the advanced medical care, the life expectancy of DS individuals has greatly increased, reach to sixties and seventies years. Therefore, pathological conditions that arise with aging are also being observed more frequently in the DS population. Hence, new therapeutic approaches to Down syndrome should also include pharmacological targets for neurodegenerative problems.

X CHROMOSOME INACTIVATION

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In 1961, Mary Lyon discovered that one of two X chromosomes (paternal X in some cells, maternal X chromosome in some cells) was randomly and irreversibly inactivated in the 12-16 days of the female embryo. However, there are some exceptions to this hypothesis; inactivation in X chromosomal anomalies is not random, preferential inactivation of abnormal X is mentioned, and X inactivation is reversible in the development of germ cells. Furthermore, not all X chromosome genes are inactive, but the *PAR1* (25 gene) and *PAR2* (4 gene) genes located at the ends of Xp and Xq, which show sequence identity in the pseudootosomal region between X and Y, escape from X inactivation. Besides these, the clinical significance of X inactivation is known as dosage compensation, variable expression and mosaicism in heterozygous females.

Inactivation of the X chromosome begins with the encoding of the XIST RNA molecule in an 8-cell embryo. The *XIST*, which is proximal to Xq13 and mapped in Xq13, has 8 exons, is exclusively expressed on inactive X and occupies over the encoded large RNA molecule inactive X. Inactivation continues with DNA methylation and histone acetylation and is transferred to new cells On the contrary, Tsix RNA (XIST antisense RNA) on active X also suppresses XIST-RNA and thus prevents the accumulation of *XIST* transcripts.

Mutation of the *XIST* gene or X chromosome anomalies may result in skewed (non-random) X inactivation. The silencing of the same X chromosome in a significant part of the cells is called skewed X inactivation. Many scientists have investigated the relationship of this imbalance to diseases. Many studies in recent years have found that the rate of skewed X chromosome inactivation is high in autoimmune diseases, recurrent spontaneous abortion, muscle diseases, neurodegenerative diseases.

GENETIC DELINEATION OF CONGENITAL HYPOTHYROIDISM

Hakan Cangül

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Thyroid hormone biosynthesis requires uptake of iodide into thyroid follicular cells mediated by the sodium-iodide symporter (NIS). Following its efflux across the apical membrane, facilitated at least in part by the *SLC26A4* gene product- Pendrin, iodide is oxidized and incorporated into tyrosyl residues of TG. Such organification of iodide is catalysed by thyroid peroxidase (TPO) and requires H2O2 generated by dual oxidase type 2 (DUOX2) and its accessory protein DUOXA2. Unused iodotyrosines are subsequently deiodinated by iodotyrosine dehalogenase (IYD) enabling recycling of intrathyroidal iodide. Dyshormonogenetic congenital hypothyroidism (CH) with diminished thyroid hormone biosynthesis, is known to be associated with defects in genes encoding all these proteins, but a proportion of cases remain unexplained. In this work we described the first human cases with goitrous, dyshormonogenetic CH due to homozygous mutations in the *SLC26A7* gene, and delineated a homologous, goitrous hypothyroid, phenotype in *Slc26a7* null mice. Defects in genes mediating thyroid hormone biosynthesis result in dyshormonogenetic congenital hypothyroidism (CH). We described a new type of human dyshormonogenesis associated with truncating mutations in *SLC26A7*, and showed that goitrous hypothyroidism occurs in *Slc26a7* null mice. In both species, the gene is expressed predominantly in the thyroid gland, with defective hormone biosynthesis being associated with partially impaired iodide organification in humans and reduced thyroidal iodothyronines in mice. Although SLC26A7 is a member of the same transporter family as Pendrin, it does not mediate cellular iodide transport. We have delineated a hitherto unrecognized role for SLC26A7 in thyroid hormonogenesis.

HEMOPHILIA GENETICS

Tahir Atik

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Hemophilia A (HA) is characterized by deficiency in factor VIII clotting activity that results in prolonged bleeding after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing. The beginning of the symptom and frequency of bleeding episodes are related to factor VIII clotting activity level. Classification of HA is done based on *in vitro* clotting activity:

- Severe HA <1% factor VIII
- Moderate HA 1-5% factor VIII
- Mild HA 6-40% factor VIII

HA is the most severe inherited bleeding disorder that affects humans and its prevalance is 1 in 5000 males worldwide.

Genomic organization of *F8* gene: The gene of *F8* is mapped to the most distal band of the X chromosome (Xq28). It is a large gene which spans 186 kb and codes an mRNA of approximately 9 kb. The largest, intron 22 is of special interest as it contains a CpG island acting as a bidirectional promoter for two additional genes nested within the *F8* gene—*F8a* and *F8b*, transcribing in the opposite and in the same direction to *F8*, respectively. These homolog regions are prone to intrachromosomal recombination resulting in inversion of the intervening sequences, which interrupts *F8* at intron 22.

Another interesting large intron is the intron 1, comprising a region of approximately 1 kb, 15.26 kb downstreamof exon 1 (annotated as int1h-1) and its homolog repeat approximately 125 kb upstream of exon 1 (annotated as int1h-2).

CURRENT DEVELOPMENTS IN HEMOPHILIA

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Mutations in the *F8* gene: In addition to the intron 22/1 inversions, point mutations, small and large deletions, insertions, and duplications have been reported. The most common gene defect in severe HA is an intron 22 inversion, which is responsible for 40–50% of cases. However, point mutations are found in around 47% of all HA cases. The other *F8* gene variants such as Intron 1 inversion and large deletions are less frequent.

Molecular Analysis of Hemophilia A: Genetic investigations in HA should start with testing the index patient. Depending on the degree of severity the diagnostic algorithm may start with inversion 22/1 screening (severe HA) or with direct sequencing (non-severe HA). Direct sequencing of the exons and exon/intron boundaries is performed following standard protocols. In case of negative results, the analysis is extended to MLPA for the detection of large duplications. With this approach, the causative genetic defect could be identified in 97% patients.

However, in 2 to 5% of cases with hemophilia A, a disease causing mutation is not identified in the *F8* gene. In mild FVIII deficiency where no causative mutation in the *F8* is identified, a reason for incorrect assignment of the phenotype could be related to defects in interacting partners of FVIII protein.

GENETICS OF HEREDITARY ARRHYTMIAS

Sehime Gülsün Temel

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Sudden cardiac death (SCD) is responsible for a large proportion of sudden deaths in young individuals. Inherited heart diseases can cause sudden cardiac death. Two groups of familial diseases are responsible for SCD: cardiomyopathies mainly hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic cardiomyopathy and channelopathies mainly Long QT (LQT), Short QT (SQT), Brugada syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). This review focuse on cardiac channelopathies, which are characterized by lethal arrhythmias in the structurally normal heart, incomplete penetrance, and variable expressivity. Arrhythmias in these disease group result from pathogenic variants in genes encoding cardiac ion channels or their regulators. The current knowledge concerning the molecular basis of cardiac arrhythmias will be summarized. Then, I will discuss the most recent evidence showing the picture of molecular bases of cardiac arrhythmia complexity and heterogeneity. Thus, this genetic complexity of this disease group, currently makes it necessary to screen the other cardiac genes beside known ones. And finally, the current updated knowledge is reviewed, focusing on the evidence that a single clinical phenotype may be caused by different genes, conversely a single gene may cause very different phenotypes of cardiac channelopathies. The asymptomatic nature of channelopathies is cause for concern in family members who may be carrier, making the identification of these genetic factors of significant clinical importance.

APPLICATIONS OF NEW GENERATION TECHNOLOGIES IN CLINICAL ONCOLOGY - LUNG CANCER

Ajlan Tükün

Division of Medical Genetics, Duzen Laboratories, Ankara, Turkey

Approximately 75% of lung cancer patients are diagnosed at advanced stage. The emerging treatment standard for advanced stage non-small cell lung cancer (NSCLC) treatment, the most common type of lung cancer, is testing for biomarkers and using specific targeted drugs. About 50% of lung adenocarcinoma cases have a somatic mutation in *EGFR*, *ALK*, *ROS1* or *BRAF*. For optimal outcomes, treatment should be patient specific. The earlier the targeted treatment starts, the better the chances of survival. However, delays in targeted treatment continue to be a problem. Due to the long waiting times of the biopsy results, it is reported that 80% of the patients do not have the specific gene-specific data required to plan treatment within the first 2 weeks after diagnosis. It seems necessary for physicians to coordinate their treatment decisions and to rapidly recover such test results in order to significantly improve patient care. Liquid biopsy, which is promising in this sense, is unlikely to replace tissue biopsy, the gold standard for cancer diagnosis. Because histological examination results, which are a very important part of the diagnosis and subtypes of cancers, are not accessible with liquid biopsy. However, liquid biopsy can be powerful and complementary when used in conjunction with tissue biopsy. Liquid biopsy adds rapid genotyping to the histological data to provide comprehensive information on the cancer at the beginning of the treatment. When compared to the abundant amount of DNA from non-tumor sources, the ratio of circulating tumor DNA (ctDNA) is usually very small. With so little starting material and false negatives, it is a possible source of error. For this reason, method selection is also important in tests where ctDNA obtained by liquid biopsy is used. The technology developed in the field of digital PCR now seems advantageous in terms of the capacity to deliver absolute mutation for targeted mutation screening tests.

GENETIC TESTING IN BREAST CANCER (5W1H)

Feride İffet Şahin

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Breast cancer is among the most frequent health problems in women. Diagnosis and follow up of breast cancer patients is carried on according to the contemporary guidelines. Genetic tests are performed at the time of diagnosis as well as during follow up, based on tumor type and clinical findings. Type and content of genetic tests to be performed, testing time, whom to be tested, test samples, methods and therapeutic approaches after testing will be discussed during the interactive session.

DISORDERS OF SEX DEVELOPMENT (DSD) AND GENETICS

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Disorders of Sex Development (DSDs) are defined as congenital conditions where development of chromosomal, gonadal, or anatomical sex is atypical (Hughes et al., 2006). No gender assignment at birth is one of the most stressfull situations for the families expecting normal female or male. Baby. In 2006 international endocrinology societies and patient advocates reviewed the terms used for defining various DSDs and recommended a new terminology for the prevention of stigmatization and confusion.

DSDs include a wide spectrum of disorders ranging from hypospadias to complete gonadal dysgenesis and ambiguous genitalia. The frequency of DSDs is estimated at 1 in 4500 live births. Childeren diagnosed as DSD should be followed up by a multidiciplinary team with a case spesific management strategy in mind.

Sex development occurs in two sequential stages: Sex determination and sex differentiation. During sex determination stage, bipotenial gonads evolve to testes or ovaries. This is followed by sex differention in which internal and external genital organs develops via the influences of gonadal and adrenal hormones.

In human embryos, the genetic sex is determined by the inheritance of an X or Y chromosome from the father. *SRY* genes located at Y chromosome play the most dominant role in the development of testes from undifferentiated gonads. Mutations in the *SRY* genes lead to the female development of an XY individual. Conversely, XX individuals carrying *SRY* genes develop as males.

It has been shown that, initially in the developments of bipotential gonalds, a number of specific genes, such as *NR5A1* (*SF1*), *M337/CBX2*, *WT1*,etc. are curical. In a7-week embryo, *SRY* genes on Y chromosomes start to be expresed, triggering testis development. Main function of SRY is to upregulate the SOX9 which is a transcription factor and necessary for the development of testes. NR5A1 acts together with both SRY and SOX9 and is also essential for initial bipotential gonad development. Other major genes playing roles in the testes developments are *WT1*,*DAX1*, *WNT4*, *CBX2*, *DMRT1*,and *GATA4*.

In 46,XX indivuduals, initial signals for the development of ovaries is not clear. However, it has been shown that WNT4 and RSPO1 upregulate expression of the transcription factor β-catenin (CTNNB1). β-catenin suppresses SOX9 expression and prevents male development. Granulosa cell differentiation and ovarian development are maintened mainly through expression of the FOXL2.

DSDs are classified into 3 groups:

1. Sex chromosome DSD
A. 45,X (Turner and variants)
B. 47,XXY (Klinefelter and variants)
C. 45X/46,XY (mixed gonadal dysgenesis-ovotesticular DSD)
2. 46,XY DSD
A. Disorders of gonadal (testicular) development
B. Disorders of androgen synthesis and action
C. Other (Persistant Mullerian Duct, vanishing testis,etc)
3. 46,XX DSD
A. Disorders of gonadal (ovarian) development
B. Androgen excess
C. Other (Mullerian agenesis, syndromic associations, etc.)

MOLECULAR PATHOGENESIS OF MULTIPLE MYELOMA

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Multiple Myeloma (MM) is a lymphoproliferative disorder which occurs in bone marrow due to the uncontrolled proliferation of B-lymphocyte-derived plasma cells and the production of a paraprotein which is called as M protein. MM composes 1% of all malignancies and 10% of hematological malignancies. It is the second most common hematologic malignancy after the non-Hodgkin Lymphoma.

The clinical pentad that constitutes the character of MM is as follows; anemia, monoclonal protein (paraprotein) seen in serum and urine or both of them, abnormal bone lesions and bone pains, hypercalcaemia and renal dysfunction.

A protein produced by abnormal plasma cells known as monoclonal immunoglobulin protein (M protein or monoclonal gammopathy) is secreted in the majority of patients. On the other hand, only monoclonal free light chain secretion is mentioned in 15-20% of cases whereas Ig is not secreted in 3% of cases (These are called non-secretory myeloma). Monoclonal protein, malignant cells or the cytokines secreted from malignant cells are responsible from the clinical findings.

The incidence of MM is more frequent in black race than white race and also it is more frequent in males compared to females. MM incidence is the lowest in Asian population while high incidence is seen in some ethnic groups. The median age at diagnosis is 69 in this disease.

Etiology: There are studies showing that environmental factors, chemical agents, viruses and genetic factors may play a role in MM etiology, regardless of any cause. In Japanese people who were exposed to high radiation due to atomic bomb they showed an increase MM incidence rate after many years. Radiation-related increases in the incidence of MM have been reported in patients who are diagnosed and frequently treated with radiological X-ray.

Some studies have showed increased risk of developing MM in farmers exposed to agricultural work and insecticides.

It is reported that rheumatoid arthritis, allergy and viral infections which causes chronic stimulation of the reticuloendothelial system, have increased risk of MM, although there are also totally opposite publications.

Pathogenesis, Development and Function of Normal Plasma Cells in Immune System: Although the pathogenesis of MM is not yet fully understood, it emerges with complex interactions between tumor cells and bone marrow microenvironment. Bone marrow stromal cells, osteoblasts, osteoclasts, fibroblasts and vascular endothelial cells constitute the bone marrow microenvironment. Myeloma cells play role in tumor growth and proliferation via interaction with bone marrow stromal cells and extracellular matrix proteins or growth factors, cytokines, and adhesion molecules.

NOVEL VARIANTS OF ABCA4 GENE IN TURKISH PATIENTS WITH STARGARDT DISEASE

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The aim of the study is to screen the gene encoding ATP-binding cassette transporter type A4 (ABCA4) in Turkish patients with Stargardt disease (STGD).

A total of 30 probands with STGD formed the patient group. The control group consisted of 250 unrelated healthy subjects with exome sequencing data. Both groups were analyzed using a next-generation sequencing technique. Amino acid changes were analyzed using three bioinformatics tools.

In the patient group, eight genetic variants in the *ABCA4* gene were detected. Six of the genetic variants were single-nucleotide polymorphisms. The other two detected variants were not previously defined in the literature. One of these variants was an intronic region variation (IVS40+1G>T). The other variant was the Y603H missense amino acid change in the 13th exon of the *ABCA4* gene. Both of these changes were found to be pathologic. It has been revealed that the newly detected Y603H variant is highly preserved in the species.

The variants of the *ABCA4* gene vary by ethnic group. We believe that the variant of the *ABCA4* gene seen in STGD patients, which we found via the first genetic screening of a Turkish population, may be associated with the etiopathogenesis of the disease.

MOLECULAR MODELING AND MOLECULAR DYNAMIC SIMULATION OF THE EFFECT OF A NOVEL VARIANT OF *PAH* GENE

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Phenylketonuria (PKU) is an autosomal recessive disease caused by the malfunction of the hepatic enzyme phenylalanine hydroxylase (PAH). PAH catalyzes the oxidative hydroxylation of L-phenylalanine (Phe) to L-tyrosine (Tyr) in the presence of its cofactor tetrahydrobiopterin (BH4), iron and molecular oxygen. In PKU patients, blood Phe concentrations increase dramatically if it is not treated, this increase causes various symptoms such as impaired cognitive development, hypopigmentation, autism-like behavior, aggressiveness and mental retardation. Our aim is to find novel mutations, which are implicated in PKU.

A mutation screen was performed on 81PKU patients using high resolution melting analysis followed by Sanger sequencing. A novel missense point mutation in the catalytic domain of *PAH* was identified in a 3 years old male patient. Crystal structure of the wild-type (WT) enzyme was obtained from Research Collaboratory for Structural Bioinformatics Protein Data Bank(RCSB-PDB) (PDBID:1J8T). The mutation was introduced to the amino acid sequence using Mutator extension of Visual Molecular Dynamics software (VMD). WT and mutant were then simulated for 30ns using Nanoscale Molecular Dynamics (NAMD). Nucleic acid sequences were also analyzed using Ribosome Flow Model software(RFMapp) to investigate potential differences in protein abundance and translation rates.

No significant differences in the spatial positions of catalytic amino acids between WT and mutated enzyme could be observed. However, a structural change in a neighboring tyrosine loop (Y138) which results in structural stability problems. This observation is currently being confirmed. We are investigating other domains. Taken together we showed a novel missense point mutation in the catalytic domain of *PAH* gene.

THE EFFECTIVE PROGNOSTIC AND PREDICTIVE MOLECULER MARKERS IN THE TREATMENT OF GLIOBLASTOME MULTIFORME

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Glioblastoma Multiforme (GBM), the most aggressive form of astrocytoma, accounts for 60% of brain tumors in adults. Hypoxia-inducible factors (HIFs) are essential mediators of the cellular oxygen-signaling pathway. (HIF-β) that facilitate both oxygen delivery and adaptation to oxygen deprivation by regulating the expression of genes that control angiogenesis, erythropoiesis and apoptosis. The aim of this study is suggesting the effect of HIF beta gene mutation on mortality and morbidity after GBM treatment.

Twenty-eight patients who were diagnosed with intracranial tumor at our clinic were included this study. Tissue specimens were taken from all patients during surgery. Patients were evaluated by oncology clinics after surgical treatment, followed by appropriate adjuvant treatment and patient follow-up.

Preliminary studies have reported data of patients with GBM diagnosed within the patients we have presented. It is thought that in 2 patients with HIF-β gene mutation, life shortened (average 104 days) and uncontrolled cell destruction (apoptosis) despite the effective adjuvan theraphy. We are planning additional TUNEL staining from pathological samples we have obtained.

In conclusion, the gene mutations like *IDH1*, *RAR1*-β and *HIF*-β may be effective on the diagnosis ant the treatment modalities of GMB. We tought that the mutations were effective on the adjuvan theraphy of GBM.

TRAC GENE VARIANTS ANALYSIS IN A CASE WITH NEUTROPENIA AND DEFICIENCY OF TCR ALPHA/BETA EXPRESSION

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The primary immune deficiency disorders are a complex group of disorders.They are inherited and this complexity is also reflected in the genetic heterogeneity. We aimed to investigate the gene variations of *TRAC* gene in patient with neutropenia and deficiency of TCRα/β expressions.

A 22-year-old female patient suffering from neutropenia.The lowest of neutrophils was found to be 250/mm^3.The peripheral blood lymphocyte profiles assessed by flow cytometry in patient.TCRα/β expression was compared between normal healthy individuals.For TCRα/β mutation analysis: Blood samples were collected and DNA was extracted with isolation instrument. Primers were used to investigate the variants of exons 1-3 of *TRAC* gene.DNA sequencing performed amplification of gene by sequencer.

TCRα/β expression was detected in T cells by flow cytometer and mutation of *TRAC* was investigated in parents.The flow cytometric peripheral blood lymphocyte profiles were evaluated and CD3+Tcells were present but there is no expression of TCRα/β.The patient percentage of cell population CD5:87,2%; CD8:33,2%; CD4:45,6%; CD2:90,2%; TCRα/ß:1-2%; TCRɣ/δ5%; CD11b:6,7%; HLA-DR:10,4%; CD19:7,2%; CD3:87,6% and CD16+56:4,2% respectively. Three distinct of nucleotide changes were identified. Variants were located in introns.Sequencing of the gene revealed three intronicmutations between exons 1-3. Detected variants wereregistered in the HGMD database.

The regulator regions have the feature of increasing and decreasing the gene expression. Thus,detected regulator gene changes in*TRAC* may alter the binding sequences of the activator proteins,affecting the expression of gene and/or affecting the possible association with other genes and proteins. There are only two cases were detected deficiency of TCRα/β in the literature. It has been observed that some clinical and laboratory features are similar to our case. We believed that different molecular defects may lead different phenotypes with the clinical severity of the diseases.

WHAT WE NEED FOR DIAGOSIS? WITH CLINICAL EXPERIENCES, AN ELUSIVE CILIOPATHY: JOUBERT SYNDROME

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Joubert syndrome is an inherited disease belonging to the ciliopathy group such as Meckel and Bardet–Biedl syndromes. The syndrome is firstly described by Dr Marie Joubert in 1969. Joubert syndrome displays considerable genetic heterogeneity and phenotypic variability. Additionally, in Joubert syndrome both intra- and interfamilial variation are seen.

The estimated prevalence is 1:80.000–100.000 live births but the prevalence of Joubert syndrome has not been well defined in Turkey due to the clinical variability and insufficient molecular testing facilities.

Since 1969 the researches on Joubert syndrome continues rapidly. The aim of this presentation is to draw attention to the basic clinical and genetic characteristics used in the diagnosis of Joubert syndrome.

Main features and genetic applications that can be used in the diagnosis of Joubert syndrome are told together with the clinical experiences in Health Sciences University, Kayseri Education and Research Hospital, Medical Genetics Department.

The molar tooth sign, hypotonia in infancy with later development of ataxia and developmental delays/intellectual disability are the main clinical characteristics of the disease. Advancing genetic technology and next generation sequencing techniques (WES and WGS analysis) increases the possibility of molecular diagnosis of clinically thought Joubert syndrome patients. Targeted gene panels commonly used in clinical practice but because of the rapid development in joubert genetics, updated gene panels should be prefered. Nevertheless, if it is possible WES should be prefered owing to its high diagnostic yield.

WHOLE EXOME SEQUENCING IDENTIFIES CAUSATIVE MUTATION IN A CASE WITH PONTOCEREBELLER HYPOPLASIA

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An eighteen-day male patient was referred to our clinical genetics department with hypotonia and feet eversion from pediatrics neurology department. He was born at full term with spontaneous vaginal delivery birth from first pregnancy of the family. His parents were first cousins, mother's parents were first cousins and father's parents were first cousins, too. His birth weight was 2500 gr, length and head circumference were not available. His first four months growth parameters were <3 percentile. In physical examination on the 18th day of birth, he was hypotonic and had mild dysmorphic face - relatively broad forehead, typical eyebrows with mild arch, widening medially and thinning laterally, mild beaked nose, thin lower lip, micrognathia and prominent ears. He had clenched hands and rocker bottom feet in eversion.

Brain MRI showed pontocerebellar hypoplasia and cerebral cortical atrophia. G-banded karyotype analysis performed on peripheral blood samples from the patient revealed the karyotype without any pathology and genomic DNA from the patient was analyzed by using the CytoScan750K Array (Affymetrix, Santa Clara, CA, USA) according to the manufacturer's instructions was with no pathology. Because of the physical, radiological findings and consanguineous marriage whole exome sequencing (WES) was planned for the patient. Whole exome sequencing (WES) was performed considering the findings, a homozygous mutation in *EXOSC3* (Exosome Component 3) at position Chr 9:37783991:NM_001002269:exon2:c.G394T:p.D132Y was detected. This mutation was found to be associated with pontocerebellar hypoplasia and the role of WES analysis in determining the molecular etiology of genetic diseases is becoming increasingly important.

GALT MUTATION SPECTRUM INCLUDING FOUR NOVEL ALTERATIONS IN TURKISH CASES WITH GALACTOSEMIA

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Classical galactosemia is a disorder caused by mutations in the *GALT* gene, which are leading to deficiency of the galactose 1-phosphate uridyl transferase enzyme. We aimed to investigate the frequency and distribution of *GALT* mutations in Turkish galactosemia patients.

Clinically diagnosed 71 patients with galactosemia were included in this study. DNA samples were isolated from peripheral blood and used for PCR amplification of *GALT* gene (NM_000155.3) coding exons and exon-intron boundaries. Molecular characterization was performed by Sanger sequencing.

We identified 11 known mutations and 4 novel variations (p. R67Pfs*19, p.S236Rfs*30, p.S156*, p.V243I) in 71 patients. The mutation detection rate was 91%. Sixty-six patients were homozygous and twelve patients were compound heterozygous for mutations.

CONCLUSIONS: In this study, p.Q188R mutation was the most common (38%) GALT mutation in Turkey as in Europe. Second most frequent mutation was p.E340* (14%), which is known to be specific for Turkish population. The third most frequent mutation (%) was a novel single nucleotide deletion leading to frame shift and early stop codon (p. R67Pfs*19), found to aggregate in patients from eastern Turkey. Classical galactosemia is frequently associated with p.S135L, p.Q188R and p.K285N mutations in Europe while p.Q188R in exon6, p.E340* in exon10 and p.R67Pfs*19 in exon 2 in Turkey. Algorithmic analysis of exons 2, 6 and 10 would delineate molecular genetic diagnosis for 60% of the patients from Turkey.

UNCOUPLING PROTEIN 2 GENE (*UCP2*)-866G/A VARIANT IS ASSOCIATED WITH NICOTINE DEPENDENCE AND SCHIZOPHRENIA

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Schizophrenia (Sch) is a severe and complex psychiatric disorder. Previous studies have shown that oxidative stress, mitochondrial impairment, and oxidative cell damage may play roles in Sch etiopathogenesis. It is known that most Sch patients have increased prevalance of cigarette smoking. Uncoupling proteins (UCP) are members of an anion-carrier protein family located in the mitochondrial inner membrane. The aim of this study was to evaluate the correlation of *UCP2* gene -866G/A variant (rs659366) with Nicotine dependence (ND) and/or Sch.

In this case-control study, genomic DNA collected from 100 Sch+ND cases, 133 ND subjects and 100 healthy controls. The *UCP2* - 866G/A variant was genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

A significant difference was found between the control group and the patients with ND and/or Sch as for genotype distribution of *UCP2* -866G/A variant. The *UCP2* -866G/A variant GG genotype was associated significantly with Sch+ND and ND (p=0.001; p=0.001, respectively) while AA genotype was associated significantly with a decreased risk of Sch+ND and ND, (p=0.002; p=0.001, respectively). The UCP2 -866G/A variant G allele was found to be increased in the ND group compared to the controls (p=0.001) and A allele was found to be decreased in the Sch+ND group (p=0.001).

In summary, this case-control analysis reveals that the GG genotype and G allele of *UCP2* - 866G/A variant probably increase ND and/or Sch risk in a Turkish population. These preliminary exploratory results should be confirmed in larger studies.

A LARGE DE NOVO DELETION OF CHROMOSOME 7q

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The 7q terminal deletion is a rare genetic disease that symptoms start during the intrauterine period and show wide phenotypic variability. Our patient was referred to us with complaints of dysmorphic facial appearance, microcephaly and hypotonia about five months of age. The first symptom was intrauterine growth retardation during the pregnancy. Although preterm birth seems to be common, our patient was born at 40th gestational weeks. In physical examination, we observed frontal bossing, temporal flatting, epicanthus, unilateral microphthalmia, depressed nasal bridge, thin upper and lower lip, dysplastic ears, unilateral facial hypoplasia and long filtrum. The mother complained of baby's feeding problem and constipation. Chromosomal analysis showed: 46,XX,del(7)(q3?5),inv(9)(p11q13). Parent's chromosome analysis was performed and it was seen that deletion was not inherited. Chromosomal microarray analysis revealed a 14-Mb terminal deletion of 7q35-7q36.3; arr[hg19] 7q35-q36.3(144,946,326-159,119,707)x1. It can be argued that this is a large deletion that includes a total of 111 genes, 58 of which are OMIM annotated. By reviewing of the 14-Mb deletion of chromosome 7 at the region of 7q35-7q36.3, we revealed 12 pathogenic variant recordings within the ClinVar database. Because clinical findings may vary according to the size and region of deletion and few cases have been reported overlapping the deletion of this region, we aimed to contribute to the literature and to shed light to the genotype-phenotype correlation of this rare disease with the findings of this patient.

CHARACTERIZATION OF A NOVEL HISTONE PHOSPHORYLATION AT HISTONE H3 ARGININE 128 (H3R128P) REVEALS A NEW MARK FOR CYTOPLASMIC HISTONES

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Genomic DNA is compacted into chromatin by wrapping the naked DNA around the histone octamer. Histones are composed of a globular domain and unstructured N- or C-terminal tails that are subjected to several covalent modifications such as methylation, acetylation and phosphorylation; which play important cellular functions. This study aimed to characterize a novel histone phosphorylation of histone H3 at arginine 128 (H3R128P).

H3R128P specific rabbit polyclonal antibodies were raised using H3 C-terminal peptides (Ac-LApRRIRGERK-OH), purified and tested in dot blotting and western blotting analyses for their specificity and sensitivity. Subcellular localization of H3R128P was examined by cellular fractionation experiments and immunofluorescence stainings on NIH 3T3 cells.

Dot blot analysis showed that the α-H3R128P antibodies recognize only the phosphorylated immunizing peptide, at a concentration as low as 3 pmoles. The H3R128P antibody specifically detected histone H3 and the pre-incubation of the antibody with the immunizing peptide in peptide competition assays resulted in the loss of signal. Western blot analysis showed H3R128P presence in the cytoplasmic fraction, which was further verified by the immunofluorescence stainings.

Newly synthesized histones are found in the cytoplasm before they are assembled into chromatin and previous studies indicated that these cytoplasmic histones have certain modifications such as H4K5ac and H4K12ac. Our results suggest that H3R128P could be a novel cytoplasmic histone modification that marks the newly synthesized histones.

idic(Y)(q11.2) ABNORMALITY IN CASES WITH MIXT GONADAL DYSGENESIS AND INFERTILITY

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In the literature, data with regard to the clinical picture in infertil male patients with an idic (Yq) chromosomal abnormality is very limited and is often referred to as case report. We present cytogenetic and clinical findings of 25 idic (Yq) male patients who were diagnosed with infertility.

Conventional karyotype analysis technique, SRY Fluorescence in situ hybridization (FISH) and Y chromosomal microdeletion test were applied.

In 16 patients, the karyotype was mos 45,X/46,X,idic(Yq)? and FISH analysis with SRY probe showed that the karyotype was mos 46,X,idic(Y)(q11.2). These patients were diagnosed as mixed gonadal dysgenesis. The other 9 patients had the 46,X,idic(Y)(q11.2) in non-mosaic form.

On Y microdeletion analysis, in 23 patients AZFb and AZFc regions were deleted, while in the remaining two only the AZFc region was deleted. (In all the patients with MGD, both the AZFb and AZFc regions were deleted).

The idic(Y) chromosome may be difficult to detect in karyotype analysis. Therefore, the Y chromosome should be carefully examined in patients with mixed gonadal dysgenesis (MGD) who have 45,X/46,XY karyotype, with special attention to idic(Yq). idic(Yq) may also be in a non-mosaic form as in our study (9 patient), and a small Y chromosome in an infertile male should be evaluated for idic(Yq). According to our findings, incidence of this rare chromosomal abnormality may be higher than expected.

ISOLATED BALANCED TRANSLOCATIONS IN NEWLY DIAGNOSED ADULT AML

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Acute Myeloid Leukemia (AML) is the most common type (5/100 000) of leukemia in adults. One of the important parameters determining the diagnosis and prognosis of the disease is acquired cytogenetic and molecular genetic anomalies. In cases with translocations as the only anomaly in the karyotypes, the prognosis is better than the complex karyotypes. In this presentation, we will share our three years experience of detecting cytogenetic anomalies in AML cases. We will also describe previously unreported isolated translocations in newly diagnosed cases.

In our retrospective study, 265 adult AML patients who were newly diagnosed among 655 AML cases sent for cytogenetic analysis between 2012 and 2015 were examined in Istanbul University Medical Faculty Medical Genetics Science Laboratory. 18 isolated balanced translocations detected by bone marrow culture HRB method were analyzed according to their frequency and genetic characteristics and interpreted with literature support.

The frequency of isolated translocations in our newly diagnosed AML population is 17.35%. Translocations were found in 46 cases (21 female and 25 male). Translocations of t(1;3)(q25;22), t(1;17)(q32;21),t(2;8)(p23;q22),t(6;15)(p21;q22), t(8;8)(p23; q22) and t(9;20)(p13;q13), which were shown to be non-constitutional, have not previously been reported in AML.

Cytogenetic analysis with HRB from bone marrow culture is a method that should be preferred as the first stage basic approach in the diagnosis and prognostic features of all leukemias and to guide the treatment in an algorithmic manner. Cytogenetic analysis is a method that should be applied routinely in diagnosis in order to detect major anomalies that have never been reported.

THE IMPORTANCE OF MICROARRAY ANALYSIS IN THE IDENTIFICATION OF UNBALANCE TRANSLOCATION

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Chromosomal microarray analysis (CMA) is a method that can detect microdeletions and microduplications in the size of hundreds of kilobases in the genome. In 2010, ACMG recommend that CMA analysis became first-line cytogenetic test in patients with developmental delay, multiple congenital anomalies, and autism spectrum disorders. Many microdeletion and microduplication cannot be identified due to low resolution by conventional G band chromosome analysis. In this study, the microarray results of two sibling who have speechless, MMR, and another patient who have MMR, operated cleft palate and major dismorfic features is presented.

CMA tests were performed with Affymetrix CytoScan Optima Array Kit and a GeneChip GCS3000dx V2 scanner according to the manufacturer's instructions. The array had 315 608 markers,based on genome build hg19. The results were analyzed with Chromosome Analysis Suite ver. 3.1 (Affymetrix). Chromosome analysis was also performed on patients and parents.

RESULTS: In this study, we identify two unbalance chromosomal structure in 3 patients from two different families by microarray analysis. However, G-band chromosome analysis could not reveal balanced translocations in parents and unbalanced chromosome structure in patients. The result of the microarray of two siblings was Arr[hg19] 10q26.13 q26.3(123,589,266-135,427,143) x1, Arr[hg19] 12q24.33(130,916,684-133,777,902) x3. Another patient's microarray showed as Arr[hg19] 10q26.2(130,497,634-135,427,143) x1, 12p13.33(173,786-13,152,328) x3.

When chromosome analysis is not recognized the translocation bearing individuals due to low resolution, patients with unbalance translocation may occur. CMA is an effective method to diagnose these unbalance translocations. The clinical, phenotypic, and genotype features of patients are also discussed.

DEVELOPING A NEW SCREENING KIT FOR DETERMINATION OF SPINAL MUSCULAR ATROPHY CARRIER PATIENTS WITH REAL-TIME PCR METHOD

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Spinal muscular atrophy (SMA) is a group of hereditary diseases that are inherited autosomal recessively characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of anterior horn cells of the spinal cord. The prevalence of SMA disease is 1-2/100,000 and the incidence is 1/6.000-1/10.000 live births and the carrier frequency ranges from 1/40-1/60. In this study, we aimed to design/develop an inexpensive, reliable and easy-to-use screening kit using Real-Time PCR technique to determine SMA carriers in our country.

100 patients who were investigated by MLPA for *SMN1* and *SMN2* genes with the result of carrier, mutant or normal for SMA, were included to the study. The combination of the tecnologies as "Amplification-refractory mutation system analysis", "5' nuclease assay" and "Allel specific PCR" are both used to quantify *SMN1* deletion mutation with Real-Time PCR. Sequence specific primers for reference (*SMN2*) and target (*SMN1*) gene were designed and marked with different fluorophore dye. DNA standards marked with dual-labeled probes with Locked Nucleic Acid are used to provide separate quantification of two genes.

The results were obtained using the quantitation data in the Excel table generated by the device with the help of a software. The outcomes acquired with the method used in the research were one-to-one compatible with MLPA results.

Due to the severity, treatment costs and carrier frequency of SMA disease; carrier screening programs would be appropriate in countries that consanguineous marriages are frequent. The method for screening must be cheap, feasible, and accurate.

SPINAL MUSCULAR ATROPHY TYPE III-B GENOTYPE-PHENOTYPE CORRELATION: TWO FAMILIAL CASES

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Spinal muscular atrophy (SMA) is an autosomal recessive inherited neuromuscular disease. The International SMA Association clinically allocated SMA patients into four groups. SMA type III-b is also known as Kugelberg's Walender disease and the symptoms usually start after three years of life. Mutations in the *SMN1* gene should be demonstrated along with clinical findings for diagnosis.

The results of different phenotypic features, electromyography (EMG) tests and genetic analysis of two brothers with SMA diagnoses genetically tested will be discussed to the accompaniment of the current literature.

Two brothers aged 37 and 34 years old complained of muscle weakness starting from the second decade of their lives. In the first patient, there were findings of predominant muscle atrophy and tetraparesis in the bilateral distal region. The little brother had proximal tetraparesis and the patient was dependent on the wheelchair.

The findings of the younger brother EMG were consistent with SMA. In genetic analysis homozygous deletion was detected in *SMN1* gene exon 7-8. Severe sensoromotor axonal polyneuropathy findings were detected in older brother in EMG. Genetic examination revealed a heterozygous deletion of the same gene.

SMA type III-b can occur with different phenotypic and genotype characteristics even within the same family.

A REPORT OF MOSAIC 7p DUPLICATION SYNDROME WITH NEW FINDINGS

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We report on a rare case of a 4-year-old female with mosaic duplication of the 7p14.3-22.3 chromosome region. We report a pulmonary stenosis which has not been reported with chromosome 7p duplication.

Chromosome analysis and microarray were performed from the patient and her parents. The patient's chromosome analysis resulted in 46,XX,dup(7)(p14.3p22.3)[17]/46,XX[4]. In the microarray test, the number of copies increased to 30 Mb in the same region. The results of her parents' chromosomal analysis and microarray were normal.

The patient applied us with mental and growth retardation. She has typically dysmorphic features, mental retardation, atrial septal defect, pulmonary stenosis, hypoplasia of corpus callosum and cleft palate.

We present a *de novo* mosaic 7p duplication syndrome with pulmoner stenosis which is rare disorder.

COLON CANCER MUTATION IN ADIPOSE TISSUE? A CASE REPORT OF CLOVES SYNDROME

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Skeletal overgrowth syndromes were conventionally diagnosed as Proteus syndrome or hemihyperplasia, and those with vascular anomalies were named as Klippele-Trenaunay syndrome. Recently, patients with congenital lipomatous overgrowth, dysregulated fat deposits, and mixed vascular malformations has been classified as CLOVES (congenital lipomatous overgrowth (CLO), vascular malformation (V), epidermal nevi (E), and scoliosis and spinal deformities (S)) syndrome. CLOVES is a rare disease with 150 reported cases available. *PIK3CA* gene mutations in various somatic lipid tissue in the body is held responsible from CLOVES.

We present here an 18-year-old boy with CLOVES syndrome from Adiyaman City, Turkey. His DNA was isolated from his underarm-vascular nevi tissue. We applied smMIP-sequencing (single-molecule Molecular Inversion Probe) to screen for point mutations among all the exons of *PIK3CA* gene. The library was prepared and sequenced by using Illumina MiSeq platform. Reads were aligned against GRCh37-human reference genome by BWA-mem-algorithm, and all the paired-end reads from the same read group (with identical position and single-molecule-barcode) were merged into a consensus sequence.

After excluding any common variants which were present in dbSNP or 1KGP, we identified *PIK3CA* p.G1049R mutation in his nevi-tissue-DNA, adjacent to the p.1047 mutation which was previously reported in patients of CLOVES syndrome. The mutant allele fraction was 6.4% (59 out of 928 read groups), highlighting the somatic origin of this mutation.

Although this mutation was found in various types of tumor samples in COSMIC database, it has never been reported before in lipid tissue and any patients of CLOVES syndrome,confirming diagnosis.

APPROACH TO A CASE WITH 1p36 DELETION VIA MOLECULAR GENETIC AND CYTOGENETICS METHODS

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The application of the advanced genetic analysis methods including DNA microarray and floresan in situ hiybridisation (FISH) has beeen tested here to elucidate a case presenting with growth and developmental delay and dysmorphic face findings and a family search has been planned.

Analysis of karyotypes have been done for the patient and his parents with high resolution banding technique. Copy number variation screening has been applied for the patient by DNA microarray anlaysis. Floresan in situ hybridisation study has been performed to examine subtelomeric regions of first and sixteenth chromosomes of the parents.

Karyotype anlaysis of the index case has been found to be consistent with 46,XY. On the later DNA microarray analysis, there have been obtained a deletion about 1.652 Mb size comprising 1p36.32-1p36.33 regions and a duplication at 16p13.3 region estimating about 1.925 Mb. His mother and father's karyotypes have been found as 46,XX and 46,XY, respectively. A resiprocal translocation between the subtelomeric regions of the short arms of the mother's first and sixteenth chromosomes has been detected by FISH method.

The methods like microarray and new generation sequencing are being the first steps of the diagnostic field as the time passed by. Although the conventional and molecular cytogenetical approaches have some limitations, are still beneficial and maintaining their importance in the diagnose of the patients and genetic counselling. In this case report, we also emphasise the approach to the del1p36 case and its clinical findings for one more time.

MOLECULAR GENETIC DIAGNOSTIC EFFICIENCY OF TARGETED NEXT GENERATION SEQUENCING ON "DISORDERS OF SEX DEVELOPMENT"

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Chromosomal abnormalities or point mutations of related genes can cause gonadal or anatomic incongruous is called as disorders of sex development (DSD). Newborn incidence is 1/5500 and clinical spectrum can be change from mild hypospadias of 46,XY and from mild cliteromegaly of 46,XX to sex reversal phenotypes.

The first stage for genetic diagnosis is to reveal chromosomal sex and/or chromosomal abnormality and second stage is to perform molecular examinations of the related genes or regions to determine causative mutations for either syndromic or non-syndromic DSD.

44 cases with no abnormal karyotype initially searched for gross deletion/duplications by MLPA probes (P185 and P334). This is followed by next generation sequencing (NGS) of the cases by in house designed targeted gene-panel (31 genes) on Ion Torrent PGM platform. Coverage of targets was 98.29% and ~210 deep. Uncovered regions sequenced by Sanger method.

Unrelated 17 cases had one or more pathogenic or possible pathogenic variants (10 cases of 46,XX DSD, 7 cases of 46,XY DSD) on eight different genes (*HSD17B3*, *DHH*, *NR5A1*, *LHCGR*, *WT1*, *POR*, *ZFPM2* and *HOXA4*), 13 variants were novel. Mutation detection rate was 38,6%. This rate is compatible with other investigations in the literature, using either targeted NGS panels or clinical exome studies.

This work suggested that our in-house gene-panel is effective for identifying the causative DSD mutations which in turn very valuable for management of the cases and genetic counseling of the families.

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HAPLOINSUFFICIENCY OF *ZNF462* GENE IN A PATIENT WITH INTERSTITIAL DELETION OF CHROMOSOME 9q

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Interstitial deletions of the long arm of chromosome 9 are rare and show large differences in size and localization. Deletions of this region have been reported to cause neonatal hypotonia, intellectual-motor developmental delay, intracranial anomalies, cardiac anomalies and dysmorphic facial features. Here we present a patient diagnosed with a 21.2 Mb interstitial deletion in the 9q31.1q33.2.

The female patient was born with a caesarian section at 37th gestational week due to intrauterine growth retardation. The anthropometric measurements were found below the third percentile and dysmorphic facial findings including arched eyebrows, ptosis, epicanthus inversus, down-slanted palpebral fissures, broad and flattened nasal root and short upturned nose with bulbous tip were detected on physical examination when she was 54 days old.

As a result of conventional cytogenetic, FISH and microarray (Agilent 8x60K ISCA) analyzes, it was found that the q33.2-qter region of the chromosome 9 was localized on the long arm of the chromosome 10 and also the 9q31.1q33.2 regions (21.2 Mb) were deleted. The terminal region of the long arm of the derivative chromosome 10 was found to be intact. Parental karyotypes were normal.

Similar clinical features and dysmorphic findings have been reported in patients with small deletions containing the *ZNF462* gene localized in 9q31.2 and point mutations in the same gene. In this context, this clinical similarity could be explained via the consequence of haploinsufficiency due to deletion of the entire *ZNF462* gene. The other genes deleted in the patient may contribute to the phenotype.

GENETIC INVESTIGATION IN PARKINSON DISEASE

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Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease and in general, more than 1% affected over the age of 65 years and more than 4% of the population affected by the age of 85 years. Approximately 5% of the cases are defined to be genetic. Presently pathogenic variants in 10 genes are associated with different inheritance form of PD. Identification of the causative genes and their inheritance model are very important for the genetic counseling of the families and for the presymptomatic diagnosis of under risk individuals.

All patients (n:50) referred with PD between the years of 2015–2017 were investigated with in house designed panel gene test including 42 genes for the screening of pathogenic sequence variant and with Multiplex Ligation-dependent Probe Amplification (MLPA) kit for gross deletions/duplications concurrently.

A causative mutation has been found in 12 patients (24%). Gross mutations in *SNCA*, *PARK2*, *PARK7* were found responsible from 66%, point mutations in *PARK2* gene was responsible from 34% of the patients.

Our results will contribute to the establishment of molecular genetic algorithms, identification of new mutations in our population and counseling for families

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DIAGNOSTIC COMPETENCE OF let-7c-5p AND mir-223-3p SERUM LEVELS IN DIFFERENTIAL DIAGNOSIS OF PROSTATE DISEASES AND PROSTATE CANCER

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The study purpose is to examine the diagnostic competence of let-7c-5p and miR-223-3p serum levels in prostate cancer differential diagnosis. Considering the role of miRNAs in chronic inflammation, it is also aimed to assess the interfering characteristic of chronic prostatitis in differential diagnosis of prostate cancer and benign prostatic hyperplasia (BPH).

Serum samples from patients with BPH (n = 25), chronic prostatitis (n = 10) and prostate cancer (n = 33) were used in the study. RNA isolation, cDNA synthesis and qRT-PCR steps were performed with SYBR Green method. The patients were informed and they signed an approval form and the ethics committee approval was also obtained.

For statistical analysis, -ΔCt values, obtained from the use of ce-miR-39 Ct values in normalization, were used. Differences between groups were tested by t test and variance analysis. ROC analysis was performed to calculate the diagnostic competence. "Fold change" calculations were performed online. In all analyzes, alpha error level was accepted as 0.05.

It was observed that miR-223-3p and let-7c-5p differ significantly between prostate diseases and prostate cancer groups. It was assessed that the sensitivity of miR-223-3p and let-7c-5p to differentiate prostate cancer from other prostate diseases is higher than prostate specific antigen (PSA) and chronic prostatitis may be an interfering condition in BPH and cancer differential diagnosis.

A FAMILIAL CASE OF HYPOCHONDROPLASIA WITH GYPSY ORIGIN

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Hypochondroplasia (HCH) is a skeletal dysplasia with autosomal dominant inheritance. It is characterized by near-normal craniofacies, short stature, shortened tubular bones with mild metaphyseal flare, narrowing of the spinal canal, and lumbar lordosis. HCH is caused by mutations in the *FGFR3* gene. Here we present a familial case of HCH. A 13-year-old Gipsy girl with short stature was referred to our department. She was the second child of a family. Disproportionate short stature, short extremities, genu varum, lumbar lordosis, relative macrocephaly, synophrys, low nasal root, and high arched palate were detected in physical examination. Her height was 137 cm and his weight was 39.8 kg and head circumference was 55.5 cm. The X-ray showed shortening of long bones and mild metaphyseal flare. No structural chromosome anomaly was detected. HCH was diagnosed according to clinical and radiographic findings. The affected six individuals of the family were also examined physically and found to have similar clinical manifestations. The father, three siblings, uncle and grandfather of our patient also had short stature. *FGFR3* gene sequence analysis was performed for definitive diagnosis of HCH. The heterozygous c.1620C>G mutation in the *FGFR3* gene was detected in our patient, her father and all three siblings. Genetic counseling was given to the family. An ethnic predisposition is not expected in HCH. The Gipsy origin of the patient is a coincidental event. Although, HCH with c.1620C>G mutations are frequent all over the world; to our knowledge, our patient with c.1620C>G mutation is the second case reported in Turkey.

A CASE MIMICKING CHRONIC MYELOPROLIFERATIVE LEUKEMIA WITH t(8;22)(p11;q11)/*BCR-FGFR1* AND SEQUENTIAL TRANSFORMATION TO B-ALL AND AML

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Rearrangement and constitutive activation of *FGFR1* result in a group of rare diseases which features a myeloproliferative neoplasm that commonly progresses to lymphoblastic leukemia/lymphoma or acute myeloid leukemia (AML). Cases with t(8;22)(p11;q11) *BCR-FGFR1* fusion gene may be misdiagnosed with chronic myelogenous leukemia (CML), due to very similar morphologic and clinical profile. In the case of t(8;22)(p11;q11), *BCR* gene is the partner gene of *FGFR1*, not *ABL*. The current patient was a 48 year old woman who had splenomegaly, eosinophilia and elevated white blood cells.

Conventional cytogenetic analysis was carried out 24 and 48 hour bone marrow cultures. *BCR-FGFR1* fusion was assessed by FISH. Reverse transcription quantitative polymerase chain reaction (RT-QPCR) for *BCR-ABL* fusion transcripts was performed with a commercial kit based on Taqman technology.

Conventional G banding analysis of the bone marrow cells showed 46,XX,t(8;22)(p11;q11). Transcripts of *BCR/ABL* p210 were negative. Using the *BCR-ABL* FISH probe, the *BCR-ABL* fusion was found to be negative but an additional signal was detected for the BCR gene. *BCR-FGFR1* fusion was detected in the FISH study using the FGFR1 Breakapart/Amplification probe. *BCR-FGFR1* fusion was also verified by Sanger seguencing. During the chronic phase the patient was treated with hydroxurea. The first transformation to B-ALL was treated with ALL protocol and for the second transformation to AML 3+7 protocol was given.

The disease with rearrangement *FGFR1* is more aggressive. For this reason, detection of this translocation at diagnosis is very important, in terms of prognosis therapeutic choice.

DESMOID TUMOR OF THE SCALP

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Desmoid tumors are quite rare, frequency is believed to be between 1/250.000-500.000. The exact molecular pathogenesis of the desmoid tumors are still unknown but pathogenic variants in APC gene is responsible for 15% of sporadic cases. Mutations in *APC* cause desmoid tumors which are usually associated with FAP.

Here we report 3 months female infant presented with swelling on the scalp. On examination, there was a scalp swelling involving the left temporal region, which was hard, non- tender and fixed to the bone. On transfontanel ultrasound, soft tissue mass of 48 mm in diameter and 15 mm in thickness was found in the left temporal region of the scalp. A wide surgical excision of the mass was performed and histopathology revealed desmoid tumor of the scalp.

APC gene sequencing was performed. A heterozygous c.5528C>T (p.Pro1843Leu) variant is detected. It was defined as pathogenic in HGMD. The same variant was detected at the proband's 30 years old mother and 55 years old grandmother. There were no clinical findings of FAP or tumoral development in both of them yet. Penetrance of colon cancer is virtually 100% on FAP and therefore we have concluded that the variant might not be pathogenic for FAP, but it may cause attenuated FAP which is another form of FAP and shows incomplete penetrance. Tumorogenesis in the early infantile period may arise from the double hit phenomenon of the tumor suppresor genes. Further analysis are planned.

RESPONSE TO THERAPY IN A CASE OF CML WITH COMPLEX VARIANT Ph TRANSLOCATION

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Chronic myeloid leukemia (CML) is a clonal hematological disorder of hematopoietic stem cells and is characterized by the Philadelphia chromosome (Ph). The 5–10% of patients with CML harbor variant Ph translocations. That variant Ph may be in a simple or a complex form. The clinical profile and the prognostic significance of those translocations have not been well established.

Samples from the patient with CML in chronic phase were investigated. Cytogenetic analysis on bone marrow and molecular analysis on peripheral blood were performed both in the diagnosis and treatment processes. Conventional cytogenetic analysis were carried out on unstimulated 24 and 48 hour bone marrow cultures. Reverse transcription quantitative polymerase chain reaction (RT-QPCR) for *BCR-ABL* fusion transcripts was performed with a commercial kit based on Taqman technology.

The patient didn't respond to the first line CML therapy with imatinib. *ABL* kinase domain mutations (KDM) were investigated by Sanger sequencing and no mutation was detected. Therapy with dasatinib was started as a new treatment option. *ABL KDM* were investigated again due to the partial cytogenetic response and T315I mutation was detected. Then therapy with Ponatinib was started and this patient responded to Ponatinib well. An allogeneic stem cell transplantation is considered in this patient.

The better identification of gene abnormalities will give important information of leukemic disease progression.

IDENTIFICATION OF BI-ALLELIC *POLR3A* MUTATIONS AS A LIKELY CAUSE OF NEONATAL PROGEROID SYNDROME

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Wiedemann–Rautenstrauch syndrome (WRS; OMIM: 264090), or neonatal progeroid syndrome, is a rare autosomal recessive disorder that includes premature aging phenotype at birth, with fewer than sixty cases reported to date. Clinical characteristics of WRS are prenatal and severe postnatal growth retardation, unusual facial features, dental anomalies, generalized lipodystrophy with localized fat masses, and sometimes progressive ataxia and tremor. The possible association of WRS with bi-allelic *POLR3A* variants (c.1909+18G>A, c.2617C>T) has previously been shown in one patient only. The current study presents the case of a four-year-old female with clinical manifestations suggestive of WRS, such as premature aging phenotype, bilateral ponto-mesencephaly, psychomotor disability, osteopenia, lipodystrophy with localized fat tissue in the caudal and thoracic areas, and alopecia areata. Two novel compound heterozygous *POLR3A* variants (c.3337-11T>C, c.3568C>T [p.Q1190*]), which have been inherited from both parents, were found to be associated with WRS through next-generation sequencing. Based on in silico analyses, the c.3337-11T>C variant was predicted to cause abnormal gene splicing, while the truncating p.Q1190* variant was predicted to reduce the catalytic activity of RNA polymerase III and/or impair the interactions between the *POL3RA* product (C160) and its interacting partners, such as several other components of the enzyme and assembly factors/class III transcription factors. Overall, the proband's genotype suggests alternative phenotypic roles for *POLR3A* variants and may expand the clinical spectrum. Further studies on the functional significance of both *POLR3A* variants as well as more patients diagnosed with WRS are required to confirm the increasingly recognized association between *POLR3A* and WRS.

RISK MANAGEMENT AND GENETIC COUNSELLING IN HEREDITARY CANCER SYNDROME DISEASES: EXPERIENCES OF A HIGH-RISK CLINIC

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Genetic counselling of cancer patients and/or individuals with high-cancer-risk is crucial for disease management. Genetic testing for cancer patients should be informative about disease perpetuation and response status of treatment modalities. People within high-risk should be informed and given an option for cancer susceptibility testing. Therefore, in our medical genetics department, we do high-risk-clinic for the cancer patients and the individuals with cancer risk based on family history and pedigree analysis.

Risk analysis and genetic counselling were performed to 70 individuals in high-risk-policlinics between 2016-2018. The comprehensive hereditary cancer panel performed via next generation sequencing by Illumina MiSeq platform.

Among 70 patients, 88.6% (n=62) were referred to genetic testing. While 33 of these 62 patients (53.2%) had been diagnosed as a cancer patient, 29 individuals (46.8%) categorized in high risk group. Four of 33 patients accepted family screening after genetic counselling whom only one individual had positive genetic testing. With one exception all of cancer diagnosed patients had stories of different cancer types in their lineage. Within the high-risk group (n=29), 10.3% of the patients had a family history with the same cancer type in different generations, and 26 (89.7%) of them had family members with various cancer types.

High positivity rates of our study shows the importance of the proper genetic counselling and patient selection for further analysis in which preventive medical care becomes possible.

ISCHIOSPINAL DYSOSTOSIS IN A BOY WITH A NOVEL HOMOZYGOUS MISSENSE MUTATION IN THE "*BMPER*" GENE

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Ischiospinal dysostosis (ISD) is a polytopic dysostosis characterized by minor facial dysmorphism, ischial hypoplasia, short stature with a short spine caused by vertebral anomalies including hypoplasia of the lumbosacral spine, scoliosis etc., and occasionaly associated with nephroblastomatosis. ISD is associated with homozygous or compound heterozygous mutations of bone morphogenetic protein-binding endothelial regulator (*BMPER*) gene.

Here we report on a 3-year and 7-month-old boy with ISD a third child born to a consanguineous couple. He was born at 36 weeks with a birth weight of 1600 gr and delivered via cesarian section.

The main clinical findings, high forehead, micrognathia, broad bifid nose, long philtrum, bilateral ezotropia, strabismus, hyperlordosis, short trunk and short stature. Extremitles were normal. He is ambulatory, walks with severe hyperlordosis and neck hyperextension balancing his posture. He prefers to bend his body forward when he eat, looks at objects. He has mild stridor and a hoarse voice, yet has no tracheostomy. Spinal computerized tomography (CT) showed sacrum agenesis, thoracolumbar lordosis, vertebral cleft formation and posterior fusion defects in low lumbar vertebrates. Kidney CT was normal.

Sequencing of *BMPER* gene in the proband revealed the presence of one novel homozygous missense variant c.1166T>G, this variant leads to a p. Val389Gly change in *BMPER*. This variant was neither found in ExAC nor 1000G databases and regarded as disease causing and damaging based on the in-silico prediction tools (mutation taster, SIFT, Polyphen and Provean).

Despite severe skeletal findings, this ambulatory patient extends the phenotypic spectrum of BMPER-related skeletal disorders.

UTILIZATION OF COMPREHENSIVE CANCER TESTING IN MALIGN MELANOMA: EXPERIENCES OF A GENETIC DISEASES DIAGNOSIS CENTER

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BRAF-targeted therapy is the most common pathway in malign melanoma cases. Although there are several assays to detect specific variants in *BRAF* gene, a comprehensive genetic testing via next generation sequencing is a necessity for *BRAF* negative patients to identify the genetic changes in other malign melanoma associated genes. Thus, in this study a multi-gene panel was next generation sequenced in malign melanoma patients.

FFPE samples from 33 malign melanoma patients were collected and sequenced via a new NGS system (Qiagen, GeneReader) using a multigene panel including 12 actionable cancer related genes (*KRAS*, *NRAS*, *KIT*, *BRAF*, *PDGFRA*, *ALK*, *EGFR*, *ERBB2*, *PIK3CA*, *ERBB3*, *ESR1* and *RAF1*).

We detected 22 clinically significant variants in 20 (60.6%) of 33 patients. We observed 16 (72.7%) variants in *BRAF* gene in 80% (n=16) of 20 patients. More than that, 27.3% of the patients (n=6) had variants in other than *BRAF*. These other variants had also been reported due to the relation of therapy sensitivity (n=2), familial predisposition (n=2) and ongoing clinical trials (n=1).

Variant specific assays may detect the majority of the actionable *BRAF* mutations but still a delicate number of variants on other genes should not be underestimated. Overall, our results point out the clinical use of multi-gene panels in malign melanoma cases.

COMPARISON OF THE COST AND LABORATORY EFFECTIVITY BETWEEN NEXT GENERATION SEQUENCING AND PYROSEQUENCING IN FMF PATIENTS

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Next generation sequencing has become the golden standard in genetic testing although pyrosequencing is still a common method for the diagnostics of well-known single gene related diseases such as Familial Mediterranean Fever (FMF). On the other hand, NGS provides a wider perspective but also requires an expensive laboratory equipment as well as qualified and experienced staff. Therefore, we present our comparison of FMF testing results by NGS and pyrosequencing to determine the cost-effective methodology.

Peripheral blood samples were collected from 679 clinically FMF diagnosed patients. Next generation sequencing was performed for *MEFV* gene including all exons and exon-intron junctions via Illumina MiSeq platform to detect all the variants. Results were compared to the mostly used pyrosequencing kit (Qiagen, FMF Pyrosequencing) in the market to differentiate the variants.

We found 611 reportable variants in 424 patients. There had been 313 (51.2%) variants in 184 (42.5%) patients that cannot be detectable by pyrosequencing. More than that, there is one patient with a novel mutation while there was no variant detected in 255 (%37,6) patients.

According to our results, pyrosequencing still is the most cost-effective methodology for diagnosing *MEFV* mutations. However, there are still a number of patients around more than 25% needs further investigation. Therefore, the better algorithm for FMF genetic testing should start with screening of well-known variants than the other methodologies.

THE SIGNIFICANCE OF LIQUID BIOPSY FOR MONITORING AND THERAPY DECISION OF LUNG ADENOCARCINOMA: A CASE BASED REVIEW

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Liquid-biopsy studies via next-generation-sequencing has become an efficient tool in cancer diagnostics and cancer based research. Since, it has a clinical application, it also becomes more important in order to provide a better health care service and therapy guidance for the cancer patients. Here, we report a metastatic lung adenocarcinoma patient who underwent a next-generation-sequencing based profiling with *EGFR* exon 19 deletion and later on with *EGFR* T790M mutation in the liquid biopsy sample.

A multi-gene cancer panel with 12 genes were sequenced by GeneReader NGS system from the FFPE tissue sample. Then after a year the cancer has progressed, thus the study is repeated with a comprehensive-cancer-panel including 19 lung-cancer related genes from the liquid-biopsy sample.

We detected the E746_A750del variant with a ratio of 18% during the first diagnosis. This variant was reported as the "Erlotinib" sensitivity and "Carboplatin/Paclitaxel" resistance. After a year, liquid-biopsy was performed and resulted with 2 (two) secondary mutations in *EGFR* gene (T790M and C797S) in two clones which both are related to "Erlotinib" resistance without the deletion reported in the first instance.

Our findings, highlight the cruciality and reliability of the liquid-biopsy studies to gain a better understanding on cancer progress through the personalized medical approach. Our results also show the importance of a well-arranged patient follow-up by periodic liquid-biopsy studies. Through this case, we overall emphasize the clinical utilizability of frequent liquid biopsy via NGS but within clinical and laboratory guidelines that should be well established.

INTELLECTUAL DISABILITY ASSOCIATED WITH A SEX CHROMOSOMAL ANEUPLOIDY: PRESENTATION OF TWO CASES WITH 48,XXYY

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48,XXYY syndrome is a sex chromosome aneuploidy characterized by tall stature, small testis, hypergonadotropic hypogonadism, infertility, dysmorphism, neurodevelopmental and psychological problems.

Case 1: A 27-year-old single male patient presented with primary hypergonadotropic hypogonadism. He had type 2 diabetes mellitus. His height was 190 cm and he had mental retardation, tremor, dysmorphic facial findings, small testes and pes planus.

Case 2: A 38-year-old male patient presented with primary infertility. He was 180 cm tall. He had intellectual deficiency (ID), dysmorphic facial findings, dental crowding, microorchidism. Hormone profile was compatible with hypergonadotropic hypogonadism.

In both patients karyotype analysis revealed 48,XXYY. Parents karyotype analysis were normal.

48,XXYY syndrome is a very rare sex chromosome aneuploidy. Approximately 100 cases have been reported in the literature. The extra set of chromosomes almost always comes from the sperm due to non-disjunction during meiosis-1 and meiosis-2. In case-2, we detected that excessive number of X and Y chromosomes originated from the father with STR analysis This syndrome is similar to the Klinefelter syndrome in terms of its phenotypic features, but it is also associated with neurodevelopmental findings (seizures, intention tremor, hypotonia, and tics), dysmorphism, cardiac anomalies, endocrinological disorders (DM type 2, hypothyroidism) and other systemic anomalies. In both patients, in addition to the findings of Klinefelter syndrome, intellectual disability and dysmorphism were noted. Additionaly in case-1 tremor and DM type 2 and in case-2 dental crowding were noted.

In patients with ID, tall stature and hypergonadotropic hypogonadism, 48,XXYY syndrome should come to mind.

ANTI-INFLAMMATORY AND APOPTOTIC EFFECTS OF QUERCETIN AND CURCUMIN ON CHRONIC MYELOID LEUKEMIA CANCER CELLS

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Chronic myeloid leukemia is a myeloproliferative disorder. It has recently been reported that the polyphenols quercetin and curcumin have anti-carcinogenic, anti-inflammatory and pro-apoptotic properties.This study, we investigated anti-inflammatory and apoptotic effects of quercetin, curcumin and their combination on CML cancer cells.

In this study we have demonstrated the synergistic effect of curcumin and quercetin on cell proliferation by WST-1 cell proliferation assay. Apoptosis have been observed by Annexin-V staining and then we have analyzed ROS, JC-1 and intracellular GSH using flow cytometry. Apoptosis-related protein and mRNA expressions were determined by Western blot and PCR.

We have observed that quercetin and curcumin combination induced apoptosis accompanied by increased ROS and decreased GSH levels as well as loss of mitochondrial membrane potential. Our mRNA and protein expression results suggested that cytochrome c was released from mitochondria causing PARP and caspase-9 cleavages, the hallmarks of mitochondrial apoptotic pathway. We believe that triggering of apoptosis is mostly via mitochondrial pathway and ROS generation may induce impairment of mitochondrial membrane potential. The combined treatment of quercetin and curcumin inhibited the proliferation and induced apoptosis significantly higher than the quercetin and curcumin-treated group alone. Interestingly, the combined treatment with quercetin and curcumin significantly down-regulates the expression of the pro-inflammatory mediators cyclooxygenase-2 (COX-2). Furthermore, the effect of combined treatment with curcumin and quercetin was stronger than the individual treatment.

Thus, combination of curcumin and quercetin has the potential to be used and considered in drug development studies for CML treatment.

BRIP1 VARIANT ON A FAMILIAL BREAST CANCER CASE

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BRIP1 (BRCA1 Interacting Protein C-Terminal Helicase 1) is a RecQ DEAH helicase family protein coding gene which plays an important role with BRCA1 for the double-strand break repair function and several essential pathways for the maintenance of the cell. Pathogenic variants on *BRIP1* is associated with early onset breast carcinoma. 35 years old female patient, recently diagnosed with breast cancer was reffered to our clinic for genetic consultation. She had unilateral invasive ductal carcinoma and had total mastectomy. On the pedigree analysis, we learned that her father was diagnosed with breast cancer at the age of 58 and her grandmother was diagnosed with lung cancer at the age of 50. We have performed next generation sequencing and MLPA analysis for *BRCA1* and *BRCA2* genes initially and no pathogenic variants were detected; so, we performed familial cancer panel which consists of fourteen genes associated with familial carcinomas with next generation sequencing. We identified a missense p.Ile246Val (c.736A>G) variant on *BRIP1* gene. The variant was not reported on HGMD and Clinvar previously and there were only one article that has classified this variant as "likely pathogenic". It was scored as pathogenic on multiple in silico analyses and its prevelance was statistically increased on patients over controls. The same variant was also found on the father diagnosed with breast cancer. We classifed the p.Ile246Val (c.736A>G) variant as "likely pathogenic" by ACMG criterias and gave genetic counselling to the patient about complications and inheritence of the familial breast cancer syndrome.

SEVERE PELIZAEUS - MERZBACHER DISEASE ON A CASE WITH DEVELOPMENTAL DELAY AND ABNORMAL MYELINATION

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Pelizaeus-Merzbacher Disease (PMD) is a rare disorder characterized by nystagmus and myelination abnormalities. The disorder is caused by pathogenic variants of *PLP1* (Proteolipid Protein 1) gene and it is inhereted in X-linked manner. Here we report a 3 years old male investigated in our clinic for severe neurodevelopmental delay. He was born at 39th week after noncomplicated pregnancy and the parents recognized he could not hold his head up and track objects on the 3rd month. He has had epileptic seizures similar to tonic clonic and gelastic seizures since he was two years old. He also had pharyngeal weakness and required percutaneous endoscopic gastrostomy for feeding. He has never lifted his head, walked or spoke. Microcephaly, pendular nystagmus, scoliosis, hypotonia and decorticate posture were found on physical examination. On the brain MRI, diffuse hypomyelination noticed and metabolite levels were found to be normal on MR Spectroscopy. We learned that his mother's 2 male cousins and his grandmother's 2 brothers had died due to same disorder. His karyotype analysis was normal, so we performed TruSight One sequencing panel which includes more than 4800 disease associated genes but we could not find any pathogenic variant on that either. We thought his clinical findings were compatible with PMD, so we performed MLPA analysis for *PLP1* and duplication of the gene was detected. His mother was also carrier for the duplication. He was diagnosed with connatal form of Pelizaeus-Merzbacher Disease, the family was informed on genetic inheritance and complications of the disease.

ASSESSMENT OF EXPRESSION LEVELS OF *DNMT1* AND ITS STABILITY RELATED ENZYMES IN AGE RELATED CATARACT

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DNA methylation may contribute to silencing gene expression which is a major mechanism of epigenetic gene regulation. This epigenetic modification is catalyzed by the DNA methyltransferases (DNMTs). Regulatory mechanisms of DNA methylation in lens development and pathogenesis of cataract represent exciting areas of research that open new avenues. The formation and development of age-related cataract is associated with DNA hypermethylation/hypomethylation of some genes in lens epithelial cells. This study aimed to investigate the expression levels of *DNMT1* and enzymes responsible for its stability, *UHRF1* and *USP7*. The expression levels of these genes were evaluated by qPCR in anterior capsule (n=30) and blood samples (n=30) of cataract patients. As control, blood sample of healthy individual and human lens epithelial cells (HLE B3) used. Our results indicated that *DNMT1* mRNA decreased in anterior capsule samples compared with HLE B3 cells and healthy blood sample ($p<0,05$). On the other hand, *DNMT1* and *USP7* expression levels increased in blood sample of cataract patients while expression of *UHRF1* decreased ($p<0,05$). Alteration of *DNMT1* expression level depends on *UHRF1* and *USP7* expression levels. The study supports the notion that DNMT1 and its stability related enzymes (UHRF1 and USP7) might contribute to age-related cataract pathogenesis. Also, these results would allow us to identify possible molecular targets for treatment of age-related cataract.

LETHAL MULTIPLE PTERYGIUM SYNDROME RELATED WITH *RYR1* GENE MUTATION

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Lethal multiple pterygium syndrome (LMPS) is a rare autosomal recessive disorder, characterized by intrauterine growth retardation, multiple pterygia, flexion contractures and fetal akinesia. In severe cases, affected fetuses may develop subcutaneous edema, hydrops fetalis and cystic hygroma. The etiology of LMPS is heterogeneous caused by variations in several genes including *RYR1* recently described in LMPS.

Chorionic villus sampling (CVS) procedure was performed due to the detection of cystic hygroma at the 13th week of the 3rd pregnancy of the consanguineous couple who had history of two abortus with hydrops/cystic hygroma. Cytogenetic and array-CGH analyzes of CVS material were normal. Popliteal pterygium was detected in the postmortem examination following termination of the pregnancy with hydrops developing at week 15. No mutation was detected in the sequence analysis of *CHRNG*, *CHRNA1*, *CHRND* and *RIPK4* genes. Whole exome sequencing (WES) of the parent ended with the heterozygous frameshift mutation c.5927_5927delG (R1976Pfs*6) of the *RYR1* gene while a homozygous mutation was detected in the CVS material.

Pathogenic variants of the *RYR1* gene have been implicated in a number of different disorders including congenital myopathy with fiber-type disproportion. The spectrum of RYR1-related myopathies is also expanding with the recent characterization of polyhydramnios and fetal akinesia leading to arthrogryposis multiplex congenita, also known as lethal multiple pterygium syndrome. The result emphasizes the utility of the WES for diagnosing fetal akinesia which is clinically and genetically heterogeneous and usually has also diagnostic difficulties because of it results in intrauterine death.

GENETIC COUNSELLING CHALLANGES IN PANEL TESTING OF HEREDITARY BREAST OVARIAN CANCER SUSCEPTIBILITY

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Hereditary predisposition accounts for approximately 10% of all breast and ovarian cancers. Formerly, we used to test germline mutations in *BRCA1-2*, which are high-penetrance genes, and clinical decision making was being made by the data obtained from this testing strategy. With the utilization of multi-gene panel testing, genetic counselling has become a challange in these patients. The main reason is that germline mutations with unknown association with cancer risk, known as variants of uncertain significance (VUS), are being increasingly identified. Besides, not all the tested genes are highly penetrant. So, its clinical utility is still a dilemma, mostly due to the lack of conclusive evidence on the impact of newly discovered genetic variants on cancer risk and lack of evidence-based guidelines for the clinical management of their carriers. However, the introduction of multigene panel testing for hereditary breast/ovarian cancer screening has improved clinical decision making, efficiency, speed, and costs.

We would like to report the identified mutations, and variations of genetic panel tested in our 100 high-risk families, other than BRCA1 and 2, namely, 24 genes were tested from Multiplicom's Hereditary Cancer Panel (Multiplicom.inc): *ATM, BARD1, BLM, BRIP1, CDH1, CHEK2, EPCAM, FAM175A, MEN1, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53* and *XRCC2*.

We would like to discuss the genetic counselling issues in these situations. These results improved the identification of risk-relevant alleles impacting on the clinical management of their carriers and clinical decision making of patients.

ASSOCIATION BETWEEN HYPOXIA INDUCIBLE FACTOR-1A (*HIF1A*) GENE POLYMORPHISM AND OBSTRUCTIVE SLEEP APNEA

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Obstructive Sleep Apnea Syndrome (OSAS), which is the most common sleep-related respiratory disease is characterized by recurrent episodes of apnea and accompanying intermittent hypoxemia during the night. It is a complex disease that is affected by numerous genes and various environmental factors.

Hypoxia inducible factor-1a (HIF1A); is an important transcription factor that regulates the expression of genes that induce cellular response in oxygen deficiency. In particular, the cellular response due to chronic intermittent hypoxia may provide insight into the internal aspects of pathophysiological signaling pathways of OSAS.

For this reason, we aimed to evaluate the relationship between OSAS and *HIF1A* polymorphisms in our study.

This case-control study included 80 OSAS patients and 80 healthy controls. Genotypic and allele frequencies of *HIF1A* gene related polymorphisms were determined by using MALDI-TOF MassArray method among the DNA samples obtained from peripheral bloods.

Significant results were obtained between patient and control group in terms of allele and genotype frequencies of *HIF1A* polymorphisms rs1957757 and rs12434438.

When the patient and control group were statistically evaluated at the allele level, the T allele increased the OSAS risk and this increase was statistically significant in terms of HIF1A *rs1957757* polymorphism (p=0.00297). Similarly, *HIF1A rs12434438* polymorphism was assessed at allel level, indicating that the G allele increased the OSAS risk and this increase was statistically significant (p=0.00097).

In the results of our study we observed that there may be a association between *HIF1A* gene polymorphism and OSAS, supporting the possible role of *HIF1A* in OSAS pathophysiology.

FOCAL *MED12* GENE EKZON 2 MUTATION AND FOCAL microRNA 124 LEVELS IN THE PATIENTS WITH MYOMA UTERI

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Uterine myomas are the most frequently seen tumors of female reproductive system. Myomas are mainly confronted with vaginal bleeding, infertility, pelvic pain, pelvic pressure in women. Myomas are particularly effected by the estrogen secretion. Many risk factors have been identified in myomas. These are mainly; fertility trait, diet, race, menstrual story, weight gain, hormone therapy, smoking. physical activity, family story, tube ligation story, hypertension. Many studies have been carried out in myomas in the genetic background but a major gene has not been blamed.

The recognition of the myomas can be done very quickly in these days. The most important diagnostic tool is TVUSG. When many different methods are used in the diagnosis of myomas, TVUSG is the most common and fastest diagnostic method. Although medical treatment can be applied in the treatments of myomas, the main treatment in patients is surgical treatment.

In our study, we try to explain the mechanisms of myoma formation. We investigate the focal *MED12* Exon 2 mutation and microRNA-124 expression differences in patients with hysterectomized myomas from patients with their normal myometrium tissues and from paraffin blocks of their own myomas of patients. In this study, it is aimed to investigate the effect of focal changes in the genetic structure of the patient on the formation, location and number of myomas.

A NOVEL MUTATION IN *FBN1* GENE IN A FAMILY WITH THORACIC AORTIC DISORDERS

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Thoracic Aortic Disorders (TAD), are a group of diseases including aneurysms and dissections of the thoracic aorta and important causes of morbidity and mortality. Etiology is complex and heterogeneous. The genetic forms can be divided into syndromic and nonsyndromic. The prototype for syndromic H-TAD is Marfan Syndrome. It is an autosomal dominant multisystemic disorder affecting ocular, skeletal, cardiovascular system caused by mutations in the *FBN1* gene.

Our patient is 39-year-old male born from a non-consanguineous parent. His height was 175 cm and weight was 56 kg. He had myopia, astigmatism, scoliosis, pectus carinatum, chest asymetria, malar hypoplasia, striae, aneurysm of ascending aorta and aortic regurgitation. He fulfilled the Ghent criteria. His one brother, nephew, father, aunt and grandmother died at early ages because of aortic disorders. Also, their mean height were taller then normal. Proband has 4 healthy sisters.

FBN1 gene analysis was performed with Ion Torrent NGS systems, analysed with Ion Reporter software and visualised with IGV. NM_000138.4:c.7487G>C, p.Cys2496Ser mutation was found.

DISCUSSION: H-TAD is genetetically heterogen. Uptill now *FBN1*, *MFAP5*, *MAT2A*, *TGFBR1/2*, *TGFB2/3*, *SMAD2/3*, *ACTA2*, *MYH11*, *MYLK*, *PRKG1* genes have been identified. *FBN1* mutations are the most common. 2 patients with the same aminoacid change have been diagnosed with non-syndromic H-TAD. But our mutation's nucleotid change was different. This variant is also estimated pathogenic with in silico prediction tools. Mutation analysis of affected family members are planned.

In families with multiple premature deaths, H-TAD must be kept in mind and genetic analysis should be performed for early diagnosis, prognosis and prevention.

LYSINURIC PROTEIN INTOLERANCE AND HOIP DEFICIENCY IN A BOY WITH HOMOZYGOUS MISSENSE MUTATION IN THE *RNF31* GENE AND HOMOZYGOUS DELETION OF *SLC7A7* GENE

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Lysinuric protein intolerance (LPI) is a rare metabolic disease resulting from recessive-inherited mutations in the *SLC7A7* gene encoding the cationic amino-acids transporter. LPI is a multisystemic disease with a variety of clinical symptoms such as hepatosplenomegaly, osteoporosis, hypotonia, developmental delay, pulmonary insufficiency or end-stage renal disease.

Inherited, complete deficiency of human RNF31 (HOIP), a component of the linear ubiquitination chain assembly complex, underlies autoinf lammation,immunodeficiency and infections.

Here we report on an 8 months old boy with LPI and HOIP deficiency a third child born to a consanguineous couple and delivered via caesarian section. The main clinical findings developmental delay, pulmonary insufficiency, hepatosplenomegaly and hypotonia. Laboratory findings anemia, trombocytopenia, hypertriglyceridemia, high serum ferritine (35.000) and lactate dehydrogenase levels. Bone marrow morphology is compatible with hemophagocytosis. During follow-up respiratory distress was progressively increased, recurrent infections and autoinflammation findings were observed.

Whole exome and targeted sequencing in the proband revealed the presence of one homozygous missense variant c.1573C>T, this variant leads to a p. Arg525Cys change in *RNF31* and deletion of exome 4-? of *SLC7A7* gene, respectively. Heterozygous *RNF1* variants were confirmed in both mother and father. This variant was found in ExAC and in CentoMD databases as heterozygote manner and regarded as disease causing based on the in-silico prediction tools (mutation taster, SIFT, Provean). MLPA and Rna expression studies are ongoing projects. As far as we know our case is the first reported case of homozygous *SLC7A7* deletion and homozygous *RNF31* variation seen together, and the second reported case of HOIP deficiency.

MUTATION SPECTRUM OF *TSC1* AND *TSC2* GENES IN PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX: IDENTIFICATION OF 3 NOVEL MUTATIONS

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Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutenous syndrome. It results from mutations in either *TSC1*, at 9q34, or *TSC2*, at 16p13.3. A causative mutation for the disorder can be identified in approximately 85-90% of patients with a clinical diagnosis of TSC. Herein, we report molecular analysis results and phenotype-genotype correlations in 6 TSC patients.

Six patients clinically diagnosed as TSC were referred to our department for molecular analysis. *TSC1* and *TSC2* genes were analyzed using a targeted next generation sequencing panel (TruSight® Cancer Sequencing Panel). Variant interpretation was done in accordance with American College of Medical Genetics recommendations. Sequencing failed to detect a mutation in one patient. In this patient, Multiplex ligation-dependent probe amplification (MLPA®) was performed

Three patients carried a heterozygous mutation in *TSC1*, while remaining three carried mutations in *TSC2*. Three novel mutations (one in *TSC1*, two in *TSC2*) were defined. A large deletion of the *TSC2* gene was detected in one patient. The patients showed a wide spectrum of phenotypic features.

In addition to the 3 novel mutations reported herein the spectrum of *TSC1* and *TSC2* gene mutations has been expanded by this study.

SCREENING OF CANDIDATE PROGNOSTIC BIOMARKER GENES IN PEDIATRIC PRECURSOR B-ALL

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ALL is the mostcommon malignancy diagnosed in children, representing nearlyone-third of all pediatric cancers. BCP-ALL is characterized by recurring cytogenetic and molecular genetic abnormalities. In our study, we aimed to investigate recently identified genomic risk factors that affect the pathogenesis of BCP-ALL, with affects on their molecular mechanism and prognostic significance by NGS and geneexpression analyses in childhood BCP-ALL. The secondary aim of this study was to correlate the data obtained from study with some biological and clinical features as characteristic of pediatric BCP-ALL patients, cytogenetic/molecular aberrations and prognosis based on treatment protocol criteria.

Blood samples were obtained from 45 patients with BCP-ALL who were admitted to Hospital and 10 normal healthy children. We used NGS method to study the *ZAP70, TSLP, JAK2, CRFL2, IKZF1, PAX5, EBF1, CREBBP, FOXO3, RB1, ZNRF1, NR3C1, NF1* and *ERG* genes. Hot spot regions of these genes were sequenced and gene expression leves were performed using qRT-PCR.

Among the 14 gene analyse of the 45 pediatric BCP-ALL patients, we identified 328 gene variants including 104 deletions, 28 insertions, 75 duplications, 47 indels, 74 single nucleotide mutations and polymorphisms by NGS in the genes. Fifteen of the identified mutations were novel mutations in present study. Among them, the most commonly mutated gene was *CRFL2* (14,3%), followed by *NR3C1* (12,8%), *RB1* (9,7%), *IKZF1* (9,1%), *PAX5* (8,8%), *EBF1* (7,9%), *JAK2* (6,0%), *CREBBP* (5,45%).

We detected that *ERG* and *JAK2* gene expressions were associated with different pathophysiological and clinical features, such as peripheral blood cell count and treatment protocols in our study groups. In conclusion, this study has revealed important findings that canbe reported for the first time in the literature.The variants are likely to lead to ending of the products of genes, the different splicing of the possible transcripts and transformation of the amino acids. Our data suggest a prognostic role of studying genes expression levels and mutation profiles in pediatric BCP-ALL.

ANALYSIS OF THE *CD40* AND *CD40LG* IN TURKISH HYPER IGM SYNDROME: MUTATION PROFILE AND DESCRIPTION OF FIVE NOVEL MUTATIONS

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Hyper IgM syndromes (HIGM) is a group of primary immune deficiency disorders characterized by defective CD40 signaling. Five types of hyper IgM syndrome have been characterized: Hyper-IgM syndrome type 3 (autosomal recessive) (MIM: 606843) is characterized by mutations of the *CD40* gene and Hyper-IgM syndrome type 1 (X-linked) (MIM 308230), characterized by mutations of the *CD40LG* gene. Patients with HIGM syndrome are susceptible to recurrent and severe infections and in some types of HIGM syndrome opportunistic infections and an increased risk of cancer as well. The disease is characterized by decreased levels of immunoglobulin G (IgG) in the blood and normal or elevated levels of IgM.

The aim of this study was to evaluate the spectrum of *CD40* and *CD40LG* gene mutations in Turkish HIGM patients. We present a molecular analysis of 8 Turkish HIGM patients. All mutant alleles were identified, including 6 *CD40LG* mutations 3 of which were novel and 2 novel *CD40* mutations. *CD40LG* mutations were c.31C>T (p.Arg11Ter), c.755G>A (p.Gly252Asp) were previously reported whereas c.89 T>A (p.Val30Asp), c.446G>A (p.Ser149Asn), c.616_619delCTCA (L206EfsX35) mutations were novel. Novel *CD40* mutations were c.170_172delTAA and one stoploss mutation c.830_833delAGTG.

Herein, we describe on 8 HIGM patients of Turkish origin and report five novel mutations in *CD40* and *CD40LG* genes.

A CASE WITH MACROCEPHALY AND MOTOR-MENTAL RETARDATION: A NOVEL MUTATION IN *PTEN* GENE

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The term *PTEN* hamartoma tumor syndrome (PHTS) refers to a spectrum of disorders including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus-like syndrome, and caused by germline mutations in the phosphatase and tensin homolog (*PTEN*) gene. The diagnosis of PHTS was established in the proband by identification of a heterozygous germline pathogenic variant in *PTEN* gene. Here, we report a family with PHTS and a novel mutation in *PTEN* gene.

A 4-year-old male was referred to pediatric genetics outpatient clinic because of macrocephaly and motor-mental retardation. On clinical examination, macrocephaly, coarse face, hypoplastic alae nasi, micrognathia and a papillomatous lesion in the axillary region were detected. The patient's mother and brother had also macrocephaly. With these features, he was considered to have as PHTS. Sequence analysis of *PTEN* gene revealed a novel heterozygous c.345_346insTG (p.D116Wfs*19) mutation in exon 5. This mutation was predicted to be disease causing using in-silico analyses. The parents of the patient were analyzed and the mother was detected to carry the same heterozygous mutation.

The most serious consequences of PHTS is related the increased risk of cancers. In this regard, any individual with a *PTEN* pathogenic variant should be regularly screened for detection of any tumors at the earliest and most treatable stages. Therefore, regular controls were planned in affected family members.

Additionally, nearly 40% of pathogenic variants in *PTEN* gene are found in exon 5, which encodes the phosphate core motif. In this respect, the mutation in our patient is compatible with the literature.

HOW DOES GENETIC VARIATIONS AFFECT CLINICAL OUTCOMES IN TETRALOGY OF FALLOT CASES?

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TOF (Tetralogy of Fallot) is one of the most common cyanotic heart disease. The most important problem after corrective surgery is PR (pulmonary regurgitation) which creates volume load in the RV(right ventricle). For this reason, reoperation for pulmonary valve replacement is necessary usually. Postoperative changes are not affected by operation style and timing. Therefore, genetic determinants of remodelling of the RV seem to be important. The aim of study was to assess the effects of changes in *HIF1A* gene in remodelling of the RV.

DNA amplification was performed by PCR. The study included 32 TOF patients and 30 healthy children. Patients and control group were evaluated for *HIF1A* gene polymorphism. The distribution of *HIF1A* allele frequencies was as follows: *HIF1A145T* allele was present in 24(75%) and *HIF1A145C* in 8(25%) of the patient group. *HIF1A145T* allele was detected in 19(63%) and *HIF1A145C* in 11(37%)of the healthy group(p: 0,27). Pro582Ser missense mutation in 12th exon was detected in 6(18%) of the patients and only 1(3%) of the control(p=0.05). Patients with this mutation were found to have 2. and higher degrees of PR. Patient and healthy group were evaluated in terms of GT repeats in 13th exon. The GT13 repeat was observed in 6(19%) patients and none of the healthy group(p: 0.013) where the GT15 repeat was significantly lower in the patient group(p: 0.025). Patients with GT13 repeat were also found to have 2 and higher degrees of PR.

In the case of TOF, variations in the *HIF1A* gene affect the right ventricular remodelling.

Poster Presentation Abstracts

A NOVEL INSERTIONAL TRANSLOCATION IN A PATIENT WITH INFERTILITY AND UNDIAGNOSED MILD INTELLECTUAL DISABILITY

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Infertility is defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. In approximately 40% of the cases the etiology is unclear. Balanced chromosomal rearrangements such as autosomal reciprocal translocations and insertions can be related to infertility. The frequency of balanced chromosomal rearrengements in azoospermic men and oligozoospermic men is 0.6% and 1.7%, respectively. A 39-year-old man with primary infertility and mild intellectual disability was presented.

Conventional cytogenetic technique was used for cytogenetic analysis. Array-based Comparative Genomic Hybridization (aCGH) analysis applied by Agilent SurePrint G3 CGH+ SNP Microarray Kit (4x180K) and also multiplex PCR protocol was applied for the Y chromosomal microdeletion test.

Sperm analysis showed complete azoospermia. Classical chromosome analysis revealed that our patient carried a *de novo* insertional translocation 46, XY, inv ins(18;2)(q11.2;q13q22). On aCGH test no deletion or duplication was found arr(1-22)×2,(XY)×1. Also Y microdeletion test showed that the AZF region was intact.

Although such translocations are generally unharmful for the carrier, they are associated with decreased fertility and an increased risk of unbalanced gametes. Balanced chromosome abnormalities detected by conventional karyotype analysis can be found to be unbalanced at the molecular level. Small microdeletions and duplications may not be catched by aCGH. In addition to infertility on physical examination patient was noted to have mild intellectual disability. Therefore, it needs to be sequenced by a next generation sequencing (NGS) technique in order to understand whether there is any variation in this region.

THE AUTOIMMUNE REGULATOR (*AIRE*) GENE VARIANT ASSOCIATED WITH AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 1

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Autoimmune Polyendocrine Syndrome Type 1 (APS1) (OMIM #240300) is an autosomal recessive genetic autoimmune disease of juvenile onset, combining chronic mucocutaneous candidiasis and various autoimmune endocrinopathies, the most common of which are hypoparathyroidism and adrenal insufficiency. APS1 is caused by mutations of both sets of the autoimmune regulator (*AIRE*) gene. The *AIRE* gene located on chromosome 21q22.3 and normally confers immune tolerance. We investigated cases with homozygous mutations in *AIRE* gene and chronic mucocutaneous candidiasis and Addison's disease.

Genomic DNA was extracted from whole blood; the exonic regions of *AIRE* were amplified by Polymerase Chain Reaction (PCR), Sanger sequenced bidirectionally and then analyzed using the software Sequence Pilot. We report 16-year-old male patient, whose parents are primary cousins, is on hydrocortisone treatment with addison's disease. Chronic mucocutaneous candidiasis is present in the patient and APS1 is pre-diagnosed. On physical examination, candida infections were detected in the hands and toes. *AIRE* gene sequence analysis revealed a p.Ser412Argfs*68 (c.1233delC) homozygous variant at 10th exon. Bioinformatics programs such as mutation tester predicts that the mutation is the cause of the disease. Clinical findings and genetic analysis revealed APS1 in the patient.

Recently, typical *AIRE* gene mutations have been identified in patients who have only one of these three cardinal features, but have other less common APS1 associated autoimmunity. Pathogenic variants in *AIRE* gene result in a failure to eliminate auto-reactive T cells in the thymus, resulting in autoimmune manifestations seen in APS-1.

A CASE STUDY OF PSEUDOHYPOPARATHYROIDISM TYPE IA, A MUTATION OF THE *GNAS* GENE

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Parathyroid Hormone (PTH) affects specific plasma membranes, specific target cells called type 1 PTH receptors, which express G protein-bound receptors. The 13 exons of *GNAS* gene (OMIM 139320) localized at 20q13.32 encode the G protein subunit alpha S, which combines PTH receptors to stimulate adenyl cyclase, which plays an important role in bone development. Pseudohypoparathyroidism (PHP) Type 1 is associated with genetic and epigenetic mutations in the *GNAS* (guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1) gene. Various variants of PHP are described and all are rare. We investigated for the heterozygote mutation in the *GNAS* gene.

Genomic DNA was extracted; the exonic regions of the *GNAS* gene were amplified by PCR and Sanger sequenced. An 11-year-old male patient with no parental involvement was treated with hypoxalemia and tetanus for 3 years with calcium replacement therapy. Serum calcium was 7.9 (↓), and PTH 733 (↑) was detected in the analyzes. On physical examination, pectus excavatum, bilateral hand and foot brackydactyle 4 and 5 fingers, height, weight and head circumference were within normal limits. In *GNAS* whole gene analysis the heterozygous variant p.Pro376Leu (c.1127C> T) was detected at the first exon. Bioinformatics programs, such as the mutation tester, predict that substitution may be the cause of the disease. Clinical findings and genetic analysis revealed pseudohypoparathyroidism type 1a in the patient.

We report that the *GNAS* gene mutation is for p.Pro376Leu (c.1127C> T) and contributes to the mutation spectrum associated with these disorders.

NEWLY DETECTED 20 YEARS OLD NOONAN SYNDROME

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It is aimed to genetically evaluate a 20-year-old patient who referred to medical genetic clinic for the cause of hearing loss.

From the medical story of a patient with a hearing loss It is learned that he was born in the 36 weeks of pregnancy, had congenital pulmonary stenosis and cryptorchidism. Firstly, Echocardiography and hearing tests were performed than chromosome analysis was performed using peripheral blood. After the result of all these tests and the clinical findings, DNA extraction of peripheral blood and full gene sequence analysis of *PTPN11* was performed using Next Generation sequence analysis in the patient who was considered to have noonan syndrome

Modarate degree pulmonary stenosis at echocardiography and 60% hearing loss was detected in the hearing test. Karyotype analysis result was 46, XY. *PTPN11* gene Pathogenetic heterozygote c.923a> G p.N308S (rs121918455) mutation was detected in a complete gene sequence analysis in which all the exogenous regions and exon-intron junctions were analyzed.

More than 90 mutations causing Noonan syndrome have been identified in the *PTPN11* gene. Due to the p.Asn308Ser mutation that found also in our case, 308th codon is thought to be the hot spot. Noonan syndrome is characterized by mildly unusual facial characteristics, short stature, heart defects, bleeding problems, skeletal malformations, and many other signs and symptoms.In our case, crooked hair, low set ears, short upward nose, triangular face, micrognathia, discrete and downward nipples, short mane neck, pectus carinatus, epicentral folds, ptosis, moderate degree learning difficulty.

MUENKE SYNDROME AND NEW ADDITIONAL FINDING: BILATERALLY BIFID THUMB

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Muenke syndrome is an autosomal dominant disorder characterized by craniosynostosis, hearing loss, intellectuel disability. This syndrome is caused by mutations *FGFR3* gene, a unique point mutation c.749C>G in exon 7- P250R. Muenke syndrome shows phenotypic heterogeneity which probably caused by reduced penetrance and variable expressivity.

A 6-month-old female child referred to our clinic for the assesment of her dysmorphic features. She was the first child of healtly non-consanguineous parents. She was born at term and her birth weight was 3300 g. Her physical examination demonstrated microcephaly, asymmetry of the skull and face, brachycephaly, anterior plagiocephaly, proptosis, down slanting palpebral fissure, bifid thumb on both hands, high palate and hemanjiom in the forehead. Echocardiography, hearing test and abdomen ultrasonography were normal.

Chromosome analysis revealed a normal 46,XX karyotype. Mutation analysis of *FGFR3* revealed a missense mutation in exon 7, c.749 C>G, with a resultant amino acid change from proline to arginine at codon 250 (P250R), in keeping with Muenke syndrome.

Muenke syndrome has craniofacial, auditorial, musculoskeletal and neurodevelopmental findings. Craniosynostosis, carpal and/or tarsal bone fusion, brachydactyly, broad toes, broad thumbs, and/or clinodactyly were common skeletel findings but bifid thumb has not been described in patients with Muenke syndrome. Hearing loss is seen in about 40 to 100 percent of patients in the literature but our patient's hearing was normal. We hope the clinical features that we present in our case, would be helpful for full comprehension of karyotype/phenotype correlation in patients with Muenke syndrome.

A RARE 22q13.3 DELETION (PHELAN-MCDERMID) SYNDROME

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Genetically revealing any cause of the illness of the 9 months patient who applied with the neonatal hypotonia, not sucking and not holding head.

Karyotype and chromosome analysis was performed for parents and the current index case by using heparinised peripheral blood samples. The DNA sample obtained from the peripheral blood was studied using the Agilent Oligonucleotide Microarray 8*60K microarray system. Results was analyzed in the analysis program. Agilent CytoGenomic (Edition 2.5.8.1/GRCh37/hg19). The presented patient was dignosed by echocardiography, brain MR and urinary USG clinically

The result of karyotype analysis of patient who applied to the Suleyman Demirel University Medical Genetics Department, were found 46, XX, del 22q.At the end of the microarray study for the determination of 22q deletion region, deletion of 8911 kb including 22q13.2 and 22q13.33 regions was detected. (Marker number 226).Urinary USG and echocardiography results were normal in agreement with age but corpus callosum dysgenesis was detected in brain MR

The patient was evaluated for 22q13.3 deletion syndrome also known as Phelan-McDermid syndrome. Phelan-McDermid syndrome, is a contiguous gene disorder resulting from deletion of the long arm of chromosome 22. This syndrome is characterized by neurological deficits which include global developmental delay, moderate to severe intellectual impairment, absent or severely delayed speech, and neonatal hypotonia. In our case, the symptoms are more severe due to large deletion (8911KB). Deletion includes the gene *SHANK3* that encodes a scaffold protein in the postsynaptic densities of excitatory synapses, connecting membrane-bound receptors to the actin cytoskeleton.

CASE REPORT: A PATIENT WITH HUNTINGTON'S DISEASE WITH FAMILY HISTORY

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Hungtington's disease is an autosomal dominantly inherited neurodegenerative disorder, characterized by choreic movements, dystonia and progressive demans. The responsible protein Huntingtin occurs via increased number of CAG trinucleotide [glutamine] repeats. Since CAG repeats increase during male gametogenesis, the disease occurs earlier than 30-50 years old, in case of a transmission through an affected father. Psychiatric symptoms are a significant aspect of Huntington disease. The presentation of these symptoms is highly variable in patients, and their course does not fully correlate with motor or cognitive disease progression.

A 30 years old female patient referred to our hospital with symptoms as forgetfulness, involuntary movements, impaired coordination, inability to walk and speak, and depression since a few years. Her older sister diagnosed with Huntington's disease a couple of years ago. Her father died with Parkinson's disease when he was 45 years old. Her Cranial MR showed atrophy in caudate nucleus and putamen, seconder to diffuse cerebral volume loss. Her EEG showed low amplitudes, which is associated with cortex degeneration.

She was diagnosed with Huntington's disease by using DNA sequencing. Increased (>40) CAG repeats was shown on exon 1 of *HTT* gene (on chromosome 4p16.3).

Overall, we confirmed that our patient, who was diagnosed and treated with depression in the department of psychiatry for many years, clinically and genetically diagnosed with Huntington's disease and her psychiatric symptoms does not fully correlate with motor or cognitive disease progression.

MTHFR C677T/A1298C POLYMORPHISMS ARE CORRELATED WITH HABITUAL ABORTUS

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Folates are required for the synthesis of nucleotides, the precursors of DNA and RNA. Two common polymorphisms (C677T and A1298C) in methylenetetrahydrofolate reductase (MTHFR), a critical folate-metabolizing enzyme in nucleotide synthesis, may increase the risk for habitual abortus.

The 677TT variants, with 30% reduced activity, are 10-15% of Caucasians. Its heterozygotes have 60% reduced activity and form 40% of population. The 1298CC variants, with 60% reduced activity, are 12% of Caucasians. *MTHFR* 677TT individuals who maintain adequate folate levels have normal homocysteine (Hcy) levels, because folates stabilize the enzyme and enable it to function normally. When folates are low, they have mild hyperhomocysteinemia. The *MTHFR* 1298A→*C* polymorphism has been associated with lower MTHFR activity, but not associated with decreased plasma folate levels or increased plasma Hcy levels. However, individuals who are heterozygous for both polymorphisms have higher plasma Hcy levels and reduced plasma folate levels.

All 30-40 years old 33 female patients referred to our hospital with habitual abortus for last six months. Five of them were diagnosed with *MTHFR* C677T homozygosity and eight of them were diagnosed with *MTHFR* C677T/A1298C double heterozygosity by using DNA sequencing. All *MTHFRTT* and five of the double heterozygote patients had low plasma folate levels, and their folate supplementation were started to normalize their MTHFR activities.

We would like to illustrate the critical effect of MTHFR expression on nucleotide synthesis, and the importance of genetic testing for the *MTHFR* or other folate-metabolizing enzymes' polymorphisms for prenatal folate replacement to normalize the patient's enzyme activity.

TWO PATIENTS WITH MOWAT-WILSON SYNDROME

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Mowat-Wilson syndrome (MWS) is characterized by distinctive facial appearance in association with variable moderate to severe intellectual disability, epilepsy, Hirschsprung disease (HSCR) and multiple congenital anomalies including agenesis of corpus callosum and hypospadias, congenital heart disease and eye defects. MWS is caused by deleterious *de novo* heterozygous mutations in the *ZEB2* gene. We present two patients diagnosed as MWS with a novel and a previously reported mutations.

Four-year-old female patient has been followed with developmental delay, typical dysmorphic face and epilepsy. In the natal history, she was operated for Hirshprung disease during newborn period. Her weight, height and head circumference were under third percentile. She could say 10-15 words, but could not make a sentence. She had generalized tonic-clonic seizures. Mutation analysis of *ZEB2* gene revealed heterozygosity for c.1672 A>T(p.Lys558) which is a previously reported mutation.

A fourteen-year-old boy was diagnosed as MWS with a distinctive facial appearance such as widely-spaced eyes, broad nasal bridge with a rounded nasal tip, prominent columella, prominent and pointed chin, medially flaring large eyebrows, large and uplifted ear lobes with a central depression, and smiling expression. He had been investigated for moderate mental retardation and diagnostic tests were performed previously by another clinic. A novel mutation, c916G>A (p.Gly306Ser) (heterozygote) in *ZEB2* gene was found.

Although MWS was firstly defined in 1998, the diagnostic criteria and genotip-phenotype correlations have not been established yet. Reporting novel mutations and clinical features will be valuable in establishing these issues.

MLPA METHOD DOES NOT ALWAYS CONFIRM THE RESULTS OF ACGH: A STUDY OF *KANSL1* GENE DELETION PATIENTS

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Microdeletion and microduplications are detected on chromosomes as a pathological subgroup of copy number variants of DNA. It has become easier to identify such chromosomal syndromes after use of array-based comparative genomic hybridization (aCGH) technology. One of them is the 17q21.31 microdeletion and microduplication syndrome.

A 500-650 kb sized copy loss on 17q21.31 results in a phenotype which was described as Koolen-de Vries Syndrome (KdVS) including mental retardation, epilepsia, hypotonia and characteristic facial features. Today, we know that haplo-insufficiency of *KANSL1* gene located in this region is responsible for these findings.

A total of 30 patients with *KANSL1* deletion detected during aCGH analyses were enrolled in the current study. All patients were analyzed by Multiplex Ligation-Dependent Probe Amplication (MLPA) method in order to confirm the results.

As a result of this study, only three of the 30 patients had a deletion of *KANSL1* gene detected by both methods and duplication was found in one patient.

As a result of the study, our results showed that when we detect a copy number variation by aCGH, before making a conclusion and genetic counseling, we need to confirm or decline the results with another method such as MLPA and clinical assessment should be done by evaluating the results of both methods.

TRANSCRIPTOME ANALYSIS OF IMMUNOSUPPRESSIVE CHARACTERISTICS IN BONE MARROW AND WHARTON'S JELLY-DERIVED HUMAN MESENCHYMAL STEM CELLS

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Nowadays, due to their immunosuppressive properties, Mesenchymal Stem Cells (MSC) are used in allogeneic transplants and can be isolated from different tissues. In this study, it was aimed to investigate the immunosuppressive properties of bone marrow (BM) and wharton jelly (WJ) originated immunotherapeutic agents in terms of bioinformatics, which are among the most studied sources for renewable medicine.

RNA sequencing data(Illumina/HiSeq 2500, 35X) was retrieved from open access databases via Gene Expression Omnibus (GSE). The dataset contains BM-MSC and WJ-MSC (GSE35585). Reference transcriptome was aligned using TopHat2 tool. Gene expression profiles were determined using EBSeq tool which is a package of R programming language. At least 2 times the change and $p<0.05$ significance of gene expressions were filtered and analyzed.

In whole transcriptome analysis, 26229 genes were annotated and 414 of these genes were found to be significantly altered. In consequence of our clustering with pathway analysis, we have reached 17 genes. The expression of *CASP8, CHUK, CD59, SERPINB2, DUSP6, OASIS3, THBD, BCL10, ECSIT,TYK2* genes decreased significantly; the expression of *DUSP4, THY1, NFKBIA, MME, IGF2R, DPP4, TP53* genes increased significantly.

In the sequel of gene expression and pathway analysis, the immune suppressor properties of WJ-MSCs have been shown to be significantly increased compared to those of BM-MSCs. In consequence of our previous studies, we observed that IL-10 increased in the WJ-MSCs, which was co-cultured with stimulated T-cells. IL-10 affects the Jak-STAT pathway, which plays a key role in immunological regulation. *SOCS5* gene is the negative regulator of this pathway, it is significantly reduced in WJ-MSCs. Owing to these properties, WJ-MSCs are important candidate for allogenic use in the clinic.

A PATIENT WITH TWO SYNDROMES DUE TO PATERNAL UNIPARENTAL DISOMY OF CHROMOSOME 2 (pUPD2) RELATED WITH HOMOZYGOUS NOVEL MUTATIONS OF THE *RAB3GAP1* AND *UNC80* GENES

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Warburg Micro syndrome (WARBM) is a rare, genetically heterogenous, autosomal recessive syndrome characterized by severe mental retardation, microcephaly, ocular defects including microphthalmia, congenital cataracts and optic atrophy, brain anomalies in particular corpuscallosum hypoplasia, truncal and axial hypotonia, spasticity and hypogonadism. The four WARBM subtypes which are clinically indistinguishable is caused by mutations of *RAB3GAP1, RAB3GAP2, RAB18* or *TBC1D20* genes, *RAB3GAP1* being the most common gene involved.

In records of a 14-year-old male patient whose parents are not relative, with characteristic WARMB findings was no mutation in *RAB3GAP1* and *RAB3GAP2* genes detected by direct sequencing when he was 1 year and 8 months of age. Whole exome sequencing (WES) analysis of the patient revealed two novel homozygous mutations in both *RAB3GAP1* (p.P222fs) and *UNC80* genes (p.P487T). Sanger sequencing confirmed that the same mutations as heterozygous was present only in the patient's father. In the homozygosity analysis showed that both copies of the patient's chromosome 2 were of paternal origin. In the patient, because of overlapping findings of the both syndrome, the presence of IHPFR2 syndrome in the patient was undiagnosed until the end of the analysis.

Medical genetics focuses on the relationship between observed phenotypes and their underlying genotypes, modes of transmission, and risks of recurrence. When two overlapping Mendelian diseases in the same patient creates phenotypic complexity and diagnoses may be difficult for the physician. Diagnostic whole-exome sequencing affords opportunities for providing insights into relationships between multi-locus genomic variation and disease.

BACKGROUND OF A CARRIER FAMILY WITH A LONG INVERSION OF CHROMOSOME 2 DETECTED VIA KARYOTYPING AND aCGH ANALYSIS

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Inversion is an almost innocuous chromosomal rearrangement inside the entire chromosome which breakpoints occur and reattach in the reverse direction on a single arm or both on a short and on a long arm, namely as paracentric (0.1 to 0.5‰) and pericentric (0.1 to 0.7‰) inversion, respectively.

Here, we report one exception to belie the reputation of being harmless; a carrier family spreads over a three generation with a long pericentric inversion that comprised about two-third of the chromosome 2 (p11.1q37) who has the risk of producing nonviable recombinant gametes. The proband is a healthy young woman suffering with a loss of two pregnancies in the seventh weeks of gestation. The cytogenetic analyses of the related family members; healthy father, two healthy elderly brothers, and one nephew who has epilepsy, autistic behavior and dysmorphic feature; ended with the same pericentric inversion. To detect the possible relationship between the inversion and the clinical findings of the affected nephew, array comparative genomic hybridization (aCGH) analysis was performed and no gain or loss was detected on the breakpoint regions. More likely, these associations are fortuitous; aCGH analysis endorse this interference.

As a rule, any chromosome with a long inversion segment, about the 70% of the whole chromosome like the presented case; would imply the highest risks. Because of this, to have a viable healthy gamete, it seems premature to recommend prenatal and preimplantation genetic diagnosis of all individuals in this situation, is well taken.

A CASE OF POLAND SYNDROME ASSOCIATED WITH CONGENITAL HYPOTHYROIDISM AND DEXTROCARDIA

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Poland syndrome (PS) is a group of congenital anomalies characterized by complete or partial agenesis of the pectoralis major muscle variably associated with other thoracic malformations and ipsilateral hand deformities. The syndrome is more common in males and affects predominantly to the right side. The incidence varies 1-10 in 100,000. In some cases, dextrocardia, lung herniation, renal, vertebral malformations have been described. Congenital hypothyroidism has not been reported and here, we presented a boy who has PS with dextrocardia and congenital hypothyroidism.

A 6-year-old boy was referred to our department with chest deformity. He was also diagnosed congenital hypothyroidism. There was no family history of interest. Patient has depressed left thorax with amastia and brachysyndactyly in left hand. Radiological examinations showed dextrocardia and absence of the left hand intermediate phalanxes. Thorax CT revealed hypoplasia of the left pectoralis major and confirmed dextrocardia. Thyroid and abdomen US were normal. TSH and free T4 were 6,74 (0,34-5,60) mU/l and 1,07 (0,54-1,24) pg/ml respectively under medication.

PS is a very rare thoracic deformity syndrome which is reported to be seen predominantly in males and right side of their bodies. However, as recognised in our case, left side affected patients could be accompanied with dextrocardia. In addition, hypothyroidism has not been reported in PS previously. In our case, congenital hypothyroidism was diagnosed. Although it can be coincidental, being part of the syndrome can not be ignored.

10q26 DELETION SYNDROME AND 22q13 DUPLICATION SYNDROME, IN TWO CASES

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We present here two cousins with 10q26 microdeletion in a family. The first case is a 2-year-old female who was referred by facial dysmorphism. She was the second child of healthy, non-consanguineous parents. Two cousins of the case described the developmental delay. Growth retardation was reported in the antenatal period. Medical history revealed postnatal growth retardation, atrial septal defect, patent foramen ovale, hypothyroidism developmental dysplasia of the hip. Facial dysmorphism, proximal radioulnar synostosis, neuromotor growth retardation and strabismus were detected in physical examination. The other case was a 9-month-old female who had growth and psychomotor retardation, atrial septal defect, peripheral pulmonary stenosis, kidney stones, facial dysmorphism.

Findings suggest that both cousins have the same microdeletion syndrome and chromosome analysis was normal in both cases. An array CGH analysis was showed a 9.57 MB loss in 10q26, a 2.49 MB gain in 22q13 and 11 MB loss in 10q26, a gain of 2.8 MB in 22q13 in first and second cases, respectively. Chromosome analysis of both parents was normal. But a high-resolution banding (HRB) and a FISH study with subtelomeric probes revealed a translocation between 10q and 22q in the father of the first case and the mother of the second case who are siblings.

In the cases of microdeletion syndromes repeating in families, translocations in the parents should be investigated carefully using karyotyping, HRB, array CGH and FISH methods.

DE NOVO 10p15.3 MICRODELETION IN MONOZYGOTIC TWINS

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Submicroscobic deletion of 10p15.3 rarely reported and is associated with intellectual disability, developmental delay, motor delay, brain anomalies, hypotonia nad seizures. All reported deletions of 10p15.3 varied in size between 0,15 and 4 Mb. The severity of patients' phenotype varies between patients and doesn't correlate with the size of deletion.

Here we present a monozygotic twin female with *de novo* 10p15.3 deletion with the size of 0,85 MB. The index patient (twin 1) is 1 years old and twin 2 died at 40 days old.

The index patient has high palate, strabismus, blue sclera, depressed nasal root, prominent ears, pectus excavatum, inverted nipples, hypotonia. Single umbilical artery was prenatal ultrasonographic findings of the patient. Her echocardiologic evaluation revealed atrial septal defect.

Twin 2 had high forehead, short neck, hypertrophic cardiomyopathy, secundum ASD, vestibuler anus, hemivertebra, hypotonia, single umbilical artery. Ultrasonographic evaluation revealed renal agenesis. The patient died due to renal insufficiency.

CGH array analysis of twins revealed a *de novo* deletion between 10p15.3ptel region with approximately 0,85 MB (breakpoints:136361-992174). The subtelomeric FISH analysis of twins confirmed the deletion of 10ptel. The array CGH and subtelomeric FISH analysis of parents are normal.

Up to date only 22 patients were reported and the phenotype-genotype correlation of 10p15.3 microdeletions is unclarified. The characterization of newly described clinical features in our patients gives important implications for prognosis and counseling of patients with 10p15.3 microdeletion. Clinical description of new patients with 10p15.3 deletion will be helpful to describe the genotype-phenotype correlation.

THE CO-EXISTENCE OF NABLUS MASK-LIKE FACIAL SYNDROME AND KLINEFELTER SYNDROME

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Nablus mask-like facial syndrome (NMLFS) is a rare microdeletion syndrome. A mask-like facial appearance is the characterized symptom of disease. Here we report the co-existence of NMLFS together with Klinefelter Syndrome in a patient, for the first time in the literature, to the best of our knowledge.

A five years old male patient was referred to our clinic because of speech delay, growth retardation, mental retardation and dysmorphic features. He was a born at 38 weeks gestational age to non-consanguineous parents. His weight, height and head circumference percentiles were <3p at the time of physical examination. Microcephaly, hyperthelorism, upper epicanthus, wide nasal base, high arched plate, micrognatia, protruding ears and hypomimic, mask-like face were the other physical examination findings. His electrocardiogram, hearing test, abdominal USG and cranial MR were normal and Denver II developmental screening test showed development delay.

The patient's karyotype was 47,XXY compatible with Klinefelter syndrome. Since this karyotype was not enough to explain the patient's dysmorphic features and motor and mental retardation we performed microarray analysis. The microarray analyses revealed a 5,024 Kb deletion on 8q21.3q22.1 which contains 17 OMIM genes. This deleted region is the region associated with NMLF Syndrome and explains our patient's clinical findings. Parental karyotypes were normal.

Nablus mask-like facial syndrome is a rare microdeletion syndrome. According to the literature, this is the first time that NMLFS and Klinefelter's Syndrome are together in a patient.

IS IT POSSIBLE THAT DOUBLE HOMOZYGOUS PATHOGENIC VARIANTS IN *CFTR* GENE ARE CAUSING FOR LETHALITY?

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Cystic fibrosis (CF), a lethal monogenic disorder is the most common among Caucasians.CF is observed in 1/2,500 live births and characterized by the mutations in Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene.Gene product is a chloride channel, secreting mucus, saliva, sweat, tears, and digestive enzyme.Symptoms can be variable, therefore transport of epithelial ion channel across cells effect many organs. Especially pulmonary infections are responsible for the clinical findings.Symptoms can be variable, therefore transport of epithelial ion channel across cells effects many organs.

A pregnant woman in nineteen weeks consulted with hyperecogen bowel, hydrops and acid in fetus. Umblical blood sampling was analysed for fetal karyotype with *CFTR* gene sequencing. Umblical blood sample was taken by perinatology clinic. We analysed fetal karyotype cytogenetically also used qf-pcr. *CFTR* gene was detected sanger sequencing from umblical blood sampling.

Fetus had normal karyotype in cytogenetic and str analysing. There was a first cousin marriage between the couple. Two pathogenic variants as c.3151A>G and c.3454G>A were detected homozygously in fetal blood. Both of the mutations had clinical significance as bronchiectasis and congenital bilateral absence of the vas deferens in slico databases. Fetus was died a few months after birth.

Cystic fibrosis is a deadlier disease in infancy and childhood. This case also shows that the presence of two rare mutations that are not reported as homozygous carrier in exac and 1000 genome databases. As a result, consanguineous marriage is one of the most important health problems in our country,especially for genetic diseases.

A FAMILIAL BALANCED TRANSLOCATION t(7;18) IN A FAMILY WITH RECURRENT ABORTION

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Reciprocal translocation is a chromosomal rearrangement caused by exchange of nonhomologous chromosomes parts. Reciprocal translocation incidence is 1/600 in birth. Although balanced translocations don't cause clinic findings, it may cause spontaneous miscarriages and may increase the risk of having descendants with a chromosomal abnormality.

A 28 years old man came to our clinic due to history of recurrent abortions in first trimester. The patient's phenotype was normal. In family history, his mother had history of abortion and irregular menstrual cycle. Karyotype analysis planned for the patient and his wife.

Karyotype analysis by high-resolution banding technique from peripheral blood sample showed 46,XY,(7;18)(q11.23;21.1). In FISH technique, probes targeted to *IGH/BCL2* and 7q(q22.1, q31) region showed signals of 7q on chromosome 18. His wife had normal karyotype. The case's parents karyotype analysis done and his father had the same translocation of 46,XY,(7;18). In this result, family screening suggested for translocation carriers.

Karyotype analysis is important in couples with infertility and recurrent pregnancy loss. Reciprocal translocations have been seen around 5% of couples with recurrent abortions. We presented a case with rare translocation of t(7;18) causing habitual abortions. Genetic counseling is given to the family. The importance of PGD has been emphasized in order to ensure that they can have healthy children and to prevent recurrent abortions.

DEVELOPMENTAL DELAY DUE TO *DE NOVO* MOSAIC CHROMOSOME 14Q PARTIAL DUPLICATION

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The aim of study is genetic evaluation of a 10 months old infant who was unable to sit unassisted.

Cytogenetic analysis with G banding showed mos 46,XX,dup(14)(q24.1q32.3)[16]/46,XX[34] karyotype. Microarray analysis confirmed partial duplication 14q. Her parents' karyotypes were normal. Brain magnetic resonance examination, echocardiographic evaluation, electroencephalography, ophthalmologic examination, abdominal ultrasonography and hearing test of patients were normal.

A chromosome 14 duplication is a rare condition caused by an extra segment of genetic material from one of the body's 46 chromosomes, resulting in extra copies of the genes present on that segment. The extra piece of chromosome 14 comes either from the mother or the father and it is possible that the effects may be different depending which parent it comes from. This is due to a phenomenon known as imprinting, where certain parts of chromosomes have different effects depending on the parent of origin. Here we reported a case with developmental delay without dysmorphic features who had mosaic chromosome 14q partial duplication. Genomic imprinting or the presence of the chromosomal mosaicism may be responsible for the absence of severe congenital anomalies and the neurological manifestations in this case.

CLINICAL FINDINGS OF THE TWO FETUSES WITH THE PERICENTRIC INVERSION OF CHROMOSOME Y; RELEVANT OR COINCIDENTAL?

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In postnatal period, the pericentric inversion of chromosome Y is one per 1000 in the general population and is practically innocuous which mostly implies no risk for having an abnormal baby. The disharmony for this condition is, detecting this alteration in the prenatal period because of the obscure phenotype of the fetus. Here we report a living and an aborted fetus with the relevant karyotype.

Cytogenetic analyses of the amniotic fluid and trophoblastic tissue, derived from a viable fetus at the 19th week of gestation with ultrasonographic anomalies and from an abortus with no detectable heartbeat, respectively, revealed a pericentric inversion of chromosome Y (p11.2q11.23). The chromosomal rearrangement was familial as both of the cases' paternal karyotyping ended with the same inversion. In terms of genomic loss and gains the prenatal case was evaluated with genome-wide microarray analysis, and also PCR amplification of *SRY* gene and *AZF* a,b,c regions were performed and no alteration was found.

In prenatal period, there is a need to further studies for the fetus with abnormal findings, regardless of the result like this fortuitous inversion of the chromosome Y. In case of no relationship, it could be thought that the breakpoints of the relevant inversion are far away from the pseudoautosomal region, which may underline a possible non-disease causing alteration. Still, further molecular and clinical studies are needed to explore the nature and the fate of the related abnormality.

THE IMPORTANCE OF *TTK* GENE EXPRESSION IN WOMEN WITH BREAST CANCER

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In recent years studies have emphasized the importance of damage to the organization of cell cycle, breast cancer and other cancers. At each of these control points, it is decided whether or not the protein of interest should progress or stop. The control of these decisions is made by protein kinases, an enzyme family that selects and phosphorylates target proteins, and Cyclin proteins, which control the functioning of the cell cycle. The *TTK* gene is a bifunctional kinase family carrying serine / throne and tyrosine kinase activity. Studies on the treatment of breast cancer with the inhibition of increased *TTK* gene expression are also continuing.

The amount of expression of normal tissue and tumor tissue in female patients who were diagnosed with breast cancer was examined. Normal and tumor tissues were marked by light microscopy from the preparations. Sections were taken from platelet blocks and RNA isolation and RT-PCR analysis were performed.

Our study was conducted on female patients with 30 breast cancers. The control group of the same patients looked at the amount of *TTK* gene that was expressed in normal breast tissues and tumor nipples. Statistically, the amount of expression in tumor tissue was found to be higher than in normal tissue.

Therefore, the inhibition of *TTK* gene, which is investigating effects on breast cancer, has played a role in new therapeutic approaches. In addition, our research is similar in nature to published studies and supports the literature.

CAN miR196a2T/C VARIANT BE A BIOMARKER FOR ANKYLOSING SPONDYLITIS IN A TURKISH COHORT?

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Ankylosing spondylitis (AS) is a chronic inflammatory disorder. Micro RNAs (miRNAs), small, noncoding RNA molecules, can function as either oncogenes or tumor suppressor genes. Altered miRNAexpression has been implicated in the pathogenesis of several human diseases. Therefore, we aimed to explore the effects of miR-196a2 T/C (rs11614913) profile on susceptibility to AS in a Turkish population.

Blood samples were collected from 78 AS patients and 79 healthy controls. miR-196a2T/C variant was genotyped by polymerase chain reaction and restriction fragment lenght polymorphism (PCR-RFLP). Oddsratio (OR) with 95% confidence interval (95%CI) were calculated using the $\chi 2$ test to evaluate the association between AS susceptibility and miR-196a2 T/C variant.

The frequency of TC and TT genotype of the miR-196a2 T/C was much higher in AS patients than in healthy controls, respectively (p=0.034, p=0.028,). The subjects carrying the miR-196a2 T/C variant TT genotype showed a 2.542-fold increased AS risk (OR:2.542, 95% CI: 1.108-5.834) than control group. However, no difference was observed in the distribution of miR- miR-196a2 T/C alleles between patients with AS and controls (Pc>0.05). It was found that CC genotype of miR-196a2T/C variant was more frequent in AS patients with enthesis than AS patients without enthesis (p=0.042). However, there was not significant difference between miR-196a2 T/C genotype distributon and clinical features including *BASDAI*, *BASMI*, *BASFI*, *BASRI*, *AS-QoL* and *HLA-B27*.

In conclusion, the miR-196a2 T/C variant represent genetic risk factor for increased susceptibility to AS and its association with enthesis in a Turkish cohort.

A NOVEL MUTATION IN THE *COLEC11* GENE IN A PATIENT WITH 3MC SYNDROME

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3MC Syndrome is rare autosomal recessive disorder characterized by distinctive facial features (hypertelorism, blepharophimosis, highly arched eyebrows), cleft lip, cleft palate, developmental delay, intellectuel disability and short stature. Other features of 3MC syndrome can include abnormal fusion of certain bones in the skull (craniosynostosis) or forearm (radioulnar synostosis), umblical anomalies and abnormalities of the kidneys or genitals. 3MC syndrome is a rare disorder; its prevalence is unknown. 3MC syndrome can be caused by mutations in either *COLEC11* or *MASP1* gene. *COLEC11* is a gene at chromosome 2p25.3 that codes for the CL-K1 protein and involved in the lectin complement pathway. This pathway is thought to help direct the migration of cells during early development of the body.

In this study, 3MC syndrome case with a novel mutation in the *COLEC11* gene is presented. A two years old male patient was referred to our clinics with abnormal facial features. He was the first live birth of the consanguineous parents. He had hypertelorism, blepharophimosis, epicantus inversus, corneal opacity, umblical hernia, diastasis recti, hypospadias, scoliosis, radioulnar synostosis. Taking into consideration the clinical features, they were diagnosed to have 3MC syndrome. Molecular analysis revealed a novel homozygous mutation in the patients: a deletion mutation (c.80_92delCGGCTGGCGATGA; p.Ala28Profs*69). Parents analysis showed that the mother and father were heterozygous for this mutation.

In conclusion,a novel mutation defined in this study may help to make phenotype genotype correlation in patients with 3MC.

GOLTZ SYNDROME: TWO CASE REPORTS OF A RARE DISEASE

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Focal dermal hypoplasia (FDH) or Goltz syndrome is a multi system disease characterized by developmental anomalies of ectodermal and mesodermal tissues. FDH is inherited in an X-linked dominant pattern. Characteristic skin manifestations include congenital patchy skin aplasia, subcutaneous nodular fat herniation, and hypo/hiperpigmentations following Blaschko'lines. Limb malformations, eyes findings and dental abnormalities often accompany skin findings. FDH is caused by mutations or deletions in *PORCN* gene. We present here a FDH case report on two cases seen in our department.

First patient was nine years old female. She was the fifth live born of the consanguineous parents. She had sparse thin hair, loss of helix in righ tear, bilateral nipple hypoplasia, surgically repaired syndactyly between the third and fourth fingers of both hands. There was ectrodactyly and syndactyly of her between the third and fourth toes right foot. Echocardiography showed bicuspit aortic valve in patient. Moleculer analysis revealed heterozigous mutation (p.His247Tyr,c.739C>T).

Second patient was a four-year-old female born at termtonon-consanguineous parents.She had spare hair, protruding ear, iris coloboma, asymmetric breast, umblical hernia, syndactyly between the third and fourth fingers of the her left hand, patchy dermal hypoplasia on the cheast and extremities. A novel mutation (p.Val371Leufs*42, c.1111_1112delGT) in *PORCN* gene was identified.

FDH is a multisystem disorder, which requires multi-specialty care. Although clinical diagnosis of FDH is possible in some patients, there are identified mutations and deletions in *PORCN* gene. This novel mutation will help to expand the genotypic spectrum of this rare disorder.

LOSS OF HETEROZYGOSITY (LOH) OF THE *TBX18* AND *MRAP2* GENES IN A CASE WITH UNILATERAL RENAL AGENESIS AND CENTRAL OBESITY

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People with unilateral renal agenesis (URA) are usually diagnosed at forth-decade and seen in 1/1000 ratio at the population. To determine URA is important because of morbidity risk with hypertension, proteinuria and renal failure. Renal agenesis could be syndromic or nonsyndomic and URA+obesity could be seen at 16p11.2 deletion syndrome too.

Here we report 49-year-old sporadic male case, complained of central obesity (BMI>35), abdominal pain attacks,arthralgia and proteinuria. URA was incidentally diagnosed six years before.

SurePrint G3Human-CGH 180K microarray analysed for CNV and LOH detection. *MEFV* mutation analysis was normal and he has only a likely benign variant at *NLRP3* gene.

We detected a LOH between 6q14.1 and 6q14.3 locus encompassed *PGM3, RIPPLY2, MRAP2, TBX18, NT5E, SNX14* morbid OMIM genes in the presented case.

CGH+SNP arrays are very effective tools for detecting LOH and CNV's.It has been concluded that the LOH of *TBX18* gene related with Congenital Anomalies of Kidney and Urinary Tract 2 [MIM#143400], and *MRAP2* gene responsible for Obesity, susceptibility to, *BMIQ18* [MIM#615457] phenotypes,may be related with the renal agenesis and obesity of the patient. A congenital anomaly of the kidneys and urinary tract (CAKUT) encompasses a spectrum of developmental disorders of the urinary tract that can range from mild vesicoureteral reflux to severe renal agenesis. Our patient has severe phenotype with renal agenesis. The results of the current case showed that not only CNVs but also LOH should be consider for the explaining of disease etiologies. In order to concretize our hypothesis, we plan to sequence these two genes with direct Sanger sequencing in our further studies.

NEWBORN SCREENING FOR CYSTIC FIBROSIS IN TURKEY: THE VIEW FROM THE GENETIC DISEASES DIAGNOSIS CENTER

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Cystic Fibrosis (CF) is a well-known autosomal recessive genetic disease that may have a negative impact on the life span and the quality. Since 2015, Health Ministry of Turkey implemented the test into the newborn screening program. Cukurova University AGENTEM had been assigned to the program since 2017 for 7 cities in the region. Thus, patients with positive screening test referred to our center. Here we report the genetic testing results from April 2017 to date.

Peripheral blood samples were collected from 140 patients with positive screening test results. Next generation sequencing was performed for *CFTR* gene including all exons and exon-intron junctions via Illumina Miseq platform to detect disease related variants.

Thirty-five (25%) of 140 patients carries at least 1 (one) homozygous or multiple heterozygous CF related variant. Within all patients, 9.3% (n=13) have only 1 (one) heterozygous disease related variant while 65.7% (n=92) of the patients have none. Moreover, 2 novel variants were classified as pathogenic via in-silico analysis and parental testing.

Our analysis found that even though the possible high false-positive newborn screening results, clinical and genetic follow-up to identify the mutations of *CFTR* gene is an essential component for communication with parents to improve and to maximize the benefits of newborn screening process.

FAMILIAL MEDITERRANEAN FEVER MOLECULAR DIAGNOSIS EXPERIENCE OF ISTANBUL MEDICAL SCHOOL, DEPARTMENT OF INTERNAL MEDICINE, DIVISION OF MEDICAL GENETICS

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Familial Mediterranean Fever (FMF), is a hereditary autoinflammatory disorder characterized by recurrent fever, severe abdominal pain, and arthritis. Although it's an autosomal recessive disease its effects can be seen in heterozygous mutation carriers. In every FMF attactk serum amyloid A levels increase and accumulate in tissues and organs. This causes second amyloidosis. Especially amyloidosis in kidney leads to renal failure and death. The other important complications are arthritis, infertility and miscarrige in women. In this study we aimed to detect the most common mutations in the Turkish populations.

Our study involves 1025 patients who were diagnosed with FMF and sent to I.UIstanbul Medical Faculty, Department of Internal Medicine, Division of Medical Genetics to be analyzed for FMF mutations in 2017. DNA isolation was isolated from the patiens peripheral blood. Multiplex PCR was used to amplify related gene regions and QiagenPyroMark Q96ID that performed pyrosequencing was used to detect the mutations.

488 of 1025 patients were detect with FMF mutations(47.6%). The distribution of mutations in mutation positive cases's at the table.

Our findings are similar to previous studies that were performed regarding *MEVF* gene frequency in the Turkish population. Due to significant morbidly and complications of the disease, early diagnose of FMF is very important. Detecting the mutation at an early age will help to protect the patient from the complications which occure by years.

ANALYSIS OF *NRF2* GENE PROMOTER POLYMORPHISM IN MALE INFERTILITY

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NRF2 regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation. NRF2, the transcription factor, regulates the expression of genes that encode enzymes which are important for detoxification of ROS.

Our aim was to determine the functional role of *NRF2* gene promoter polymorphism on sperm DNA integrity and male infertility.

The genotyping of *NRF2* gene promoter polymorphism was studied by polymerase chain reaction (PCR) based-restriction length polymorphism (RFLP) in 100 infertile and 100 control healthy fertile males. DNA damage analysis of 100 infertile individuals was performed by Comet assay analysis. DNA damage levels were determined by calculating the total comet score according to the analysis results.

The frequencies of the genotype distributions were CC (58.6%), CA (38.4%), AA (3%) and CC (38%), CA (48%) and AA (14%) in the control and the infertile groups, respectively. The frequencies of C and A alleles were significantly different in the infertile and the control group. There was no statistically significant association between total comet scores and *NRF2* gene polymorphisms.

Although there was no significant relation between the *NRF2* polymorphism and sperm DNA fragmentation, there was significant difference for *NRF2* polymorphism between fertile and infertile males. So, this study showed that NRF2 might be related to male infertility. Further studies in large populations are required to clarify the role of NRF2 in male fertility.

THIRD FAMILY WITH THE REMARKABLY RARE OCULOAURICULAR SYNDROME (OCACS): GENETIC HETEROGENEITY?

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Oculoauricular syndrome (OCACS) is an ultra-rare autosomal recessive disorder characterized by auricular, retinal and anterior segmental malformations. It's associated with bi-allelic mutations of *HMX1*, which is a key-player in ocular development.

A 5.5-year-old boy and his similarly affected 20-year-old sister were referred for evaluation from the plastic and reconstructive surgery clinics due to auricular anomalies. Primers were designed to include coding exons and exon intron boundaries of *HMX1* (NM 018942). Genomic DNA was amplified by PCR and Sanger sequenced to investigate pathogenic variants.

Parents were 1° cousins. Both siblings had borderline microcephaly [-2/-2.5 SD], upslanting palpebral fissures, ocular anomalies comprising microcornea, corneal dystrophy and iris colobomata in the sister, and question mark ears. Hyperhydrosis of the face with little or no emotional stress was a peculiar finding. Both had normal intelligence, and systemic examination was otherwise normal. They were clinically diagnosed with OCACS due to typical findings of question mark ears, cataracts, microcornea, and excessive facial sweating. Sanger sequencing of *HMX1* revealed no mutations.

Here we report the third OCACS family in the literature. Sanger sequencing may only have left out compound heterozygous gross deletions of *HMX1*, or pathogenic variants outside the coding regions, a low possibility. Apart from these circumstances, by excluding *HMX1* sequencing variants, we propose that the entity is genetically heterogeneous. Whole exome sequencing of the affected siblings will follow, for the identification of the second causative gene.

PRENATAL DIAGNOSIS OF DOUBLE TRISOMY OF EDWARDS SYNDROME AND KLINEFELTER SYNDROME

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Double trisomy in the same individual is a relatively rare conditition. Most of the previously reported cases of double trisomy were found in spontaneous abortions. In this case we detected the fetus which was viable in the second trimester and was associated with two aneuploidies involving Klinefelter syndrome and Edwards syndrome (trisomy 18).Edwards syndrome is the second most common trisomy which has an incidence of 3/1000 newborn. Most of the chromosomal abnormalities in fetuses are detected by prenatal ultrasound findings in the first and second trimesters. It is characterized with intrauterine growth retardation, prominent occiput, micrognathia, clenched hands, rocker-bottom feet. Klinefelter syndrome is a common genetic condition which is affecting 1/600 males and usually diagnosed until adulthood because of hypogonadism and infertility.

A 31 years old woman was referred for cordocentesis at 23 weeks of gestation because of fetal abnormalities. Prenatal ultrasound revealed the polyhydramnios. Level II ultrasound revealed a omphalocele, pes eqinavarus and flattening of the occiput with pointing of the frontal bones (strawberry-shaped skull). Cordocentesis revealed a karyotype of 48,XXY,+18.

Here, we present a fetus with congenital abnormalities that has atypical clinical features of Edwards syndrome with an additional X in the karyotype. The ultrasonographic finding of the polyhydramnios should be researched for the other congenital abnormalities and is a strong indication for prenatal investigations. Fetal karyotyping is the only method that can definitely diagnose the chromosomal aberrations.

A CASE OF SEVERE HYPOCHROMIC ANEMIA: TRISOMY 10p

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Trisomy 10p is a rare chromosomal syndrome characterized by craniofacial abnormalities, organ and skeletal malformations, and impaired psychomotor development. In the majority of partial trisomy 10p cases, a balanced chromosomal abnormality can be observed in one of the parents. The most frequent breakpoint is at the p11 band level and the prognosis is poor. One-third to one-fourth of the patients are lost in the neonatal period. In this case, we present a patient with cleft lip, right renal agenesis, varus deformity and psychomotor retardation whose cytogenetic analysis was reported as 46,XY,rec(19)(19pter→19q12::10p12.1→10pter::19q12→19qter)mat and his mother's cytogenetic analysis was reported as 46,XX,del(10)(p12.1→10pter),der(19)(19pter→19q12::10p12.1→10pter::19q12→19qter). This rare case was presented to emphasize the importance of cytogenetics as the first step in the diagnosis of the complicated cases.

THE INVESTIGATION OF *PARP1* AND *DNA POL B* mRNA EXPRESSIONS ON ALZHEIMER'S DISEASE

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Alzheimer's Disease, which has a significant share among neurodegenerative diseases, is the most common form of dementia in the elderly population. In the case of illness it is seen primarily in memory impairment and memory weakness which is characterized by a decrease in cognitive activities. In addition, it seems that the nerve cells in the brain regions, which are important for thinking, speaking and orientation, have died slowly and progressively.

Studies aiming to understand the underlying mechanisms of the Alzheimer's Disease are aimed at removing the disadvantages brought by the socio-economic aspects of the disease.

Alzheimer's disease is a multifactorial disease and there is a wide effect of genetic factors in the etiology of the disease. Poly (ADP-Ribose) Polymerase 1 (PARP1) encompasses regulation of important cellular processes such as differentiation, proliferation and tumor transformation, and protects the cell against DNA damage. DNA Polymerase β, a protein encoded by the *DNA Polymerase* β *(DNA POL* β*)* gene, functions as a spacer-flanking enzyme in base excision and repair.

In the study, *PARP1* and *DNA POL* β mRNA expressions in Alzheimer's Disease were investigated. First, RNA isolation was performed from the peripheral blood from the volunteers, then cDNA was obtained and the expression levels of these two genes were examined in Real-Time PCR.

As a result, decreased *PARP1* expression was observed in patients with Alzheimer type dementia and there was a statistically significant difference with the control group; however, there was no statistically significant result for the *DNA POL* β gene.

A PATIENT WITH CORNELIA DE-LANGE SYNDROME AND A NOVEL MUTATION IN *NIPBL* GENE

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Cornelia de Lange syndrome (CdLS) is a dominantly inherited developmental disorder characterized by distinctive facial features, mental retardation, and upper limb defects, with the involvement of multiple organs and systems. To date, mutations responsible for CdLS have been identified in five genes *NIPBL, SMC1A, SMC3, RAD21,* and *HDAC8.* Here, we present a clinical and molecular characteristic of a CdLS patient having a novel de-novo mutation in NIPBL gene.

A 6-month-old girl was referred to Pediatric Genetics Clinic because of growth retardation and dysmorphic features. On examination, microcephaly, distinctive facial features including synophrysis, cup shaped ears, long philtrum, downturned angles of the mouth, thin upper lips, micrognathia, and micromelia of both hands and feet were detected. Regarding these dysmorphic features, she was diagosed to have CdLS. Sanger Sequencing of NIPBL gene showed a novel heterozygous c.6647A>G (p.Y2216C) mutation. The parents were also analyzed for NIPBL gene and they were found to be normal. This mutation was evaluated as pathogenic according to ACMG 2015 criteria.

In this report, we present a CdLS patient and we describe a novel mutation in *NIPBL* gene.

CASE REPORT: DIGEORGE SYNDROME PRESENTING WITH SEVERE PULMONARY STENOSIS AND HYDRONEPHROSIS IN PREGNANCY

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The aim of study is to report prenatal diagnosis of DiGeorge syndrome in a pregnancy with congenital heart defects and hydronephrosis in the fetus.

A 25-year-old, woman was referred for counseling at 24 weeks and 5 days of pregnancy because of abnormal ultrasound findings of severe pulmonary stenosis and hydronephrosis. She and her husband were healthy and nonconsanguineous. There was no family history of congenital malformations. There were no teratogenic exposure and no history of infection during pregnancy. Amniocentesis was performed. G-banding chromosome analysis revealed a karyotype of 46,XX. Metaphase FISH analysis on cultured amniocytes using Cytocell DiGeorge region probe [Cytocell, TUPLE 1) showed the presence of only one texas red signal and two green signals, indicating a deletion of DiGeorge syndrome Tup-like enhancer of split 1 (TUPLE 1) locus at 22q11.2 in the fetüs. The patient was offered Genetic counselling together with her family.

Prenatal ultrasound findings of congenital heart defects indicate that the fetuses are at increased risk for chromosome abnormalities. Digeorge Syndrome has significant health problems and approval of diagnosis is important for future family planning.

POLYMORPHISM OF GENES (*ICAM1*, *VEGF*, *eNOS*) THAT ARE EFFECTIVE IN THE INFLAMMATORY PROCESS IN KAWASAKI DISEASE

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It was aimed to investigate possible polymorphisms in some of the inflammatory regulatory genes (*ICAM1, VEGF, eNOS*) important in the pathogenesis of KD (Kawasaki disease) and their effects on clinical findings.

Fifty KD, 50 healthy children were included in the study. CAL (+) (Coronary artery lesions) was pozitive in 46% (n:24). Gly 241 Arg polymorphism was detected in the ICAM1 gene. In KD patients, GA and AA were more frequent while GG allele was less (p=0.022, OR=0.286, 95% CI=0.094-0.868). GA+AA was present in 78% of CAL (+) and GG in 63% of CAL (-) (p = 0.023).

There were two polymorphic locations (405 and 460) in the *VEGF* gene. In the *VEGF* 405 position, 32 patients had GG or CC homozygous forms and 18 patients had GC. In control group, 30 individuals had GC and 20 had GG or CC (p=0,016, OR=2,667, 95% CI=1,1885,985).

Four different distribution (CC, CT, TT, TC) were detected at *VEGF* 460. CT, TT was found more in the KD group and TC, CC in control group. VEGF 460 TC was not detected in KD group but present in 22 of the control group (p=0.000). The distribution of these alleles according to the CAL was detected as fallows: CAL (+): 37% CC, 37% TT, 26% CT; CAL (-): 24% CC, 33% TT, 43% CT. The CT was less common in CAL (+) than CAL (-) patients (p=0.5).

KD is a self-limmited vasculitis with unexplained etiology and genetic predispositon. In our study, polymorphisms in *ICAM1, eNOS, VEGF* genes were detected. In particular, polymorphism in *ICAM1, VEGF* is associated with CAL(+).

47,XXX, 48,XXXX, 49,XXXXX: DIFFERENCES AND SIMILARITIES

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X chromosome aneuploidies such as trisomy (47,XXX), tetrasomy (48,XXXX) and pentasomy (49,XXXXX) are generally thought to arise as a result of maternal nondisjunction during meiosis. There are not much reported cases regarding these anomalies and reported cases show significant clinical variability.

In this work we present 3 cases with 47,XXX, 48,XXXX and 49,XXXXX karyotype. 47,XXX case had only recurrent pregnancy loss and underwent a number of medical procedures and laboratory tests which could be prevented by early diagnosis and would be more cost effective. 48,XXXX had speaking problems, intellectual disability and cardiac anomalies. 49,XXXXX case has more sever clinical findings which are muscular hypotony and talipes equinovarus. Talipes and mild hydrocephalus were observed during fetal ultrasonography, so this case could be diagnosed during prenatal period.

Although, there are several common findings between these aneuploidies we observe that there is significant worsening in clinical picture as number of X chromosome increases. First case with trisomy had no clinical complaints and only had recurrent pregnancy loss, second case had intellectual disability and third one had severe muscular hypotony.

The clinical differences between these aneuploidies and within cases can be explained with random X inactivation and such cases can shed a light on functions of X chromosome located genes.

INVESTIGATION OF METFORMIN EFFECT ON MESENCHYMAL STEM CELL SENESCENCE

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Senescence is a degenerative process that results as a variety of stress factors and permanently inhibits cell division. When the senescence mechanism is activated cell division stops and the DNA content remains as during G1 phase. Size of cell increases during senescence and the lysosomal beta-galactosidase (β-gal) activity also increases. Mesenchymal Stem Cells (MSCs) can be found in variety of tissues. Depending on the cell division, the cells with damaged DNA and degraded telomere functions will enter the chronic senescence process. Metformin is a drug that is used to treat type 2 diabetes, insulin resistance and to regulate blood sugar. Recent studies had been shown that metformin inhibits the expression of cytokines during cellular senescence.

Our study is based on metformin's role in the aging process and the dilatory effects of metformin on the cellular senescence process. The main aim of our study was to investigate how the applications of metformin affect the MSC at the transcriptome level. The impacts of metformin on the cells were compared by using phenotypic tests and also expression level of DNA repair and stemness genes had been evaluated.

According to our results; Metformin delays the senescence process via decreasing the proliferation rate of the cells. qPCR analysis shows that metformin has impacts on expression of stemness and DNA repair related genes.

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