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Abstracts

GENETIC APPROACH TO PREGNANCY LOSSES

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SP01

Spontaneous pregnancy loss is the most frequent complication of a pregnancy since approximately 15% of all clinically recognized pregnancies are resulted in pregnancy loss. Just 30% of all conceptions result in a live birth. The definition of recurrent pregnancy loss (RPL) may vary among different groups working in the field of reproductive health. However, if we define RPL as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period, it affects approximately 1% to 2% of women. On the other hand, it is very difficult to detect the exact number of RPL since some of the pregnancies (chemicals pregnancies) may be lost without detected clinically. Many different problems such as genetic, anatomic, endocrine, infectious, immunologic disorders may cause to pregnancy loss. Although all improvements in reproductive medicine, approximately half of the patients with RPL have been remained without definitive diagnosis.

Furthermore, there are still some controversies about how many pregnancy losses are necessary for detailed medical supervision and definition of recurrent pregnancy loss. Hence, we focused on disorders especially genetic factors leading to RPL as well as management of pregnancy losses.

I would like to thanks to all colleagues working in Genetic Diagnosis Center in Dışkapı Yıldırım Beyazıt Training and Research Hospital and Dr. Zekai Tahir Burak Women Health and Education Hospital for the excellent scientific contribution to prepare my talk.

CANCER GENETICS

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SP02

Cancer is a complex disorder characterized by uncontrolled proliferation of cells, which can invade and spread to distant sites of the body. It is a highly heterogeneous disorder caused by multiple genetic and environmental factors. Cancer can have severe health consequences, and is a leading cause of death worldwide. Early detection, accurate diagnosis, and effective treatment help increase cancer survival rates and reduce the disease incidence. This can be achieved by the improving diagnostic methodologies, and developing preventive and personalized therapeutic strategies and only be possible by increasing the basic knowledge of underlying genetic mechanisms. Currently, more than 1% of genes in the human genome are implicated via mutation in cancer.

In this chapter, we first gave a general overview of the oncogenes and tumor suppressor genes that are key players in the carcinogenesis and related cell signalling pathways. Among them, primary attention is devoted to the most highly representative genes that underlie the common cancers. We then summarized the genetic changes associated with sporadic solid tissue cancers, followed by up-to-date information about genetic susceptibility to cancer and genetic approach to the hereditary cancer syndromes.

PROTEOMICS STRATEGIES

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SP03

Genomic sequences of humans and also of many different model organisms and pathogens detected by genome projects provide invaluable information in the path to diagnosis and treatment of human diseases, besides the great potential for human benefit in various other different areas. Techniques that provide fast and quantitative serial analysis of transcriptomes also revealed many alterations in gene regulation, under various conditions. Yet it is well acknowledged today that the information related to the genome and the transcriptome constitute just an early step in understanding complex diseases and setting novel therapeutic targets, thus in developing new and effective targeted-drugs.

In the present post-genomic era, detailed information on the protein content of cells, tissues, and organisms at a defined time, with all the isoforms, modifications, and interactions, namely the proteome, is studied widely and systematically, under the title proteomics. Proteomics has the potential to be highly useful in areas such as biomarker identification, vaccine and drug development, toxicity studies, and nutrition research, only to name a few. In this talk, proteomics, its techniques, application areas, and future potential will be discussed.

BIOINFORMATICS

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SP04

Bioinformatics deals with the development of computational methodologies and the application of computer science techniques on large-scale biological data to be able to analyze, organize, visualize and comprehend such massive data. With the advent of technology, several high-throughput wet-lab techniques have been developed and hence, the field of bioinformatics recently concentrated on the analysis of -omics and next generation sequencing data.

In this talk, starting with a brief history of bioinformatics, I will mention some success stories in bioinformatics. Then, I will talk about the role of bioinformatics in genetics and the bioinformatics analyses of genomics data to understand disease development mechanisms. Genome-wide association studies (GWAS) with millions of single nucleotide polymorphisms (SNPs) are popular strategies to reveal the genetic basis of human complex diseases. In this regard, I will give an example from the pathway and network oriented analyses of GWAS. We have recently developed such a new methodology and shown that it generates useful results regarding disease development mechanisms on rheumatoid arthritis, epilepsy, intracranial aneurysm and Behçet's disease datasets. The ability to distinguish divergent molecular mechanisms and pathways will hopefully allow us to converge on more effective treatments that can be targeted to individual patients on the basis of their molecular risk factors/determinants. As yet another hot field in the area of bioinformatics, in the last part of my talk, I will go through the analyses of exome sequencing data and give an example of homozygosity mapping using these data to identify potential disease loci in consanguineous families.

CARDIOVASCULAR DISEASES AND GENETIC

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SP05

Cardiovascular diseases are in the first reason of mortality both neonatal and adult periods. Congenital heart defects are most frequent congenital abnormalities (9:10000) and only 15-20% of these patients can survive if untreated. Mendelian inheritance, chromosomal abnormalities (both aneuploidies and microdeletions) and poligenic inheritance are responsible for Cardiovasculary disorders.

Familial Hipercholesterolemia is one of the frequent Mendelian Disorder. (Autosomal dominant, Hiperlipoproteinemi, Tip2A) is a frequent Mendelian disorder with 1:200-500 prevalance. LDLR, APOB, PCSK9 genes are responsible 60-80% of patients.

Long QT Syndrome is an important autosomal dominant cardiac rhytm disorder with 1:2000 prevalance. Cardiac electrophysyology caracterised with Long QT, T wave abnormalities and ventricular tachycardia (torse de pointes). Most frequent symptom is syncop with stress(blood sampling or waiting for vaccination). Andersen Tawil Syndrome (LQTS7) is characterised with muscle weakness and facial dysmorphism, Jervell and Lange Nielsen syndrome is chracterised with Long QTS and sensorineural deafness and inherited AR. Loss of function of K channel genes or gain of function of Na channel genes are responsible for Long QT syndrome. KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3) genes are detected 60-75 % of patients. ANK2 (LQT4), KCNE1 (LQT5), KCNE2 (LQT6), KCNJ2 (LQT7), CACNA1C (LQT8), CAV3 (LQT9), SCN4B (LQT10), AKAP9 (LQT11), SNTA1 (LQT12), KCNJ5 (LQT13), CALM1 (LQT14), and CALM2 (LQT15) genes are also responsible for Long QT Syndrome. Gain of Function mutations of SCN5A gene results LQTS and loss of function mutations results Brugada syndrome.

PYR2, CASQ2, TRDN and CALM1 genes are linked with Catecholaminargic Polymorphic ventriculary tachycardia (CPVT) (1:10000 prevalance). Symptoms usually start between first 7-12 years. PYR2 mutations also linked with sudden infant death.

Short QT Syndrome characterised with short QT interval (<350ms), atrial fibrilation and sudden deadth history of family. Gain of function at K channel genes KCNH2, KCNQ1, KCNJ2 or loss of function at Calcium channel genes CACNA1C, CACNB2b are responsible this syndrome.

Familial Atrial Fibrilation (AD) is responsible of 1:3 cardioembolic events and linked with KCNQ1, KCNE3, KCNE2, KCNJ2, KCNA5, GJA5, SCN5A, NPPA mutations.

Cardiomyopathies are one of the most frequent genetic disorders. Hipertrophic (HCM), Dilate (DCM), Arrythmogenic right ventricular (ARVC) and Left ventricular noncompaction(LVNC) types are inherited cardiomyopathies. DCM has 1:2700 prevalance, mostly diagnosed 4th to 6th decade even in familial forms. Mutations detected in more than 30 genes and most frequents are TTN, EYA4, LMNA, BAG3 genes. AD, AR, X linked and mitochondrial inheritance are possible. HCM has 1:500 frequence with sarcomeric genes mutations (MYBPC3, MYL2, MYL3, MYH7, ACTC, TPM1, TNNI3, TNNT2 and CAV3) and mostly AD but compound hetrozygous and digenic inheritance are also possible.

ARVC has 1:100-2500 frequency, usually starts at adult ages. Loss of desmosome functions are responsible for ARVC. 4-22% sudden cardiac death of athlettes are linked with ARVC. DSC2, DSP and PKP2 gene mutations detected half of the patients. Because of compound heterozygosity and digenic inheritance\all known ARVC genes should be analysed.

Congenital Heart Diseases can be chromosomal aetiology (aneuploidies or microdeletions) or monogenic aetiology as GATA4, TBX5, MYH6, CRELD1, BMP4 or NKX2-5 mutations. Syndromic (Holt Oram S, Di George S, CHARGE S, Noonan S, Williams S, et cet) or non syndromic phenotypes are possible. There are 7840 entries in OMIM about congenital heart anomalies.

Table. Warfarine dosing depends on CYP2C9 and VKORC1 genotypes

VKORC1 1639G>A	CYP2C9*1/*1	CYP2C9*1/*2	CYP2C9*1/*3	CYP2C9*2/*2	CYP2C9*2/*3	CYP2C9*3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Pharmacogenetic is very important for treatment of cardiovasculary disorders. CytochromeP450 enzymes are metabolysing many endogen molecules like steroids, lipids and vitamines and also very important roles many drug`s methabolism. Some polymorphisms are very frequent as much as 20-60%. Some polymorphisms result with poor metabolyser phenotype and some others with rapid or ultrarapid metabolyser phenotype. If drug inactivated by enzyme (Warpharine CYP2C9) and patient has poor metabolysing genotype (CYP2C9*2 (430C>T) and, or CYP2C9*3 (1075A>C), standart dose produce more advers effect (bleeding risc for warpharine) and toxicity, patiend needs less dose (10-90% depends of alleles and heterozygous or homozygous genotype) or another drug; if patient is rapid metaboliser, drug`s efficiency become less and patient needs more dose.

If drug activated by CYP enzymes (Clopidogrel CYP2C19) and patient is poor metabolyser genotype, standart dose doesn`t enough for treatment and patient has complications like seconder stroke or stent restenosis; if patient has rapid metabolyser genotype drug`s effects starts early and ends very early than expected, side effects also possible and plato level didn`t exists. While interpreting genotypes, we have to be aware some factors: Same drug can be metabolising by different enzymes at same phase; one gene has different rare polymorphisms, some produce loss of function and other can produce gain of function; CYP enzymes can inducable or repressible by other drugs or foods. Because of these, analysing more genotypes as much as possible is a better treatment; but if this is not possible, analysing major metabolic enzyme and most frequent polymorphisms is also appropriate method. Pharmacogenetic genotyping before first dose is the best choice about high risc drugs and this approach result more efficient treatment and less side effects or complications.

HEMATOLOGICAL DISEASES AND GENETICS

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SP06

Developments in all fields of genetics and genetic technology have greatly improved our ability to understand the molecular basis of blood disorders. A better understanding of the genetic origins of inherited blood disorders not only has improved diagnosis and follow up the patients with hematological disorders but also has identified therapeutic targets of pharmacologic interventions. Certain types of anemia, platelet disorders, bleeding disorders, thrombophilia, and neutrophil disorders are caused by inherited genetic factors. Molecular genetic testing and genetic counseling are among the most important components of patient management in these disorders. Genetics has a special importance in hematological malignancies, since the genetic biomarkers have become key factors in diagnosis, classification, predicting prognosis and planning treatment. New discoveries in the field of molecular genetics and developments in high throughput next generation sequencing methods have made a great change in clinical practice of hematological disorders. Recently the effectiveness of chemotherapeutics in patients with hematological malignancies has been determined using these new techniques. Collaborative work between geneticists and hematologists, and know-how in the related fields are necessary for more accurate interpretation of cytogenetic, molecular cytogenetic and molecular genetic test results.

This talk offers a perspective on the genetic factors underlying hematological disorders and how genetics and genetic testing can be used in diagnosis and management of patients with these disorders. I also focus on the genetics of inherited blood disorders which are respectively common in our population.

APPROACH TO DYSMORPHIC PATIENT

E. Ferda Perçin

SP07

The term “dysmorphic” is used to describe an individual whose physical features are not found in a person, with the same age and/or ethnic origin. A dysmorphic person generally has visible and/or detectable malformations or distinctive features. To understand dysmorphology, knowledge of normal fetal development is necessary to distinguish presence of an abnormality of structure. While some features are clearly abnormal such as single nostril, other features may be a non-significant familial trait such as epihchantic folds. The accurate recognition of distinctive features are important for accurate diagnosis and it comes with experience and trainning. It takes several years, to develop a confidence to come to a stage of making a true diagnosis and differential diagnosis. For making diagnosis; following related guidelines and looking at pictures of similar patients, field books and diagnostic databases are very helpfull. Effective genetic counselling including the prognosis, follow up and prenatal diagnosis, may be possible, when a correct diagnosis is made.

THE ROLE OF GENETICS IN INFERTILITY

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SP08

Infertility or reduced fertility affects 15% of all couples. In half of these, the etiology is male infertility due to underlying genetic conditions. When assesssing an infertile couple, two questions should be answered;

1. Is infertility the result of a genetic disease or a condition transmissible to the children?
2. Is there a possibility for the couple to have a child with an increased risk for congenital malformations?

The genetic reasons of male infertility including sex chromosome abnormalities, translocations, Y chromosome microdeletions and cystic fibrosis as well as the genetic reasons of female infertility will be discussed under the light of comtemporary guidelines.

Genetic counseling of the infertile couple is also an important issue as these couples have an increased risk for genetic diseases. Genetic tests and their results should be evaluated during genetic counseling leaving the decision on reproductive options to the couples.

GENETIC COUNSELING

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SP09

Genetic diseases have many features that need to be clearly understood by the individual and the family after the diagnosis and the monitoring process. Among these characteristics, heritability, which distinguishes genetic diseases from the others, is the most striking one. Because of the transmission of the mutation in the genetic material through generations and the effected individuals (or the ones that have the possibility of being effected), the medical, social and psychological results of the disease should be handled in detail. Genetic counseling is a communication process that provides this information. In genetic counseling; the tests, their risks, reliability, the information they will provide for the individual, for the family and also for the upcoming generations, the nature, significance, recurrence risk, life expectation and quality of the disease, options for the disease, medical needs, social labeling and discrimination and much more issues are discussed to support the family.

Genetic counseling should be provided for all genetic diseases whether it is heritable or not. There are a lot of situations that require genetic counseling. Every family and every patient is unique. Even if the diagnosis is similar, every case is different from each other; counseling depends on the needs and worries of the individual. However, fundemental principles in genetic counseling are definite and these principles establish the main frame.

ENDOCRINE DISORDERS AND GENETICS

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SP10

Endocrine disorders are commonly seen in both adults and children. In some cases it is important to diagnose the disease as quickly as possible. Because of that genetic diagnosis and genetic counseling have great impact on endocrine disorders. In order to approach this group of disorders, it is logical to divide these disorders into 6 different groups:

1. Disorders of Sex Development (DSD) and Genetics
2. Diabetes Mellitus and Genetics
3. Obesity and Genetics
4. Thyroid Disorders and Genetics
5. Pituitary Disorders and Genetics
6. Lipodystrophies

Underlying molecular mechanisms, which are playing roles on the formation of endocrine disorders, are quite different and mutations have been shown in many genes up to now. In some disorders such as lipodystrophies, underlying molecular mechanism is well defined, but in some of them, such as Type 2 Diabetes Mellitus many research projects are still running in order to identify the genes responsible for the formation of the disease. In some disorders such as monogenic diabetes, mutation analysis is just performed in limited number of genes but in DSD many genes must be investigated to properly and quickly diagnose the disease. Because of these factors genetic diagnosis of endocrine disorders was a problematic issue. But Next Generation Sequencing (NGS) technology has given us a chance to evaluate all the genetic factors in once. With the help of this technology many problems in the genetic diagnosis of endocrine disorders will be solved in the near future.

THE INVESTIGATION OF SEX CHROMOSOME ABERATIONS

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SP11

This document was prepared to evaluate the numerical and structural sex chromosome anomalies. The knowledge of possible sex chromosomal variations will give light for genetic counseling to family in sex chromosome aberations. It must be given spesific counseling for the cases who have X or Y choromosome aberation on different band levels. If any X or Y anomalies were detected in prenatal diagnosis, the condition of baby must be explained to family properly. The numerical anomalies of X chromosome such as 45,X (Turner syndrome) or structural anomalies on either Xp or Xq level give spesific clinical phenotype and cause different problems. Approachs for Y chromosome is supposed to be similar to the X chromosome evaluations. Our genetic counseling should guide the family for decision to continue the pregnancy or to accept medical abortus.

DEVELOPMENTAL GENETICS

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SP12

The formation and later development of human embryo is a complex process role on both genetics and environmental factors. The genom of the embryo composed of DNA from both parents, and the genome designates and controls how create the fetus from undifferentiated small cell group. Develpmental genetics involves how the genes initiate and control the process during constitution of a mature organism from a single cell. This complex process is not explained completly. The genes acting developmentaly effect on through diffusion of morphogens, many pathways including cell migration, proliferation, and border formation. Morphogenesis, which is defined formed an embriyo in normal shape and size, is mediated morphogens against inner and outer factors. Morhogenes need effector molecules which control gene expression, and determinate fate of the cell. This process is controled by many transcriptional factors and signal pathways. In this section the genes, transcription factors and signal pathways effect on development of central nerve system, skeletal system, limbs, craniofacial, skeletal, circulatory and urinary system are mentioned.

DEVELOPMENT OF MEDICAL GENETICS IN TURKEY

Nurettin Başaran

SP13

This article is about the development of medical genetics in Turkey, and mainly is a combination of my articles that published before in the Medimagazin newspaper. Establishment phase is not in any other disciplines as well as an independent discipline of medical genetics in Turkey are described as very abstract. Because I accepted the task of writing this article as contained in one of the oldest in this process. Otherwise I am the first medical genetics doctor (PhD) in Turkey, I am firs associated of medical genetis in Turkey, I am the founder of Turkey's first medical genetics research and training center, and Turkey's first formal medical genetics polyclinic, I am president of the first prenatal diagnosis congress, and many others.

EHLERS DANLOS SYNDROME IS HERITABLE SOFT CONNECTIVE TISSUE DISORDE

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SP14

The Ehlers–Danlos syndromes (EDSs) comprise a heterogeneous group of inherited diseases, characterized by fragility of the soft connective tissues and widespread manifestations in skin, ligaments, joints, blood vessels and internal organs. The clinical spectrum varies from mild skin and joint hyperlaxity to severe physical disability and life-threatening vascular complications. The current Villefranche classification recognizes six subtypes. Each subtype is a separate and different condition and genetic basis of many subtypes has now been elucidated, confirming heterogeneity. An awareness of the different conditions within this group is the starting point towards accurate diagnosis. Accurate elicitation of history and clinical signs is vital in selecting the correct confirmatory investigation. EDS represents a collagen disorder among the larger group of heritable connective tissue. Most forms of EDS recognized to date result from mutations in one of the fibrillar collagen genes or enzymes involved in the biosynthesis of these collagens diseases. These are; mutations in type V collagen cause classic, in type III collagen cause vascular EDS, while mutations involving the processing of type I collagen are involved in the kyphoscoliosis, arthrochalasis and dermatosparaxis type of EDS. Establishing the correct EDS subtype has important implications for genetic counseling and management and is supported by specific biochemical and molecular investigations. Current genetic studies have brought new insights into the molecular pathogenesis of EDS by mplicating genetic defects in the biosynthesis of other extracellular matrix (ECM) molecules, such as proteoglycans and tenascin-X, or genetic defects in molecules involved intracellular trafficking, secretion and assembly of ECM proteins.

MAPPING AND IDENTIFYING GENES INVOLVED IN HUMAN DISORDERS

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SP15

Genetic mapping is a powerful approach to identify genes underlying any herritable trait, including human diseases. Good clinical documentation and modelling of the disorder; genome wide genotyping using SNP arrays; narrowing the critical interval by haplotyping (fine mapping) and systematic mutation screening are essentials of a successfull mapping study. Genome wide linkage and association (GWAS) approaches are two major strategies used for mapping of Mendelian and Complex diseases respectively. Homozygosity mapping is another powerfull tool, but is only valid when searching for a mutation segregating within a small, closed population. However, it has a higher advantage over classical linkage approach to identify genes in fewer numbers of families and even in single cases per family. The increased availability of whole exome (WES) and whole genome sequencing (WGS) data underlined the importance of combining mapping information with high-resolution sequence data to detect causative variants involved in disesae etiology. In the lecture, mapping strategies will be outlined and ideal examples using a combination of mapping and high resolution sequencing approaches in gene identification of mendelian disorders will be presented.

THE SKELETAL DYSPLASIAS

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SP16

The skeletal dysplasias are a heterogeneous group of diseases which consist of 456 clinical conditions characterized by particularly abnormal growth and bone and cartilage malformations. The overall incidence of those diseases has been reported as 1/5.000. The most common ones are achondroplasia, osteogenesis imperfecta, tanatophoric dysplasia, fibrochondrogenesis and achondrogenesis. The Nosology Group of the International Skeletal Dysplasia Society classified skeletal dysplasias in 40 groups according to the molecular, biochemical, and/or radiographic criteria. More than 256 genes are responsible from 316 clinical pictures. Skeletral dysplasias are divided into 3 main groups namely, osteodysplasia, chondrodysplasia and dysostosis. Osteodysplasias are characterized by altered bone mineral density such as osteopenia or osteosclerosis; whereas chondrodysplasias have underlying genetic defect which effects cartilage tissue causing short stature. Dysostosis are different from the former two groups in which the characteristics are defective bone deformations and remaining phenotypically static during life. They result from mutations in single genes, chromosomal anomalies such as deletions or duplications, mosaicism or uniparental disomies as well as micro RNAs. One of the characteristic findings is clinical and genetic heterogeneity.

Achondrogenesis and lethal dysplasia are responsible from more than 60% of deaths in this group of diseases. Their main manifestations are short stature and skeletal abnormal findings. Less commonly, some findings of the organs and systems other than skeletal system accompany the clinical picture of skeletal dysplasias. Short stature may be proportional or disproportional. Except very few conditions, skeletal dysplasias characterized by dwarfism cause disproportional short stature. The spectrum of the clinical picture of skeletal dysplasias range from lethal conditions to early-onset osteoarthritis with normal stature. The classical diagnostic approach to the individuals with a suspicion of skeletal dysplasias comprise those steps; history and physical examination including growth parameters' measurements, pedigree analysis, imaging techniques, genetic tests, biochemical and histological investigations. USG is a very useful technique for prenatal detection of skeletal dysplasias. It has been reported that more than 80% of lethal dysplasias can be detected by USG where short limbs or polyhydramnios are cardinal features. Treatment modalities are enzyme replacement therapy for some types of mucopolysaccharidosis, growth hormone use or surgical treatment for achondroplasia. Mesenchymal stem cell therapy hold promises as a new treatment strategy in skeletal dysplasias. Genetic counseling of skeletal dysplasias and long-term care needs a multidiciplinary approach consist of particularly medical geneticists, pediatricians, radiologists, orthopaedists, physical therapists, social workers, nutritionists.

CURRENT PROGRESS IN INCRETIN BASED GENE THERAPY APPROACHES FOR DIABETES

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SP17

The incretins are gastrointestinal hormones that work to increase insulin secretion in response to food ingestion. An incretin effect is defined as a biologic process where orally taken carbohydrates induce the release of intestinal hormones augmenting insulin secretion more than what could be achieved with intravenous glucose delivery. Since reduced incretin response to food ingestion is one of the primary defects associated with glucose intolerance and hyperglycemia in T2DM, incretin based treatment strategies recently gained a significant momentum as a novel class of medications with antidiabetic potential. Thus, incretin based treatment agents currently represent a new class of medications used in the treatment of patients with diabetes (1).

Glucagon-like peptide-1 (GLP-1) is one of the two essential gut-derived incretin hormones involved in the modulation of glucose homeostasis. GLP-1 is released from intestinal L cells located in the lower intestine (ileum). Target organs include, but not limited to, pancreas, liver, stomach, muscle, adipose tissue and brain. GLP-1 also suppresses glucagon secretion from alpha cells, and stimulates somatostatin secretion from pancreatic delta cells. The action of GLP-1 related to food intake includes delay of gastric emptying, inhibition of gastric acid secretion and reduction of appetite. Because GLP-1 infusions restored down-regulated beta-cell response to glucose in T2DM patients, GLP-1 has been considered a therapeutic agent for the treatment of T2DM. However, GLP-1 has a short biological half-life (2-3 min) due to rapid truncation by the ubiquitous serine protease dipeptidyl peptidase-4 (DPP-4), which limits its therapeutic use. While frequent injections or larger quantities are needed to compensate for the short biological half-life of GLP-1, viral or non-viral vector gene delivery technologies were developed to provide a constant bioactive GLP-1 production and secretion (2). In this talk, I will review the current progress in GLP-mediated gene therapy approaches against diabetes.

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DIAGNOSIS OF CHROMOSOME ABERRATIONS; FROM CHROMOSOMAL KARYOTYPING TO MOLECULAR KARYOTYPING

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SP18

Since the first correct discovery of the human mitotic chromosomes in men in 1956, there were some milestones in the diagnosis of chromosome aberrations. The analysing of the metaphase chromosomes and later prometaphase chromosomes by using banding techniques allowed us to detect all numerical and structural chromosome aberrations greater than 10 Mb. Fluorescent in-situ hybridization technique using different probes specific for known microdeletion/duplication syndromes and for subtelomerik regions of chromosomes has widened the diagnostic capability. The use of the both techniques in a algorithm is still the gold standard in the diagnosis of the chromosome aberrations. Microarray and a-CGH techniques, which allow to detect the genomic unbalances in size of Kb's have changed the classical algorithms. On the other hand, this newest techniques are not capable to detect the low level mosaics, and also balanced structural chromosome anomalies and the difficulties in clinical interpretation of some genomic changes and also high cost of the test lead to think new algorithms in specific risk groups for chromosome aberrations.

The advantages and disadvantages of the available techniques will be discussed in this talk.

EPIGENETIC MODIFICATIONS IN HUMAN DISEASES

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SP19

Although human genome stores the genetic information encoded as DNA sequences and each of about 200 different cell types originated from a single cell in the human body harbour identical copy of the genome, they have diverse functions caused by gene expression changes. During development, the cells gain their own identity through the epigenomic integration of information encoded in the genome with all molecular and chemical signals of cellular, extracellular and environmental origin. Epigenetics is a quickly growing field encompassing mechanisms regulating gene expression in different levels that do not involve changes in the genotype. DNA methylation, DNA hydroxymethylation, regulation of chromatin by histone modifications and regulation of gene expression by non-coding RNAs work together to drive appropriate gene expression. Since the human genome was sequenced, increasing evidence in epigenetics suggests that we are more than just the sum of our genes. Aberrant epigenetic signatures are associated with abnormal development and diseases such as cancer, imprinting disorders, neurological and cardiovascular diseases. While epigenetic dysregulation is involved in every step of tumor development and progression, the epigenetic mechanisms play pivotal role in brain development and neuronal differentiation. Besides, the knowledge acquired from epigenomic reprogramming during development, stem cell differentiation and environmental influences on gene expression during aging allows us to clear mitotic, meiotic and transgenerational inheritance of epigenetic traits.

GENETIC DIAGNOSIS AND MONITORING OF CHRONIC MYELOID LEUKEMIA (CML)

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SP20

Identifying all structural and numerical genetic anomalies in new diagnostic cases Identifying variant clones, if any Quantitative measurement of genetic anomalies (+ cell% rate, RNA copy number) after treatment, qualitative and quantitative monitoring of previous genetic anomalies Identifying new genetic anomalies after treatment, if any Scanning mutations of prognostic importance.

The assessment to be conducted based on the results of genetic analysis include following;

Complete cytogenetic response: Ph+ metaphase not existing

Partial cytogenetic response: Ph+ metaphase 1-35%

Minor cytogenetic response: Ph+ metaphase 36-65%

Minimal cytogenetic response: Ph+ metaphase 66-95%

No Cytogenetic response: >95% Ph+ metaphase

Molecular Response (MR)
Complete molecular response (CMR) concept is replaced with "molecularly undetectable leukemia" and when RT-PCR or "nested" PCR method is used, not detecting BCR-ABL1. (10^{-6})

Major molecular response (MMR, $MR^{3.0}$): BCR-ABL/ABL rate being ≤ 0.1% according to the international scale

$MR^{4.0}$ response:
Detectable disease, BCR-ABL1 according to international scale <0.01 %

Undetectable disease, cDNA >10.000 ABL1 copies

$MR^{4.5}$ response:
Detectable disease, BCR-ABL1 according to international scale <0.0032%

Undetectable disease, cDNA >32.000 ABL1 copies

Genetic Diagnosis and Monitoring of Myelodysplastic Syndrome (MDS)
The most frequently observed cytogenetic anomalies are del (5q), monosomy 7 or del (7q), trisomy 8 and del (20q). Chromosomal abnormalities are observed in about half of the chromosome loss. Among partial chromosome losses the most frequently observed is the del 5q, which is followed by 20q, 11q, 7q. Del 13q is the least frequently observed one. Total chromosome loss is mainly observed in monosomy 7 and less frequently in other chromosomes (5, 17, 21, X). The most observed chromosome gain is trisomy 8 which is followed by trisomy 11 and gained trisomy 21.

Molecular Genetics
Acquired Somatic Mutations were identified in genes containing TET2, ASXL1, DNMT3A, CBL, ETV6, EZH2, IDH1 IDH2, KRAS, NPM1, NRAS, RUNX1 and TP53 Mutation has been identified in SF3B1, SRSF2, U2AF1, ZRSR2 genes coding the spliceosome components at a rate of 85% in MDS patients that have ring cideroblasts and at a rate of 44% in those do not have it and at a lower frequency in SF3A1, SF1, U2AF65, PRPF40B genes.

CELL STRUCTURE AND CELL DIVISION

Vildan Caner, Gülseren Bağcı

SP21

Cell is the basic unit of life because it can carry on all of the processes of life. Organelles, membrane-based intracellular compartments, are important cellular structures that perform many essential functions. Each cellular organelle has a special structure that evolved to allow the organel to perform its function effectively. The first part of this chapter describes the compartments of the cell and how the compartments perform their many function. The second part covers cell cycle and cell division. In multicellular organisms, cell division is essential for three major functions: growth, reproduction, and repair. Cells that are growing and dividing go through a repeating series of events called the cell cycle. These events have to be carried out in the correct order to maintain homeostasis. The cell cycle consists of DNA synthesis and mitosis phases seperated by gap phases. In this part, it will describe the events at each stage of mitosis and meiosis and discuss what are the sophisticated control processes of a cell to ensure that the cell cycle proceeds with the great accuracy. It will also emphasize the importance of cell division in medical genetics.

BIOINFORMATICS ANALYSIS OF MISSENSE SNPS RELATED WITH MALE INFERTILIT

Akın Tekcan

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OP01

Male infertility is a worldwide problem, and about 15% of the cases are associated with spermatogenesis-related gene mutation. Y chromosome microdeletions, chromosome abnormalities and single gene defects have been proposed to be involved in male fertility. Missense single nucleotide polymorphisms (SNPs) are responsible for many complex diseases. The effects of all missense SNPs of *DAZL*, *eNOS* and *MTHFR* genes are unknown on male infertility. The aim of this study, using in bioinformatics methods, was to analyze all known missense mutations that can affect the functionality of the *DAZL*, *eNOS* and *MTHFR* genes, leading to male infertility. Data on the human *DAZL*, *eNOS* and *MTHFR* genes were collected from the Ensembl database (release 83), National Centre for Biological Information dbSNP Short Genetic Variations database, 1000 Genomes Browser, and NHLBI Exome Sequencing Project Exome Variant Server. Eighteen thousand two hundred nineteen missense SNPs of the *DAZL*, *eNOS* and *MTHFR* genes were determined. Bioinformatics analysis was then performed. All missense SNPs were analyzed via multiple computational techniques in terms of protein-protein interactions, pathogenic effects, diseases related effects, protein stability effects, structural and functional features. This is the first study to analyze all missense SNPs related with male infertility. The results indicate the applicability of a bioinformatics approach to infertility especially male infertility. I think that the analysis of *DAZL*, *eNOS* and *MTHFR* genes missense SNPs using bioinformatics methods would help to diagnosis of infertility.

EXPRESSIONS ANALYSIS OF SOME GENES THAT ARE DETECTED IN FUSION WHICH ARE DETERMINED ON MULTIPLE MYELOMA HOLE GENOME TRANSCRIPTOME DATA

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OP02

Analysis of genes that play roles in Multiple myeloma pathogenesis and their pathways is a current area of research. We aim to detect expression of some genes of ErbB and insuline signaling pathway that take part in the fusion. The transcriptome data base on a research named 'Comparative Gene Expression Profilling of Multiple myeloma, Smoldering Myeloma and Monoclonal Gammopathy Undetermine Significance Caces' were investigated and 405 fusions were deteced by using bioinformatic analysis programs. These fusions were analyzed using the latest version of the human genome hg19 (Feb. 2009 (grch37/hg19) database and associated genes were identified. These genes were grouped by Venny bioinformatics program and WebGestalt database. There are 9 genes that are releated to ErbB and Insulin signaling pathways. Bone marrow were taken from three healthy volunteers and 17 untreated patients, firstly RNA isolation was made and then cDNA were synthesized. After that, spesific primers were desingned and genes expression were analysed by realtime quantitative PCR. Patients MTOR, RPTOR, PIK3CA, AKT1, ErbB4, PRKAR2A and PRKACB genes expression were detected to be 3-10 times up-regulated than control group. There were no differences between expression level of RICTOR and GYS1 genes. GYS1 gene has been analysed for the first time in this study. All these results will be useful to understand the patophysiology of the disease and to create new therapeutic approachies of the MM illness.

RELATIONSHIP BETWEEN TOLL-LIKE RECEPTOR 2 (TLR2) POLYMORPHISM AND CHRONIC HEPATITIS B INFECTION: A PRELIMINARY STUDY

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OP03

Objective: Chronic hepatitis B is one of the most common infectious liver diseases. Hepatitis B infection caused by the hepatitis B virus (HBV) has become a major health issue. Currently, most studies investigating the underlying mechanisms of HBV infection have focused on genetic variations in the human population. Toll like receptors (TLR2) play an important role in innate immunity by recognizing viral lipoproteins and glycoproteins. Viral detection by host TLRs can be controlled by genetic polymorphisms in the interaction regions between viruses and receptors. The purpose of our study is to elucidate whether the TLR2 (Arg753Gln, Arg677Trp, -194 to -174 del) gene polymorphism is susceptibility genes for the development of chronic hepatitis B infection.

Material and Methods: A total of 62 patients with chronic hepatitis B and 86 healthy subjects were included into this study. TLR2 (Arg753Gln, Arg677Trp, -194 to -174 del) polymorphism was investigated using PCR-RFLP methods. Associations between specific genotypes and chronic hepatitis B infection were examined using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results: The allel frequency of TLR2 I, D were detected as 38.2%, 20.0%, in patients with chronic hepatitis B and 61.8%, 80.0 %, in control groups, respectively. TLR2 allels were associated with the risk of chronic HBV infection (p=0.008).

Conclusions: The results of this preliminary study suggest that further research is needed to understand the role of these gene polymorphisms in chronic hepatitis B infection.

THE PREVALENCE AND HIGH-RISK GENOTYPE DISTRUBUTIONS OF HUMAN PAPILLOMA VIRUS (HPV) FROM CERVICAL PAP SEMEAR IN WOMEN FROM ÇANAKKALE COHORT

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OP04

Objective: HPV is an oncogenicvirus that has been precisely identified in cervical cancer. The aim of this study was to evaluate the HPV risk genotype profiles in women Canakkale cohort retrospectively.

Materials and Methods: In a total of 212 women with cervical erosion were evaluated in the current results. Cervical smear samples and excisional biopsies from genital area condylomas used for DNA isolation. DNA isolation was performed with spin column method and HPV genotyping was performed with multiplex fluorescent PCR amplification by HPV kit (molGENTIX SL). Viral PCR products were genotyped by capillary electrophoresis system (3130 Genetic Analyzer, ABI) and results were evaluated by GeneMapper v4.0 software.

Results: HPV DNA was positive in 47% of the current women cohort (100/212). The most frequent HPV genotypes were; 6(23%), 16(21%), 58(18%), 59(13%), 68(8%), 33(7%), 31(6%) and 56(5%) in the current results respectivelly.

Conclusion: The most frequent HPV genotpye was type 6 in the current cohort and this genotype was assessed as a low risk-factor for the cervical cancer. Results also showed the crucial role of HPV genotyping in high-risk in the surveillance of cervical cancer after treatment.

RECURRENT PREGNANCY LOSS AND PARENTAL CARRIER OF A STRUCTURAL CHROMOSOME TRANSLOCATION: A CASE REPORT OF A MOTHER WITH T(9;13)

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OP05

Objective: Parental chromosomal rearrangements are well known established causes of recurrent pregnancy loss (RPL). Balanced and/or Robertsonian translocations are the most commonly reported parental structural chromosome abnormalities that occuer in RPL. It's incidance ranges between 4% to 7% of RPL outcomes. Here we report a RPL mother with 46,XX,t(9;13)(9qter34.2;13q33t) karyotype.

Material and Methods: PHA stimulated heparinised peripheral blood sample was used for the conventional karyotype analysis and GTG and FISH techniques were used for the refine detection of numerical/structural chromosome abnormalities for the current presented case.

Case Report: A 25-year-old patient with recurrent pregnancy loss was referred to department of medical genetic in Canakkale Onsekiz Mart University-Turkey. She had experienced one alive children and two early spontaneous pregnancy losses during her ten years of marriage. No other factors which known related with RPL in this patient. A karyotyping of this patient revealed structurel abnormalities of chromosome 9. After karyotyping, we aimed to expose which chromosomal structurel abnormalities accompained to current case by FISH analysis. With FISH techniques, we established t(9;13)(9q$^{ter34.2}$;13q^{33t}).

Discussion: Structurel and numerical chromosomal abnormalities cause infertility and recurrent pregnancy loss (RPL). We need more evalution proband's family. Because familial balanced translocations related with RPL are reported in literature. The appropriate therapy can made by appropriate diagnosis.

AN İNFERTILE CASE OF 47, XYY SYNDROME WITHOUT AUTISTIC SPECTRUM: COST EFFECTIVE WELL-DEFINE OF EXTRA Y CHROMOSOME BY GTG, C BANDINGS, QF-PCR AND FISH ANALYSE

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OP06

Objective: The Autism Spectrum Disorders (ASD) were frequently reported in autosomal and sex chromosome abnormalities and limited findings pointed out the Y chromosome. In the current case it was aimed to identify a supermale case without autism profiles using combined cytogenetic and molecular techniques.

Materials and Methods: Automated karyotype analysis was made after combined methods with GTG, C bandings, QF-PCR and FISH techinuqes.

Results: The current case of 47,XYY syndrome was reported due to without autistic profiles such as language and social impairment. The proband's karyotype was determined as 47,XYY. No other numerical and/or structural chromosomal abnormalities were detected in the karyotype analysis.

Conclusion: Cytogenetic methods combined with cost effective techniques such as C, GTG banding and FISH provide well-define of extra Y chromosome in the presented case of without autistic spectrum. Both Y chromosomes were in the same size and C banded profiles in the current proband pointed out that boths are originated from one chromosome by endoredublication Y chromosome after zigot formation.

A CASE DIRECTLY REQUESTED GENETIC COUNSELLING FROM MEDICAL GENETIC OUTPATIENT CLINIC AND DIAGNOSED MOSAIC KLEINFELTER SYNDROME AFTER KARYOTYPE AND FISH ANALYSES

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OP07

Objective: Kleinfelter syndrome (MKS) is the most common chromosome abnormality and mosaicism occures 6% of cases. Most common presentation is 46,XY/46,XXY and mosaicism with 45X, 46XX and 48XXXY clones are also possible. MKS is rare disease that occures in rages from 3-10% of all X chromosome abnormalities. Here we report a young man with 5% mos46,XY/47,XXY karyotype.

Materials and Methods: PHA stimulated peripheral blood was used for the conventional GTG banded karyotype analysis and FISH techniques with nucishDXZ1 and DYZ1 probes were used for the refine detection of numerical/structural sex-chromosome abnormalities for the current presented case.

Case Report: We report a19-years-old case who directly requested genetic counselling from our Medical genetic outpatient clinic and asked " Am I KlinefelterSyndrome?". He has bilateral tanner I-II grade gynecomastia, normal axillary and pubic hair, testis lenght right 3,5/left 4cm, height 176 cm and weight 70 kg but he has not typical enucoid phenotype. Hormonal profile was in normal range with FSH 6.31mIU/mL, LH 4.32 mIU/mL and testosteron 7.88 ng/mL. Case was diagnosed as 46,XY after karyotype analysis but FISH analysis revealed that he was mosaic Klinefelter Syndrome and in mos46,XY[5]/47,XXY)[95] karyotype. The Nucish signals were in (DXZ1x2)(DYZ1x1)[5]/(DXZ1x1) (DYZ1x1)[95] appearance for the presented case.

Conclusion: Current results showed the crucial role of FISH technique for the detection of sex chromosome abnormalities in low percentages and other chromosomal mosaicism in interdisciplinary clinical diagnosis.

A MOSAIC TURNER PHENOTYPE WITH SECONDARY AMENORREA, INFERTILITY AND NORMAL HORMONAL STATUS THAT DETERMINED BY FISH ANALYSIS

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OP08

Objective: Turner syndrome refers to all kind of symptoms as consequence of absence one of sex chromosome in a female person. Only 50% of patients full 45,X karyotype, others has structural X anomalies or mosaicism. Mosaicism can diagnose with karyotyping also, but FISH has an advantage because of analyzing more cells and not only phytohemaglutinine stimulated T lymphocytes, also other types of nucleated blood cells.

Case Report: Turner phenotype is determined at clinical examination of 22 year-woman who referred to COMU Medical Genetic outpatient clinic due to infertility. This individual menstruated first time at 11 yaers old. And since her 17, she has menstrual irregularity. She is short (146 cm), low hairline, short neck and also she has horseshoe kidney. She does two mariages without child. She has mild mental retardation, and chromosome analysis indicated.

Materials and Methods: Chromosome analysis is made to blood sample in heparin containing vacutainer by GTG banding. It's scanned 20 metaphase cells. As a result of GTG banding, it's observed with 46 XX normal karyotype. FISH analysis made for diagnosis. XY FISH is studied with Xcen(DXZ1) Green, Ycen(DYZ1) Red prob set and 100 metaphase cells are scanned.

Results: 45,X,ish, (DXZ1x2)[3]/46,XX,ish, (DXZ1X2)[97] was the FISH result and the patient is evaluated as 3% Mosaic Turner Syndrome. This case is interesting because her phenotype (short stature, short neck, low hairline, horseshoe kidney and infertility) is typical for Turner Syndrome but her normal menarche age, and normal hormonal levels even though Turner syndrome.

A PATIENT WITH INTERSTITIAL 4Q21-Q25 DELETION: CASE REPORT AND REVIEW OF THE LITERATURE

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OP09

4q deletion syndrome is a distinct congenital malformation syndrome associated with clinical findings affecting multiple organs and systems including developmental delay, facial and limb abnormalities, Pierre Robin sequence, cardiovascular, musculoskeletal and gastrointestinal systems abnormalities. Its estimated incidence is 1 in 100,000. About 14 % of cases result from unbalanced segregation, but mostly they are de novo.

Here we report a 41 day-old female born to consanguinous marriage referred us because of dysmorphic facial features, ASD, cystic encephalomalacia and congenital hypothyroidism. On physical examination, large fontanelle, frontal bossing, white forelock, skin hypopigmentation at forehead and umbilical region, prominent eyes, periorbital puffiness, depressed and wide nasal bridge, sublingual frenulum, narrow palate, thin lips, low set and posterior rotated ears, short thorax were detected. Karyotype analysis showed deletion of the long arm of chromosome 4 which resulted in 46,XX,del(4)(q21q25). But subtelomeric fluorescent in situ hybridization (FISH) study was normal, Octochrome FISH confirmed that one of the chromosome 4 was shortened. Chromosome analysis of the parents revealed normal karyotypes while her mother has two spontaneous abortion.

To our knowledge, the patients carried a deletion of chromosome 4 involving the 4q21-q25 region are extremely rare. In this report, the clinical manifestations and relationship between the phenotypic features and chromosomal anomaly will be discussed.

SOTOS-2 SYNDROME WITH NFIX AND COEXISTENT EPHA2 GENE MUTATI

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OP10

Introduction: NFIX (Nuclear factor I/X (CCAAT-binding transcription factor) gene contains 11 exons and mutations of the gene causes 2 types of overgrowth syndromes. Mutations between exon 1 to 4 causes Malan syndrome (Sotos-2, Sotos-like syndrom, [OMIM:#614753], and mutations between exon 5 to 11 causes Marshall-Smith syndrome [OMIM:#602535]. The clinical features of Malan syndrome are long face, thin and long frame, mental retardation, and coxa valga deformity.

Case: Fifteen years old boy referred to our clinic with mental retardation and right sided cataract. At physical examination, he has long facial appearance, kyphosis, flexion contracture of right knee and hip, truncal asymmetry, minimal hyperextansibility, at lower extremities erythematous and desquamous skin rashes with maximum 3cm width, and right hypoplastic testicles. Height/Arm-Lenght: 1.05. Biopsy of skin lesions are reported as dysplastic nevi and echocardiography is reported as mitral valve prolapsus. Karyotype analysis is: 46;XY, homocysteine level was normal. At coxafemoral MRI, there was a coxavalga deformity. Although his hyperextansibility and skin leisions are compatible with Ehlers-Danlos syndrome, the situation is not exactly classified. ArrayCGH and Whole exom Sequencing were performed from the patient and at NFIX gene heterozygous (c.136C>T; p.(Arg46Cys) mutation was found. This mutation causes Malan Syndrome which is partially compatible with our patient but his cataract was not explainable with Nfix mutation. Thus, when the variant list was revised, at EPHA2 gene (c.1876G>A; p.(Glu626Lys)) heterozygous mutation was found, which is related with Cataract 6, Multiple Type (CTRCT6, OMIM: #116600) disease.

Conclusion: Dysplastic nevi, mitral valve prolapsus, inguinal hernia, and undescended testicles are the clinical features of our patient with Malan syndrome of which was not delineated so far in literature. The patients cataract was caused by an extra heterozygous mutation at EPHA2 gene.

UNUSUAL, EXTREMELY RARE, ABNORMAL NUMERICAL CHROMOSOMAL CONSTUTIONS: REPORT OF 6 FETUSE

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OP11

Although single chromosomal aneuploidies are frequently found in pregnancies, double aneuploidies are rare (%0.21-%2.28). Most of these cases are lost during early pregnancy. Here we report 6 double aneuploidy cases which were detected in karyotypes of a spontaneous abortion, four amniocyte cell cultures (AC) and one newborn.

Case 1: Chromosomal analysis of an eight week-old fetus (abortion material of third pregnancy of 44 years old patient with two previous abortion) yielded trisomy twenty in association with trisomy 21: 48,XY,+20,+21

Case 2: Chromosomal analysis from the 6th pregnancy of 50 year-old mother resulted. 48,XXY,21,inv(9)(p11q12) karyotype. Fetal ultrasound presented cystic hygroma.

Case 3: Chromosomal analysis from the 1st pregnancy of a 27 year-old mother, resulted 48,XXX,+18 karyotype. Cytogenetic testing was done due to the detection of bilateral chroid plexus cyst, single umblical artery and clenched hand on fetal USG.

Case 4: Chromosomal analysis from the 3rd pregnancy of a 32 year-old mother yielded regular trisomy 21. Co-occurence of two independent cell lines was observed: one with trisomy 21 and the other with monosomy X in association with trisomy 21 (35% of cells). Thus karyotype was: 46,X,+21(9)/47,XX,+21(16). The phenotype of the fetus was consistent with Down Syndrome.

Case 5: The patient born from the fourth pregnancy of a 40 year-old mother with 3 healthy previous pregnancies had Down Syndrome stigmata. Karyotype was 47,XY,+13(4)/47,XY,+21(26)

Case 6: An AC was performed due to high risk in triple screenig test, to a 30 year-old mother at first pregnancy. Chromosomal analysis from amniotic cells resulted 45,X/47,XX+18.

All cytogenetic results were confirmed with FISH analysis.

Aneuploidies are mostly seen in meiosis 1, meiosis 2 or mitosis respectively, by nondisjunction or anaphase lag; They frequently appear as autosomal trisomies and/or sex chrosome monosomies or trisomies. Extremely rare 'double aneuploidies' as well occur according to these mechanisms. It is suggested that maternal age has an impact on the development of these aneuploidies. The affected pregnancies end in abortion in an earlier period compared to single chrosomal aneuplodies. In clinical practise there is a wide range of clinical signs varying from severe multiple congenital abnormalities to asymptomatic patients. Although clinical features are variable, usualy, the clone with higher count of double aneuplodies with two clones, e.g. 47,XY,+13(4)/47,XY,+21(21) dominates the clinics. The clinical features of two clones can coexist. Since the number of the abnormal clone is important in genetic counseling, performing complementary FISH analysis shoud not be ignored. Literature data about the double aneuploidy of the same clone is limited.

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PREIMPLANTATION GENETIC DIAGNOSIS FOR FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS 2 (FHL2, PRF1 GENE) AND HLA TYPING WITH BLASTOMERE ANALYSIS

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OP12

Familial Hemophagocytic Lymphohistiocytosis 2 is characterized with prolonged fever, cytopenias, and hepatosplenomegaly (OMIM#603553) and inherited in autosomal recessive manner. FHL2 patients have benefit from allogeneic hematopoietic cell transplantation. We have a family (parents have different mutations for PRF1 gene, OMIM#170280) seeking for bone marrow donor for their affected child, compound heterozygote for PRF1 gene (c.148G>A/c.673C>T). Preimplantation Genetic Diagnosis (PGD) is planned for this family to have a healthy baby with full HLA (Human Leukocyte Antigen) match with affected child. For PGD performance, single cell genetic analysis protocol for PRF1 gene mutation is optimized together with closely linked polymorphic STR (Short Tandem Repeat) genetic markers (D10S1665, D10S560, D10S1648, D10S529, D10S676, D10S537, D10S1685, D10S1688, D10S1759 and D10S1650). Haplotyping of family members with linkage analysis was done for PRF1 gene locus and Major Histocompatibility Complex (MHC) area harboring HLA-A-B-C-DR-DQ genes. 10 blastomeres were biopsied from IVF (In Vitro Fertilization) embryos and analyzed with PGD. 5 blastomeres were c.673C>T carrier, 1 blastomere was c.148G>A carrier (trisomy 10 as well) and 2 blastomeres were Wild Type for the DNA sequences of related mutations. For 1 blastomere no genetic data was obtained. Only 1 blastomere (a c.673C>T carrier) had full HLA match genotype with affected child and used for embryo transfer resulted with clinical pregnancy. When the baby was born, genetic condition of the embryo was confirmed with peripheral blood analysis. Here we showed that PGD can be used as a reliable clinical genetic analysis method for PRF1 gene and HLA typing of IVF embryos.

EVALUATION OF CHROMOSOMAL AND THROMBOPHILIA PANEL OF RECURRENT MISCARRIAGES

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OP13

As the loss of three or more pregnancies before 20 weeks of gestation is generally defined recurrent miscarriage. Parental chromosomal translocations, thrombophilic gene polymorphisms, autoimmune factors, uterine, endocrine factors associated with recurrent miscarrige (RM). It has been a very common practice to hold responsible the hereditary thrombophilias that include Factor V Leiden, Prothrombin G20210A gene mutation, Protein S/Protein C/Antithrombin deficiency and MTHFR mutations in the pathogenesis of RM. All patients were took a full genetic analysis; full genetic examination and pedigree drawing was done to exclude known nonchromosomal causes of the anomaly. Cytogenetic analysis was done for 635 patients. The study included peripheral lymphocyte culture by a standard method using Leishmann-banding technique, centromere-banding (C-banding), and nucleolar organizing region staining was done when needed. We used pyrosequencing to genotype 392 individuals. Pure genomic DNA from EDTA anticoagulated blood was isolated either by use of the semiautomated Qiagen EZ1 Advanced XL instrument with the QIAamp blood kit (Qiagen). 392 males and females were tested for four types of hereditary thrombophilia's; MTHFR C677T/1298 polymorphisms, FV Leiden G1691A mutation and Prothrombin G20210A mutation. Among these, 152 of the men or women did not carry any of these mutations.

Table 1. The genotypes of polymorphisms in this study

	Protombin	FV Leiden	MTHFR 677	MTHFR 1298
Heterozygous mutant	18	1	168	184
Homozygous mutant	0	41	40	56
Homozygous normal	374	350	184	152

Table 2. The identified Polymorphic chromosomal variants

S No	The identified Polymorphic chromosomal variants Variants	No of cases
1	9qh+	32
2	inv(9)(p11q13)	7
3	inv(9)(p12q13)	3
4	1qh+	9
5	21qs+	7
6	Yqh+	5
7	Yqh-	4
8	22ps+	4
9	15ps+	3
10	16qh+	3
11	9qh-	2
12	14ps+	1
13	22pstk+ps+	1
14	15pstk+15cenh+	1
15	15ps+	1
16	1qh+, 9qh+	1
17	6cen+	1
18	9qh+, 15ps+	1
19	inv(9)(p12q13),9qh+	1
20	15cenh+	1

Table 3. Structural chromosomal abnormalities

S no	Structural chromosomal abnormalities identified in this study
1	46,XY,t(1;8)(q25;q22)
2	46,XX,t(1;6)(p11;q11)
3	46,XY,t(6;14)(p23;q24)
4	46,XY,t(4;10)(p14;p13)
5	46,XX,t(11;18)(p13;q11.2
6	46,XY,inv(5)(p15q31
7	46,XX,t(11;18)(p13;q11.2)
8	46,XX,rob(13;14)(q10;q10)
9	46,XY,t(2;3)(q35;q25.2)
10	46,XX,t(1;9)(p36.1;q31.3)
11	46,XX,t(8;21)(q23;q22)
12	46,XY,t(19;20)(p13.3;12.1)
13	46,XY,t(1;2)(q25;p13)

Table 4. Numerical chromosomal abnormalities

S no	Numerical chromosomal abnormalities identified in this study
1	47,XXY[3], 46,XY[47]
2	45,X[3]/47,XXX[2]/49,XXXXX[1]/46,XX[94]
3	45,X[6]/46,XX[94]
4	45,X[5]/46,XX[95]
5	45,X[4]/46,XX[96]
6	45,X(3)/46,XX (97)
7	45,X[3]/46,XX[49]

INVESTIGATION OF CYP2C9 AND VKORC1 GENETIC POLYMORPHISMS IN PATIENTS ON WARFARIN THERAPY

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OP14

Warfarin, is the most widely used oral anticoagulant drug around the world to prevent and treat tromboembolic cases. Response to warfarin differs between individuals and serious bleedings may occur due to this drug. Major genes about warfarin pharmacogenetics are CYP2C9 (MIM 601130) and VKORC1 (MIM 608547). Evaluating genetic and environmental factors together in treatment protocols assist in application of treatment more safely and individualization of the treatment.

234 patients using warfarin from Cardiology Department Bursa Uludağ University were analyzed for CYPC2C9 and VKORC1 gene polymorphisms to determine warfarin dose variations among patients and 200 healthy controls selected in Medical Genetics Department in Eskişehir Osmangazi University were analyzed for CYPC2C9 and VKORC1 gene polymorphisms to determine frequencies of the genotypes in Turkish population. PCR-RFLP technique used in our study.

In our study, frequencies of VKORC1 gene g.-1639 G>A(rs9923231) are %27,6, %48,4, %24 for G/G, G/A, A/A genotypes respectively. For CYP2C9 gene c.430 C>T(rs1799853) and c.1075 A>C(rs1057910) polymorphisms CYP2C9 genotype variant frequencies are %59,4, %19,8, %13,8, %3,7, %2,8, %0,5 for *1*1,*1*2,*1*3,*2*2,*2*3,*3*3 variants respectively. A statistically significant relation was determined among average daily warfarin dose and CYP2C9 and VKORC1 genotypes in cases using warfarin. It was statistically found that CYP2C9 and VKORC1 variant genotypes and age factors affects the rate of %29 on warfarin dose variations among cases.

Our study emphasizes importance of genetic factors in determining warfarin dose variations among cases in Turkish Population. As a result screening CYP2C9 and VKORC1 genetic variations will help reducing bleeding complications in clinical cases.

MUTATION SPECTRUM OF THE VHL GENE MUTATIONS

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OP15

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant genetic syndrome, characterised by retinal and central nervous system hemangioblastomas, renal clear cell carcinoma, pheocromacitoma and pancreatic island cell tumor. The VHL gene, a tumor supressor gene, is, located on the short arm of chromosome 3 (3p25.3). In this study, the spectrum of VHL gene mutations in VHL patients was evaluated. Fifteen family having mutations in their VHL gene were inclueded in the study. Sanger sequencing analysis was performed in all VHL families between the years of 2011 and 2015 in molecular genetics laboratory of Medical Genetics Department, Ege University. Fourteen different (ten missense, one nonsense, two deletion/insertion an done splice site) VHL gene mutations were detected in the study group. Segregation analyse could be performed in 11 families. Autosomal dominant inheritence was shown in 8 families whereas 3 families had de-nova mutations. Patients of tree probands were not available for segregation analysis. Four of 14 different mutations detected in this study were novel.

CLINICAL FINDINGS IN PATIENTS WITH 9Q DELETION ENCOMPASSING THE 9Q21.11Q21.32 REGION

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OP16

We report on a case with a developmental delay and dysmorphic craniofacial features, and a novel ~15,2 Mb interstitial deletion within 9q21.11q21.32 confirmed with array comparative genomic hybridization (aCGH). Twenty-two months old boy has inability to walk without support and absent speech. There was on obvious behavioral disorder in his examination. His craniofacial examination revealed relative macrocephaly, frontal bossing, sparse medial eyebrows, hypertelorism, ptosis in left eye, broad base to nose, large mouth, operated cleft lip, sparse and discrete teeth and facial asymmetry. Cytogenetic analysis of the proband including high-resolution giemsa banding revealed interstitial deletion on 9q21. In order to delineate the deleted genes in this region we performed molecular karyotyping. The molecular karyotype revealed 46,XY,der(9)(pter→q21.11::q21.32→qter).arr9q21.11q21.32(71,069,763-86,333,272)X1dn. A small number of cases with deletions localized on the same chromosomal region with similar clinical phenotypes have also been reported in the DECIPHER database. Genotype-phenotype correlations of thirteen patients with 9q21 deletion having different breakpoints and variable length revealed common characteristic features including severe developmental delay, epilepsy, neuro-behavioural disorders and facial dysmorphism including hypertelorism, smooth philtrum and thin upper lip. The smallest overlapping deleted region included four genes. Among these deleted genes as in our patient, especially RORB is considered to be strong candidate for neurological phenotype.

USING TARGET-DRIVEN EXOSOMES TO MEDIATE ANTI-K-RAS SIRNA FOR COLON CANCER TREATMENT

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OP17

Colorectal cancer is the third most common cancer in the world. Currently, there are different treatments available for patients suffering from cancer. Chemotherapy, radiotherapy and surgical intervention are most important therapies for colon cancer. In this study, we aim to create an alternative colon cancer treatment by suppressing the K-RAS gene, which is known to be effective in the pathogenesis of colon cancer and use the nanovesicles called exosomes which are specific to target cells for transporting siRNAs.

We designed and cloned colon cancer specific exosome constructs and transfected to HEK 293T cells. Expression levels of our construct were evaluated by real-time PCR and western blotting. Interaction between Anti-EpCAM which is in our construct and EpCAM antigen was evaluated by immunoprecipitation method.

We successfully designed a colon cancer cell specific exosome. Accuracy of construct was sequence verified by Sanger sequencing. We transfected exosome constructs to HEK 293T cells and checked the expression of our construct by western blotting. We accomplished exosome isolation from transfected cells and showed that our designed protein is located on exosomes. Also we demonstrated interaction between Anti-EpCAM and EpCAM antigen by immunoprecipitation method.

In conclusion, using exosomes for specific delivery of siRNAs to cancer cells could be considered to be a safer and effective method in treatments of cancer compared to operations and chemotherapy procedures. By changing the contents and target cells in our study, the exosome model design can be used for treatment of other diseases.

22Q11.2 DELETION SYNDROME: AN ADULT CASE

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OP18

22q11.2 deletion syndrome is known to present with a variety of phenotypes including congenital heart disease, palatal abnormalities, intellectual disability, immunodeficiency, hypoplasia of thymus and parathyroid glands, and characteristic facial features. This disorder affects an estimated 1 in 4000 people. However, the condition is underdiagnosed due to its variable expression. This syndrome has an autosomal dominant inheritance, but most cases are sporadic. Majority of cases have a interstitial deletion of approximately 3-Mb within 22q11.2 region that includes at least 30 genes like TBX1 which is responsible for the characteristic findings, especially conoturuncal cardiac abnormalities. However, some individuals may have shorter deletions in the same region. Although most cases are diagnosed in early childhood with typical presentation, because of phenotypic heterogenity, adult cases has been reported with hypocalcemic seizures or mental illnesses such as schizophrenia, bipolar disorder, depression, and anxiety. Here, we report a male patient, aged 26, who suffered from seizures and treated with antiepileptic drugs since the age of 15. He had hypocalcemia, thought to be a side effect of valproate, but did not recruit by changing the medication. Additionally, he underwent an open-heart surgery for ventricular septal defect (VSD) at the age of 12 and had mild learning difficulties during school. Physical examination was not remarkable except short stature and mild dysmorfic features. Deletion of 22q11.2 is shown by FISH analysis. Consequently, it is important to consider 22q11.2 deletion syndrome in adults with mild symptoms and atypical presentation.

THE 22Q11.21 DUPLICATION IN A NORMAL INTELLIGENCE CASE WITH PREMATURE OVARIAN FAILURE AND HIGH MYOPIA

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OP19

Objective and Aim: The 22q11.2 duplication syndrome is a rare genetic disorder that caused by a duplication of the segment deleted in Di George Syndrome. Affected individuals may have developmental delay, intellectual disability, slow growth leading to short stature, and weak muscle tone (hypotonia). In one study, about 1 in 700 people tested for developmental delay had the 22q11.2 duplication.

Case: 24 -years-old women reffered to our laboratory from the Canakkale City Hospital's Gynaecology Department because of premature menopause. She was a premature menopause from 23 years old. Her length and weight are 1.67 cm and 65 kgs. Current case has normal intelligence (attent to University), and ther isn't any other dysmorphic signs so she has normal phenotype except high myopia and premature ovarian failure. She has a 2.5 years old healthy daughter. The 22q11.21 duplication is autosomal dominant character, so her healthy daughter analysed with cytogenetics and FISH technique and shows same duplication.

Methods: Blood samples are collected into sodium heparin and EDTA tubes. 22q duplication suspected with GTG Banded chromosome analysis. FISH analysis performed with (TUPLE1,22q11.21) red, (N85A3,22q11.21) green prob set and 22q11.2 duplication confirmed. FMR1 trinucleotide repeat analysis also performed because of Premature Ovarian Failure and 56 and 63 repeats detected.

Conclusion: 22q11.2 duplication usually diagnosed with FISH, MLPA or aCGH, our case diagnosed with GTG banded metaphase chromosome analysis. 22q11.2 duplication Syndrome is a rare genetic disorder and published cases has usually have developmental delay, but our case and her doughter shows definitely normal intelligence. Premature ovarian failure is probably due to premutation of FMR1 but chromosomal duplication can also be effective. This is the first case with 22q11.2 duplication and high myopia.

"FISHED" OUT THE CORRECT DIAGNOSIS: A CASE OF DIGEORGE SYNDROME WITH MENTAL RETARDATION, SHORT STATURE AND DYSMORPHIC FACIAL FINDINGS

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OP20

Objective and Aim: DiGeorge syndrome is known 22q11.2 deletion syndrome (del22q11.2; DiGeorge/Velo-Cardio-Facial syndrome) that caused by long arm 'proximal', 'nested', 'distal', and 'atypical' microdeletions with an estimated incidence of 1 in 4,000 people.

Methods: Heparinised peripheral blood sample as used for karyotype, chromosome and FISH analyses for the presented case.

Case: Here we report a case of 13-years-old child with mental retardation, short stature and dysmorphic facial findings with 22q11.2 interval microdeletion. Heparinised peripheral blood sample was used for karyotype, chromosome and FISH analyses. The GTG – banded metaphases were revealed normal 46,XX structure but interval microdeletion was defined in long arm of chromosome 22 after FISH analysis. Case was diagnosed as DiGeroge syndrome with 46,XXish(TUPLE1,22q11.21)X1, (N85A3,22q13.3)X2 chromosome structure.

Conclusion: Presented case with DiGeorge syndrome clinical findings was "FISHed" out the correct diagnosis by using locus specific probs in the current results. Results also indicate the crucial role of FISH and related techniques as an alternative and/or combined method in correct diagnosis.

THE MOLECULAR ETHIOLOGICAL PARAMETERS IN PRELINGUAL SENSORINEURAL HEARING LOSS*

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OP21

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Objective and Aim: The genetic etiology was reported in 60% patients with prelingual sensorinöral hearing loss (PSHL). In the current study it was aimed to find out the possible mutations in GJB2 connexin 26 gene in patients with PSHL.

Methods: In a total of 46 patients with prelingual sensorineural hearing loss were enrolled in the current project. Total genomic DNA was isolated from peripheral blood –EDTA for each patient and used for genotyping. The target gene GJB2 exon 1 and 2 were amplified, Sanger sequenced and evaluated after capillar electrophoresis (3130 Genetic Analyser, Seqscape v2.6, ABI) for the presented results.

Results: Various point mutations were detected in exon 2 in the current 6 (13%) PSHL patients. No point mutation was detected in exon1 of the target sequenced gene in the current PSHL cohort. Heterozygous 35delG mutation was detected in 2 (4.3%), heterozygous V27I and V153I point mutations were detected in 4 (8.6%) in the current PSHL patients. Homozygous H100P SNP was the most frequent point mutation 33 (71.7%) that detected in the current PSHL cohort.

Discussion: Heterozygous point mutations were detected in exon 2 of GJB2 connexin 26 gene in the current results. One syndromic patient has also heterozygous for 35delG mutation and homozygous for H100P mutations. Results also showed homozygous H100P SNP profiles in high percentage of the current PSHL patients. GJB2 exon 2 sequencing is appropriate for first step molecular genetic analysis.

THE COMBINED MUTATION EFFECT OF PROTROMBIN G20210A AND ACE I/D GENES IN ESSENTIAL HYPERTENSION

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OP22

Objective and Aim: Hypertension is a major health problem that seen in one of the every three people in our country. Genetics ethiology was reported in 25 to 65% in hypertension. In this study; it was aimed to investigate the combined mutation effect of ACE I/D and Protrombine G20210A genes in essential hypertension.

Method: The Prothrombin G20210A and ACE I/D gene mutation profiles were evaluated in 80 HT patients (50F, 30 M) retrospectively in the current results. Total genomic DNA was isolated from periferal blood-EDTA samples and target genes were genotyped by reverse hybridisation StripAssay technique.

Results: Point mutations were detected in 66 (82.5%) patients that diagnosed as essential HT in the presented results. Nine pateints (11.3%) were mutated for Prothrombin G20210A and 65 patients(81.3%) were mutated [34 (52.3%) homozygous and 31 (47.7%) heterozygous mutations] for the ACE I/D SNP in the current results. Combined ACE and Prothrombin G20210A mutations were detected in 9 (11.3%) patients [4 (44.4%) homozygous and 5 (55.6%) heterozygous mutations] from current essential HT cohort.

Discussion: The current results show the combined mutation effect of ACE I/D and Prothrombin G20210A in essential HT and results need to be confirmed by large scale of sample size.

INCREASED POINT MUTATION FREQUENCY IN K-RAS ONCOGENE IN CRC TUMOURS IN CANAKKALE POPULATION

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OP23

Background and Aim: Colorectal cancer (CRC) is the fourth frequent cancer type that occurs all over the World. In the Project it was aimed to find out the frequency of most common point mutations of codons 12, 13 and 61K-ras oncogene in CRC tumours in Canakkale population.

Methods: In a total of 27 CRC tumours were enrolled in the current Project. DNA was isolated from parafine block samples and the genotyping of target point mutations were examined by reverse hybridisation StripAssay and capillar electrophoresis Sanger sequencing techniques.

Results: Various point mutations were detected in 16 (59.2%) samples current CRC tumours. Twelve (44.0%) point mutations in codon 12, 3(11.0%) point mutations in codon 13 and 1 combined 12 and 61 point mutation(4.0%) were detected in one sample in the presented samples.

Discussion: The current results showed the high rate of point mutations in codons 12 and 13 of target K-ras oncogene in the reported tumoural samples. The EGFR mediated therapy is very effective in CRC pateints but it fails when patinent has point mutation in K-ras oncogene. It is also showed that the K-ras genotyping has a crucial role before anti EGFR therapy in CRC patients.

KRAS is said to be one of the most activated oncogenes, with 17 to 25% of all human tumors harboring an activating KRAS mutation (Kranenburg, 2005). Critical regions of the KRAS gene for oncogenic activation include codons 12, 13, 59, 61, and 63 (Grimmond et al., 1992). These activating mutations cause Ras to accumulate in the active GTP-bound state by impairing intrinsic GTPase activity and conferring resistance to GTPase activating proteins (Zenker et al., 2007).

Diaz et al. (2012) determined whether mutant KRAS DNA could be detected in the circulation of 28 patients receiving monotherapy with panitumumab, a therapeutic anti-EGFR antibody. They found that 9 out of 24 (38%) patients whose tumors were initially KRAS wildtype developed detectable mutations in KRAS in their sera, 3 of which developed multiple different KRAS mutations. The appearance of these mutations was very consistent, generally occurring between 5 and 6 months following treatment. Mathematical modeling indicated that the mutations were present in expanded subclones before the initiation of panitumumab treatment. Diaz et al. (2012) suggested that the emergence of KRAS mutations is a mediator of acquired resistance to EGFR blockade and that these mutations can be detected in a noninvasive manner. The results also explained why solid tumors develop resistance to targeted therapies in a highly reproducible fashion.

THE FIFTH FAMILY WITH MACS SYNDROME

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OP24

The MACS syndrome is characterized by four cardinal findings including Macrocephaly, Alopecia, Cutis Laxa and Scoliosis, while the clinical findings of the affected patients described to this date are not strickly consistent with MACS acronym. To date, only four families with this rare connective tissue disorder, having homozygous mutation in RIN2 gene, have been reported. Here we described another family with 3 affected siblings. Twenty nine years old proband had abdominoplasty operation at the age of 20 due to excessive sagging skin. He has coarse facial features with large bulbous nose and thick lips, also brachydactyly, cutis laxa and hypergonadotropic hypogonadism. The other two affected sons of the first cousin parents had same symptoms and also hypergonadotropic hypogonadism, which is suggesting that it is not a rare symptom of the syndrome. We presented this case to contribute to delineation of the phenotypic spectrum and for the better understanding of the common clinical features of the syndrome.

CORRELATION WITH PLATELET PARAMETERS AND GENETIC MARKERS OF THROMBOPHILIA PANEL IN ISCHEMIC STROKES

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OP25

An important type of arterial thrombosis, ischemic stroke is associated with increased mortality risk, severe disability and life quality impairment. Researchers have studied the effects of genetic thrombophilia markers and level of platelet parameters on thrombotic diseases. In this study we analysed mean platelet volume, platelet count values and genetic thrombophilia markers of patients who have ischemic stroke history and searched the relationship with genetic tendency of ischemic strokes and platelet parameters. A retrospective, clinical trial was performed by reviewing the ischemic stroke history (except cryptogenic events) of 599 patients, and 100 controls. The results of the genetic thrombophilia panel were used to classify the study group and control group into low and high risk for thrombophilia groups. The high-risk group included patients homozygous/heterozygous for Factor II or Factor V mutations with any other polymorphism. The low-risk group included patients heterozygous or homozygous for MTHFR (C677T, A1298C), PAI-1, β-fibrinogen, Factor XIIIA (V34L) and glycoprotein IIIa (L33P) polymorphisms or negative in terms of both mutations and polymorphisms. The results of study showed us, high risk group mutations are important risk factors for ischemic stroke but; low risk group polymorphisms are not significant. According to platelet parameters; although there were significant difference between MPV and PLT values of ischemic stroke and control group, thrombophilia mutations and polymorphisms have not a significant effect on MPV and PLT values in ischemic stroke patients.

PRENATAL DIAGNOSIS PALLSTER-KILLIAN SYNDROME (MOSAIC TETROSOMY 12P)

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OP26

Pallister Killian Syndrome (PKS); (OMIM#601803) was first described by Pallister et al. in 1977 in two adult. It is characterized by a tissue specific mosaic distribution of an additional isochromosome 12p. The clinical manifestations of PKS include characteristic craniofacial dysmorphism, pigmentary skin anomalies, limb defect, congenital heart defects, congenital diaphragmatic hernia, hypotonia, intellectual disabilities and epilepsy. A 33-year-old gravida 2 para 1 woman was referred to the Gynecology Unit at 13 weeks' gestation because of increased nuchal translucency (3.95 mm) by a sonographic examination. The parents were healthy and non-consanguineous; there was no history of congenital malformations and the mother didn't expose to drugs, radiation or toxic environmental agents. Cytogenetic analysis on amniocentesis performed at 16 weeks' gestation revealed a male karyotype with a supernumerary chromosome consistent with an isochromosome 12p in 12/17 clones (70%). We confirmed the origin of this marker by in situ hybridization using a DNA specific for short arm of chromosome 12. Parental chromosomes controlled to be normal. This syndrome is rare but its frequency is probably underestimated because of its tissue-specific distribution. All reported cases of PKS have been sporadic, and there has yet to be a report of familial recurrence. Previous studies have demonstrated the absence of a correlation between the mosaic ratio and clinical severity. The prognosis for a fetus with the PKS is very difficult to predict at the prenatal stage.

THE USE OF CELL FREE DNA IN THE SCREENING OF FETAL ANEULOIDY AND CURRENT APPROACHES

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OP27

Prenatal diagnosis of invasive and noninvasive tests can be done in a way (NIPT), but because of the invasive methods have risks of infection and abortion, diagnosing non-invasive procedure increasing day by day. One of the widespread cell free fetal DNA in maternal blood test (cffDNA) that is increasing in clinical use has been drawing attention. The incidence of aneuploidy chromosomal anomaly of the kind in which all live births; Trisomy 21 (Down Syndrome) 1/800, trisomy 13 (Patau syndrome) 1/10,000, trisomy 18 (Edwards syndrome) is a form of 1/6000. Because of the high mortality and morbidity, it is vital that congenital anomalies should be diagnosed in prenatal period. Aneuploidy testing for high-risk pregnant women after the 10th week of pregnancy in terms of the blood sample is taken and free fetal DNA in maternal plasma is based on the measurement of the relative amount. Knowledge of the current criteria for use by healthcare professionals in the field test will allow the exclusion of maternal and fetal risks. In this study, it is aimed to demonstrate current international approaches related to the positive and negative sides of non-invasive that is one of the prenatal diagnostic methods of cff DNA tests. Noninvasive maternal blood tests should be viewed in conjunction with conventional screening tests to prevent maternal and fetal problems. In case NIPD is found negative by the health professionals, pregnant women should be informed that all chromosome and genetic diseases cannot be excluded and they have limitations. Although cffDNA is very important method but there is no definitive guidance on the correct diagnosis and genetic counselling for aneuploidy therefore nurses and healthcare workers should lead pregnant women and families and for the prevention of problems.

ASSOCIATION BETWEEN HUMAN HAIR LOSS AND THE EXPRESSION LEVELS OF NUCLEOLIN, NUCLEOPHOSMIN AND UBTF GENES

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OP28

Nucleolar organizer regions, also known as argyrophilic nucleolar organizer regions, are associated with ribosomal genes. The main function of the nucleolus is the rapid production of ribosome subunits, a process that must be highly regulated to accomplish accurate cellular proliferation and cell growth. There are no studies in the literature addressing the expression and function of nucleolar component proteins such as nucleophosmin, nucleolin and upstream binding transcription factor (UBTF) in human hair follicle cells. 19 healthy males who had normal and sufficient hair follicles on the back of the head, but exhibited hair loss on the frontal/vertex portions of the head and 14 healthy males without hair loss were included in the current study. Gene expression levels were measured by relative quantitative RT- PCR. In the individuals suffering from alopecia, the total expression levels of nucleolin, nucleophosmin and UBTF were lower in normal sites than hair loss sites of individuals suffering from hair loss. A strong correlation was detected between nucleophosmin and nucleolin, between nucleophosmin and UBTF, between nucleolin and UBTF among all groups. There was an association between human hair loss and the expression levels of nucleolin, nucleophosmin and UBTF genes.

MITOCHONDRIAL DNA DELETIONS IN PATIENTS WITH ESOPHAGITIS, BARRETT'S ESOPHAGUS, ESOPHAGEAL ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA

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OP29

Esophageal cancer is the eighth most common cancer globally. Esophageal adenocarcinoma (EA) and esophageal squamous-cell carcinoma (ESCC) are the two major types of esophageal cancer with poor prognosis. The mechanisms of the progression of normal esophagus to Barrett's esophagus (BE) and EA are not fully understood. Mitochondria play a central role in generating energy, apoptosis and cell proliferation. Mutations of mitochondrial DNA (mtDNA) have been identified in many diseases including cancers. Mutations of mtDNA were investigated as a part of carcinogenesis. In this study the frequency of the 5 kb and 7.4 kb deletions in mtDNA were studied in specimens ranging from normal esophageal tissue to BE and EA and also from ESCC. Our objective is to study whether if the 5 kb and 7.4 kb mtDNA deletions are important in the progression of normal esophagus to BE and EA. Seventy six paraffin-embedded tissue samples were studied. Four couple primers were used. The deletions were not detected in any of the samples. We can say that, these deletions are not associated with progression of normal esophagus to BE and EA and they do not have an important role in detecting esophagitis, BE, EA and ESSC.

1800 MHz ELECTRIC FIELD EXPOSED RATS IN THE STOMACH TISSUE OF HSP70 STRESS GENE EXPRESSION LEVEL OF INVESTIGATION

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OP30

Electromagnetic fields (EMF), consist of a combination of electric and magnetic fields. With the use of cell phone, it is though that electromagnetic fields could be negative effects on people healty and it is began to study in this field. The idea that exposure to electric field causes to cancer by increasing the levels of stress proteins in cell consist of one of the workspace. Hsp70 which plays role to control the activity of the regulatory proteins is one of the most studied proteins. Our study we examined the effect of electromagnetic fields on expression of Hsp70 stress protein in somach tissue. There are three groups in our study namely the experimental sham and control group. There were 9 rats in each group so 27 Wistar Female rats were included to the study. The subjects in experimental groups were exposed to 1800 MHz radiofrequency radiation for 2 hours per day during 8 weeks. Sham group was kept in device without being exposed to EMF at same time with experimental group. The rats in the control group were not exposed to any process. Hsp70 gene expression was performed from mRNA samples obtained from stomach tissue by using RT-PCR/ Real-Time PCR. There was no meaning difference in expression levels of Hsp70 gene between groups (p=0.315). Increasing EMF exposure time, Hsp's and other apoptosis-related information on this subject by looking at the expression level of genes provided significant contributions. Our study Mersin University project is supported by BAP No. 2015-AP4-1216 unit.

EXPANDING THE CLINICAL AND GENETIC HETEROGENEITY OF PAPILLON-LEFEVRE/HAIM-MUNK SPECTRUM

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OP31

Cathepsin C (CTSC) is a lysosomal protease which is required for activation of serine proteinases in cells of immune system. Biallelic CTSC gene mutations cause Papillon-Lefevre (PALS; OMIM 245000) and Haim-Munk (HMS; OMIM 245010) syndromes which are autosomal recessive disorders characterized by palmoplantar keratosis and periodontitis. Homozygous CTSC gene mutations also cause isolated juvenile aggressive periodontitis (OMIM 170650). Here we report on a consanguineous Turkish family in which two brothers had palmoplantar hyperkeratosis, skin lesions healed with scarring, acroosteolysis, joint stiffness, nail dystrophy, premature loss of both deciduous and permanent teeth, short stature and scoliosis. The history revealed that teeth of patients had erupted normally, but were lost prematurely after normal eruption due to inflammation in periodontal tissues. Palmoplantar hyperkeratosis and dystrophic nails became apparent by 2-3 years of age and showed a progressive course. Although the phenotype segregating in the family overlaps with Papillon Lefevre/Haim Munk syndromes, associated findings such as scoliosis, short stature and scarred skin lesions has not hitherto been reported in PALS/HMS spectrum. While DNA sequencing of one affected individual revealed no mutation in the CTSC coding region, whole exome study using IonProton infrastructure identified a total of 17 homozygote coding variants in one affected individual. Systematic gene identification approach including genome wide SNP genotyping followed by homozygosity mapping as well as array based copy number variation analysis are currently underway to understand the molecular pathology of this family. The patients reported here further expand the clinical and genetic heterogeneity of palmoplantar keratosis-severe periodontitis spectrum.

CLINICOPATHOLOGIC ASSOCIATIONS OF BRAF GENE IN MALIGNANT MELANOMA

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OP32

The incidence of melanoma has been increasing dramatically in recent years. Molecular heterogeneity is observed in melanoma. Various mutations have been defined in many genes in melanoma. BRAF is part of a signaling pathway known as the RAS–RAF–MEK–ERK–MAP pathway, which controls several important cell functions. Specifically, this pathway regulates the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), cell movement (migration), and the self-destruction of cells (apoptosis). Approximately 33%-55% of malignant melanomas somatic mutations in the BRAF gene, depending on the type of melanoma. The most common of these mutations results in substitution of the valine residue at amino acid position 600 to glutamic acid in the BRAF protein (V600E). BRAF-V600E mutations represent approximately 60%–80% of all BRAF-V600 mutations. BRAF-V600K mutations are the second most common mutation in BRAFV600–mutated melanomas, and other BRAF-V600 mutations, such as V600D, V600R, V600M, and V600E2, are seen in less than 5% of BRAF-V600–mutated melanomas.

In this study, the Uludag University Medical Genetics data was presented for melanoma cases; the BRAF-V600 mutation was found in 47 (38.8%) of the 121 patients with primary and metastatic malignant melanoma. There were 36 (77%) V600E, 10 (21%) V600K, 1 (2%) V600R mutation in patients detected BRAF mutation. In this presentation, the relationship between the clinical and pathological features of patients with the BRAF mutation was discussed.

GENETIC SCREENING FOR CFTR AND AZF REGION OF Y CHROMOSOME MICRODELETIONS IN IDIOPATHIC CASES OF AZOOSPERMIA AND OLIGOZOOSPERMIA: A MOLECULAR AND CYTOGENETIC APPROACHE

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OP33

Backgraund and Aim: Infertility affects approximately 15% of couples; and half has male-related etiology. The most common form of male infertility is Spermatogenic failure. Up to 30% of cases; monogenic disorders (eg, cystic fibrosis [CF], Kallman syndrome) cytogenetic abnormalities (eg, Klinefelter syndrome [KS; 47,XXY]), and Y chromosome deletions responsible for male infertility. In the present study; we aimed to evaluate the frequencies of cytogenetic anomalies, Y chromosome microdeletions and CFTR mutations of infertile males with azoospermia and oligozoospermia from the central Canakkale population.

Method: Results of 158 infertile male patients was screened retrospectively. All patients chromosomes analyzed with GTG banded karyotyping and fragment analysis for AZFa, AZFb, AZFc microdeletions (25 STR region) of Y chromosome and CFTR gene Sanger sequencing (4 exons), performed for diagnosis.

Results: Numerical X choromosome abnormalities (47XXY) were detected in 3 (1.89%) patients, 3 (1.89%) patients showed Yqdel and 5 (3.1%) patients showed Y chromosome long arm duplication in cytogenetic evaluation. In the genotyping of Y choromosome AZF region microdeletions were detected in AZF gene region in 3(1.89%) patients and CFTR mutations detected in 15 patients (9.49%) of the current oligo-azospermic infertile male cohort.

Conclusion: CFTR gene analysis, karyotyping and Y chromosomal microdeletion analysis will be useful before IVF and other ART techniques to help for true diagnosis of etiology, appropriate genetic counselling and better results at assisted reproduction in male based infertility.

GUIDELINES FOR THE EVALUATION OF THE SEQUENCE VARIANTS

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OP34

The cost of sequencing dramatically decreased and speed of obtaining sequencing data increased in last ten years through commercial launch of next-generation sequencing (NGS) technologies in 2005. Current sequencing cost of whole genome just over $1,000.

Detailed catalogues of genetic variation in both disease patients and the general population was generated through the widespread use of NGS in the clinical genetic laboratories. Because of the large amounts of data output, evaluation of sequence variants become difficult. False assignments of pathogenicity of variants can have severe consequences for patients' health. For these reasons, many clinical genetic laboratories have developed their own variant classification criteria and guidelines. To standardize these classifications American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) published a revised standards and guidelines for interpretation of sequence variants in 2015. They suggested a five-tier terminology system using the terms "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign".

These guidelines and suggested criteria for classifying pathogenic variants will be discussed and application of guideline on sample cases data will be performed.

MOTOR DISORDER IN HUNTINGTON'S DISEASE MAY BEGIN LIKE TIC DISORDER: ATYPICAL CLINICAL PRESENTATION IN LARGE FAMILY

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OP35

Introduction: Huntington's disease (HD) usually causes movement, cognitive and psychiatric disorders with a wide spectrum of signs and symptoms. The pattern of motor symptoms tends to change over time, with chorea declining and dystonia, rigidity, and bradykinesia becoming more marked. Other unwanted movements include tics, comparable to those seen in Tourette syndrome, but these are fairly rare. We describe herein the case of a young HD patient presenting with symptoms similar to tic disorder who belonged to a large family with a variety of clinical symptoms.

Family description and movement disorder: The family history includes seven affected members and five healthy subjects who all had clinical presentations consistent with autosomal dominant HD. Our patient (age 29 years) had experienced involuntary movements like tics since childhood in addition to lack of attention. Therefore, he had been misdiagnosed with attention deficit hyperactivity disorder. Now, he has several tics. These are often seen on his face, leading to rapidly changing facial expression. Also, he has mild chorea involving the upper limbs. All affected cases (his mother, grandfather, two maternal uncles and one maternal aunt) presented psychiatric disorder (schizophrenia), involuntary movements (chorea) and cognitive disorder onset in early adulthood. They had all passed away several years ago. His sister (aged 26 years) has had symptoms of depression since adolescence. However, she has had no movement disorders up to now.

Conclusion: The signs and symptoms in HD can be caused by a number of different conditions. Therefore, it's important to get a prompt, thorough diagnosis. In conclusion, we report a large variety of clinical symptoms in a family with HD.

CLINICAL FINDINGS OF A CASE WITH SUBMICROSCOPIC DELETION AT XP22

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OP36

Submicroscopic deletions of Xp22 have rarely been reported. We present the case of a nine-year-old girl with dental anomaly(diastema), facial dysmorphisms (microcephalia, long face, prognathism, prominent nose, wide mouth and large ears) and intellectual disability (mild moderate mental retardation). A routine chromosome analysis showed a normal 46,XX karyotype. Further investigation by array-based comparative genomic hybridization (CGH) revealed a 3.66 mb microdeletion on chromosomal band Xp22 region chrX:16390643-20050349 (GRCh37/hg19). The deleted region encompasses 17 OMIM genes and some genes associated with disorders such as NHS, CDKL5, RS1, PKAH2, PDHA1. The findings of our case may be helpful in further analyzing the phenotypes associated with Xp22 deletions.

MOLECULAR ANALYSIS IN A RARE RIBOSOMOPATHY PHENOTYPE: DIAMOND BLACKFAN ANEMIA

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OP37

Ribozomal proteins (RPs) are critical components of the ribosome and haploinsufficincies in RPs are responsible for rRNA maturation defect. Impaired ribosome biogenesis and function lead a collection of disorders, ribosomopathies, with specific clinical phenotypes. Diamond Blackfan Anemia (DBA; OMIM 205900) is a rare congenital pure red cell aplasia that is diagnosed during the early infancy. Erythroid failure is the most distinctive feature of the disease and 40% of all cases present variable congenital malformations such as craniofacial, cardiac, thumb and urogenital anomalies. Autosomal dominant and X-linked mode of inheritance have been reported. DBA is considered a "ribosomopathy" since the disorder affects the ribosome biogenesis. It is a genetically heterogeneous disorder. Point mutations and deletions in several RP and non-RP genes have already been reported. However, the genetic cause of 1/3 of all DBA cases still remains unknown. In this study a total of 18 DBA cases and their families were included. De novo point mutations, c.237T>G (p. Tyr79Stop); c.280C>T (p. Arg94Stop), and heterozygous deletions in RPS19, the most common cause of DBA, were identified in four cases by Sanger sequencing and Q-PCR respectively. Whole exome sequencing using Illumina Hiseq infrastructure followed by variant filtration revealed novel candidate genes which might involve in the pathogenesis of this disorder. Our analysis showed that RPS19 mutations are also common in Turkish population. Thus, heterozygous mutation screening of RPS19 genes should be the first-line test in DBA (Supported by: Hacettepe University Research Fund-THD-2015-5201; TUBITAK-315S192 under the frame of ERA-Net for Research on Rare Diseases, EURODBA consortium).

INVESTIGATION OF NF-KAPPA-B 1 GENE AT 94 POSITION ATTG AND 561 POSITION A/C POLYMORPHISM IN BREAST CANCER PATIENT

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OP38

NF-κB1 is an important transcription factor at located 4q24 and affecting more than one phenotypic property. There are different single nucleotide polymorphisms (SNP) determined in NF-κB1 gene. These SNPs indicates the degree of susceptibility of patients and differences of response to treatment status. NF-κB1 gene demonstrated the presence of the relationship with certain types of cancers including lung cancer, hepatocellular carsinoma, colorectal cancer and breast cancer. This study aims to find the relationship between NF-κB1 94 ATTG polymorphism of the breast for the first time. NF-κB1 gene was studied in many cancer but to determine whether of A/C polymorphism by the Pst1-HF restriction enzyme are not investigated in breast cancer.

In this study we analysed NFKB1-94 ATTG and NF-κB1-826 A/C polymorphisms by restructed with PfıMI ve Pst1-HF enzyme accordingly to RFLP method in primary tumor core biopsies from 60 high-risk primary breast cancer patients.

By digestion of PfıMI enzyme, for ins/ins 281 bp, del/del 240 bp and 45 bp and ins/del 281 bp, 240 bp and 45 bp size bands should be seen. After PCR amplification and PfıMI enzyme digestion of NFκB1-94 ATTG gene results for ins/del were observed 86% of patients. However, del/del genotype were observed in 14% of patients. On the other hand for digestion with PstI-HF enzyme of NFκB1 S128R gene only 281 bp band size were seen and there is no correlation between the NFκB1 S128R gene polymorphism and breast cancer progression.

Our study is important as being the first study that analyzes association of NFκB1-94 ATTG polymorphism with breast cancer risk.

DNA SEQUENCE ANALYSIS OF THE NRAMP1 PROMOTER REGION IN TULAREMIA

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OP39

Tularemia is an intracellular bacterial disease that can lead to severe morbidity and mortality, which is caused by the bacteria Franciella Tularensis. It is observed endemically in some areas of Turkey. Tularemia has 6 clinical forms as ulceroglandular, glandular, oculoglandular, oropharyngeal, thyphoidal and pneumonic forms. The most common clinical form in Turkey is the oropharyngeal type. Natural Resistance Associated Macrophage Protein 1 (NRAMP1) gene have been found to play important roles in macrophage activity. NRAMP1 gene polymorphism has been associated with disease like tuberculosis and leprosy that have similar pathogenesis with tularemia.

Case-control study was performed to determine plausible association between NRAMP1 5'(GT)n microsatellite polymorphism and tularemia. The study group consisted of 120 patients who had been diagnosed with oropharyngeal tularemia and control group consisted of 120 healthy volunteers. Genomic DNA was isolated from frozen whole blood–EDTA according to a standard procedure. 5'$(GT)_n$ microsatellite analysis was performed as a sequence analysis, using a genetic analyzer. The frequencies of allele 2 and allele 3 of the $(GT)_n$ were 24% and 76% in tularemia, 19% and 81% in control subjects. No association was found between tularemia and NRAMP1 5' promoter $(GT)_n$ microsatellite polymorphism (p=0.09).

Our findings suggest that NRAMP1 polymorphisms do not play a role in tularemia susceptibility. In conclusion, the current study's findings will contribute to the understanding of the mechanisms responsible for host defense and pathogenesis during cases of tularemia.

SILENCING OF IMPORTANT MOLECULES HAVING ROLES IN PATHOGENESIS OF IDIOPATHIC PULMONARY FIBROSIS VIA RNA INTERFERENCE AND DEVELOPMENT OF NEW THERAPEUTIC MODALITIES

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OP40

Idiopathic pulmonary fibrosis (IPF) is a poorly understood, devastating, progressive fibrotic lung disease and characterized by excessive fibroblast proliferation and lung scarring. Despite our better understanding of IPF pathogenesis, the etiology and the precise cellular and molecular mechanisms involved are not well known. There is currently no effective therapy for this fatal disease, which has a median survival of only 3 to 4 y and leads to death within 5 years of diagnosis. In this study, we examined whether inhibition of the Osteopontin, Twist and Wnt-5a genes could attenuate pulmonary fibrosis.

Method: A549 cell line was induced with TGF-β for in vitro experiments and followed by introduction of Small inferring RNA (siRNA). After 48 hour from the application of siRNAs for the three target genes, changes in expression of genes responsible for the formation of fibrosis and Epithelial-mesenchymal transition (EMT) were evaluated by using real-time PCR and Western blot analysis. In second part of the study, bleomycin-induced mouse model of pulmonary fibrosis was induced in C57BL/6N mice by intratracheal instillation of bleomycin. GAPDH siRNA was intranasally administered in different concentration to optimize ideal siRNA knockdown concentration for in vivo experiments. After dose optimization SPP siRNAs were administered (5 µg in 40 µL).

Results: EMT is induced in vitro by TGF-β administration. siRNA targeting SPP significantly suppressed SPP expression and significantly increased E-CDH expression. Also, suppression of Twist significantly inhibited the Fibronectin expression. Intranasal delivery of SPP siRNA successfully knock-down SPP expression in mouse lung tissue.

Conclusion: These results indicate that SPP gene may play an important role in the development of fibrosis via the mechanism of EMT and Twist gene may have important role in fibrosis formation. Targeted therapies for these two genes may be a therapy option for IPF patients in the future.

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CHROMOSOME ABNORMALITIES AT PRIMARY AMENORRHAE FEMALE PHENOTYPES AND CLINICAL EVALUATION: A CASE SERIES REPORT

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OP41

Primary amenorrhae is absence of menarche by age 15 years. It should prompt a thorough evaluation to identify the cause. Primary amenorrhea is usually the result of a genetic or anatomic abnormality. According to large case series of primary amenorrhae nearly half of the cases have chromosomal abnormalities causing gonadal dysgenesis. So chromosomal rearrengements is the most common etiology of primary amenorrhae. Turner syndrome 45, X is the most common reason as well as other types of Turner and other cytogenetic aberrations also seen at gonodal dysgenesis patients.

Here, we present 8 different cases admitted to our clinic with complain of primary amenorrhae and cytogenetic analysis found with spesific karyotype anomalies. The results of chromosome analysis from peripheric blood samples of patients are; one isochromosome X/mosaic Turner Syndrome 45,X[21]/47,X,i(X)(q10),i(X)(q10)[2]/46,X,i(X)(q10)[27], one mosaic Turner/Triple X mos45,X[6]/47,XXX[3]/46,XX[41], one derivative X:X translocation 46,X,der(X)t(X;X)(p11.2;q27)dn, one partial X deletion 46,X,del(X)(q13), one autosomal pericentric inversion 46,XX,inv(2)(p11.2q13) and 3 sex reversal syndrome 46,XY female cases. Due to cytogenetic aberrations gonodal dysgenesis and primary amenorrhea seen at our cases. And also some phenotypical differences are such as short stature and incomplete secondary sex characteristics observed.

We evaluate these cases according to their karyotypes and phenotypes. We have a presentation for disorders of sex development and cytogenetic anomalies and phenotypic correlations of our patients.

In conclusion, we can clearly say that karyotyping and genetic counseling is an essential issue for understanding the mechanism of primary amenorrhae especially hypergonadotrophic hypogonadism cases and background of other phenotypic differences.

A PARTIAL DELETION(XP)/DUPLICATION(XQ) CASE DUE TO MATERNAL PERICENTRIC INVERSION(X) CONFIRMED BY MICROARRAY

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OP42

Carrying a parental pericentric inversion can cause deleted/duplicated offsprings. According the literature, del(Xp)/dup(Xq) is a rare chromosomal aberration in males due to maternal pericentric inv(X).

A seven days old male patient was referred us from pediatric intensive care unit because of dysmorphic features. He was born at 35 weeks gestation age by C/S because of oligohydramnios. His birth percentiles were in normal ranges.

Physical examination findings were narrow biparietal diameter, broad nasal root and nasal bridge, depressed nasal tip, short columella, long, flat philtrum, thin upper lip and retromicrognathia. The patient's karyotype was 46,XY. We performed subtelomeric FISH analysis because of non-sendromic dysmorphic faetures. Two signals for Xqter were detected on each tip of X chromosome, but no signal was detected for Xpter. His microarray analysis revealed that there were 3.7 Mb deletion on Xp22.33p22.31 which contains 9 OMIM genes, 2.5 Mb deletion on Xp22.33 pseudoautosomal region which contains 23 OMIM genes, 2 Mb duplication on Xq28 which contains 52 OMIM genes and 270 Kb duplication on Xq28 pseudoautosomal region which contains 3 OMIM genes. Chromosomal analysis from both parents were performed for possible pericentric inversion of X chromosome and another chromosomal aberrations. Paternal karyotype was normal, but his mother had pericentric inversion of X chromosome which was confirmed by subtelomeric FISH analysis. His brother also had pericentric inversion (X).

We present this case in order to contribute to the literature. It is important to provide genetic counseling that pericentric inversion carrier parents have risk of deleted/duplicated offsprings and affected children.

A CASE WITH 22Q11 DELETION SYNDROME AND ANAL ANOMALIES

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OP42

Chromosome 22q11 deletion syndrome is the most common microdeletion syndrome characterized by cardiac anomalies, dysmorphic features, hypocalcaemia and velopharyngeal insufficiency. Most published reports has focused on classical features of 22q11 deletion syndrome, especially cardiac defects. Anal anomalies are rarely described but reasonably well recognised features of this syndrome. Here we report a 12-days-old boy with anal atresia and inguinal hernia. He had 2.8 Mb size deletion of 22q11 (18628019-21505417) detected by array CGH and confirmed via fluorescent in situ hybridization technique. The purpose of this presentation is to emphasize the anal anomalies which are the rare components of this syndrome.

A CASE WITH INTRACTABLE SEIZURES, 46, XX, R(14) KARYOTYPE AND HYPOTHYROIDY

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OP44

Chromosome 14 Ring is an extremely rare chromosomal disorder that first described in 1971 by Gilgenkrantz et al., with over 70 cases reported by Zollino M et al. (2012) so far. Clinical manifestations include typical facial appearance, intellectual disability, development delay, microcephaly, ocular abnormalities and seizures. It has appeared to affect males slightly more often than females. We describe a 3 years old male had ring chromosome 14 with associated developmental delay, mental retardation and dysmorphic features. Our patient had anintractable seizures particularly occured during sleeping and infection with early onset at 3 months old. EEG and Cranial MR findings were normal. On his physical examination, his height was 93 cm (10-25p),his weight was 12.3 kg (3-10p) and his head circumference was 43.5 cm (<3p). He had microcephaly, low set cup-shaped ears, broad nasal root, bilateral epichantus, bulbous nasal tip, high arched palate, thin upper lip, down-turned mouth. Karyotype analysis was performed from peripheral blood cells and GTG banding was done. The 46, XX, r(14) karyotype was detected. There was no relationship between parents and he had a healthy brother. It seems to be a sporadic case. He interestingly had hypothyroidy. He had dry skin and scaly skin was available. Thus he was consulted to dermatology department. He had strabismus and no hearing defects. Althought there are few studies about the intractable seizures and 46, XX, r(14), to do best of our knowledge this is the first case with intractable seizures, 46, XX, r(14) karyotype and hypothyroidy. Therefore we thought that the case may provide additional knowledge to the literature about the current topic.

ARGYROPHILIC NUCLEOLAR ORGANIZING REGION-ASSOCIATED PROTEIN SYNTHESIS IN THE CELLS OF RAT KIDNEY TISSUES DURING ISCHEMIA-REPERFUSION INJURY

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OP45

Ischemia indicates to insufficient blood supply to tissues due to obstruction of the arterial inflow. Reperfusion injury cause the tissue damage that occur via blood supply returns to the tissue after an ischemia period or lack of oxygen. Nucleolar-organizing regions (NORs) are genetic loci on chromosomes and they can be stained with silver when they are active. Therefore these proteins are named as argyrophilic-NOR (AgNOR)-associated proteins. We aimed to investigate whether are there any possible effects of renal I/R injury on the NOR protein synthesis and an association between the AgNOR proteins amount and histopathological injuring score.

Nine female wistar-albino rat with weight 200-250 g were included the study. The animals were randomly divided two groups as Control and I/R Group. In I/R group, Rats were subjected to 45 min of renal pedicle occlusion followed by 24 hours reperfusion. In Control Group any drug injections or ischemia reperfusion was not performed to animals. Then histopathological injuring score, mean AgNOR number and total AgNOR area/nuclear area (TAA/NA) were detected for each rat. There were significant differences between control and I/R groups for histopathological injuring scores ($p<0.05$). The differences between I/R group and control group were significant for mean AgNOR number ($p<0.05$) and TAA/NA ratio ($p<0.05$). A positive correlation was detected between TAA/NA ratio and histopathological injuring score ($p<0.05$) and between mean AgNOR number and histopathological injuring score ($p<0.05$).

AgNOR proteins amount may be used as an indicator to obtain the knowledge about the I/R injury and celular damage levels.

HYPERMOBILITY CASES, OUR CLINICAL EXPERIENCE

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OP46

Aim and Objective: The joint laxity (hypermobility) is a common condition, and can also be seen with approximetely 5-15% of healthy individual without any symptom in the community. The Ehlers-Danlos Syndrome (EDS) is a heterogeneous group of heritable disorders of connective tissue diseases, charatecterized by hypermobility, skin hyperextansibility affecting skin, joints, ligaments, blood vessels and internal organs with a wide clinical variability. Classical type, hypermobile and kyphoscoliotic types are common forms of this diseases; vascular, artrochalasic and dermatosparactic types are quiet rare. In this study we discuss 34 patients referred to our clinic with hypermobility.

Results: 34 hypermobility cases, admitted to and followed up by Marmara University Pediatric Genetic Clinics between 2000-2015 years. The patients were evaluated according to their age, gender, Beighton score, consanguinity, positive family history, skin, joint and skeletal findings, involvement of other internal organs and complications. The patients included in this study, the age is between 2-25, mean age: 11.2.18 (%52.9) of the patients were male and 16 (%47.1) were female. %29.4 of cases have the history of consanguineous marriage. 22 cases (%64.7) have positive family history. Hyperelastic skin in 23 patients (%67.1), 14 patients (%41.1) has at least one of those findings (scoliosis, pes planus and pes eqinovarus deformity) as a clinical finding. Beighton scores were 5 and upper in 23 patients (%67.6), 6 patient (%17.6) had a history of congenital hip displasia and 10(%29.4) had a history of recurrent dislocation of other joints.

Discussion: The diagnosis is often confusing for clinicians, and mainly based on clinical symptoms and family history. Histopathologically, slight decrease in the dermal collagen, irregularly shaped and a relative increase in elastic fibers but they are in normal configuration. Thus, tissue biopsy is not helpful for the diagnosis. There is no specific treatment for the disease. Patients may benefit from physical exercises. Average life expectancy is not different from general population. Genetic counseling should be offered to patients.

SPONDILOCOSTAL DISOSTOSIS TYPE 1, 2 CASES WITH DLL3 MUTATION

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OP47

Aim and Objective: Spondlylocostal disostosis (SCDO), with the other name Jarcho-Levin syndrome is hereditary disease is characterized by multiple vertebra and costa anomalies. Axial skeletal malformatons is detected clinically and radiographically. Even if accompanied with multipl organ anomalies in sporadic mutation is more frequent in this group of diseases, but also autosomal dominant (AD) and autosomal recessive(AR) forms are also known as inheritance. 4 gene mutation is defined for AR-SCD: DLL3, MESP2, IFNG ve HES7 gene mutations. DLL3 gen mutation is responsible for AR-SCD, SCD type1.

Case 1 (SŞ): 4.5 year, girl was born to a G6P3A3Y3, 28 years mother by C/S, 3300 grams. Her parents were 1. degree cousin marriage as consanguinity. She was admitted to our clinic with short stature and growth retardation. BW: 8.75 kg (<3p), Height: 135 cm (3-10p), HC: 48 cm (2-50 %p). Her physical examination has thin and dry hair, kyphosis, pectus carinatus, mild scoliosis and lordosis. Multiple vertebra and costa anomalies in her X-Rays.

Case 2 (EMS): 8 year, boy was born to a G5P5A0Y5, 47 year mother by NVB, 3200 grams. No consanguinity between parents. He was admitted to our clinic with short stature. BW: 22.3 kg (<3p), Height: 117 cm (<3p), HC:50 cm (2-50 %p). His physical examination has hypotelorism, narrow forehead, low hair line, significant scoliosis. Block and hemi vertebra, butterfly shaped vertebra is seen in his X-rays.

SCD is suspected as a diagnosis with the present clinical findings. In gene analyses DLL3 mutation is detected.

Conclusion: The SCD cases present with short neck when servical spine is effected. Also present with respiratory problems due to multiple vertebra and costa anomalies, kyphosis, scoliosis and pectus deformities and short stature. Patients should be examined carefully for anomalies that may be associated with the other systems. Families should be given genetic counselling and patients should be followed up appropriate intervals.

DEATH TO LIFE/BACK TO THE FUTURE: DETAILED PREMORBID CLINICAL AND FAMILY HISTORY CAN SAVE THE LIFES AND ADDRESS THE FINAL DIAGNOSIS IN SUDDEN UNEXPLAINED DEATHS WITH NEGATIVE AUTOPSY

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OP48

Background: Sudden cardiac death (SCD) is responsible for a large proportion of sudden deaths in young individuals. In forensic medicine, many cases remain unexplained after routine postmortem autopsy and conventional investigations. These cases are called sudden unexplained deaths (SUD). İnherited cardiac disorders such as Long Qt, Brugada syndrome and cardiomyopaties comprise a substantial proportion of SUD cases. In this study, two forensic SUD case and their family members are investigated for inherited cardiac disorders.

Case Presentation: A 35 and 31 years old unrelated asymptomatic males died suddenly during sleep. There was another SUD individual in the first case's family and secod case had a syncope history. Postmortem examinations excluded the extracardiac causes of sudden death as well as the absence of structural abnormalities. But, we had no available material for the first case. Luckly, first case had a sister whose cardiologic examination indicated Brugada syndrome with positive ajmaline test by chance; intracardiac defibrillator was planned and implanted to her. So, we performed 68 gene cardiac panel to the sibling of the first case and the second forensic SUD case.

Methods: Whole blood was obtained from the SUD family members with informed consent. Genomic DNA was isolated with Wizard® Genomic DNA Purification Kit, Promega. Targeted sequencing was performed on ion Personel Genome Machine using Ion Ampliseq Panel comprising 68 genes known to be associated with cardiological arrhythmias. Torrent Suite Software was used for data analysis. The missense mutations were confirmed by GenomeLab™ GeXP Genetic Analysis System, Beckman Coulter.

Results: Three heterozygote missense variations in TRPM4, AKAP9 and RANGRF genes in the sibling of the first case. Molecular autopsy of the second case was revealed 3 missense variations in KCND3, AKAP9 and KCNE1. RANGRF variation was novel, KCNE1 and TRPM4 variations were reported as pathogenic allele and the remaining 2 were reported as "unknown'' allele. Carriers were identified in two families, also. For future directions functional analysis of found variations are under estimated.

Conclusion: Irrespective of genetic testing; all SUD family required detailed clinical testing to identify relatives who may be at risk. Molecular autopsy and detailed premorbid clinical and family history can survive family members of SUD cases.

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MICRODELETION ON 17P11.2 IN A SMITH MAGENIS SYNDROME PATIENT WITH DYSMORPHIC AND BEHAVIORAL FEATURES

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OP49

Smith Magenis syndrome (SMS) is a rare microdeletion syndrome characterized by intellectual disability, dysmorphic features, early onset obesity, sleep disturbances and a number of distinctive behavioral abnormalities including outbursts, attention deficit/hyperactivity disorders, self-injury and stereotypies. Ninety percent of the cases are caused by a deletion in region 17p11.2, which includes RAI1 gene, other cases are linked to mutations of the RAI1. Its prevalence is estimated at 1 in 25,000, although this data may be an underestimation.

A thirteen year old male patient was referred to our clinic for obesity, mental retardation and minor dysmorphic features. There was no consanguinity between the parents and no evidence for the increased risk of familial disorders in family history. On clinical examination of the patient, dysmorphic craniofacial features (brachycephaly, low hair line, broad square-shaped face, midfacial hypoplasia, synophrys, deep set eyes, tented upper lip, prognathism), scoliosis, obesity, brachydactyly and mental retardation was determined. Daytime somnolance and behavioral disturbance including impulsivity, self-injury and decreased sensitivity to pain were also reported. Chromosomal analysis from peripheral blood showed a normal male karyotype. The microdeletion was detected by FISH analysis with specific probe including RAI1 gene in the 17p11.2 region.

SMS is a complex genetic disorder. Many of its features that appear in the SMS may occur in other genetic syndromes, which may cause diagnostic difficulties. The characteristic facial phenotype can be a clinical guide to the diagnosis, but presence of typical behavioral and sleep disturbances also provides important clues for the differential diagnosis to the clinicians.

COAGULATION FACTOR X GENE MUTATIONS IN FIVE PATIENTS WITH FACTOR X DEFFICIENCY

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OP50

Factor X deficiency (OMIM #227600) is a rare hemorrhagic autosomal recessive bleeding disorder with severe clinical manifestations including prolonged nasal and mucosal hemorrhage, menorrhagia, hematuria, and hemarthrosis. Mutations of F10 gene (NG_009258.1, *613872) resulting either with reduced levels of the encoded factor X protein (NP_000495.1) or synthesis of a dysfunctional factor X protein are resposible from the disease. Here we summarize the results of molecular genetic analysis of five patients with suspicion of Factor X defficiency.

DNA samples of each five patients were isolated using EZ1 DNA Isolation Kit. Coding regions of Factor X gene (NM_000504.3) were amplified by polymerase chain reaction with in-house designed primer pairs. Exo-Sap purified PCR amplicons were sequenced on the with ABI 3130 XL after chain termination reaction with Big Dye Terminator Kit and Dye-Ex purification with Sephadex G50. Same primer sets were successfully used for analysis on Miseq Platform for one of the patients. For this purpose, F10 coding regions were captured by PCR followed by Nextera XT protocol.

Three different homozygous mutations were determined. c.785G>A(p.Gly262Asp) missense mutation found in three out of five paients, whereas c.205G>A(p.Glu69Lys) missense mutation was found in one of the patients. A novel nonsense mutation, c.1231C>T(p.Gln411Term) was determined in one patient.

The novel mutation, c.1231C>T, classified as disease causing in Mutation Taster, score was 34 according to CADD (Combined Annotation Dependent Depletion), and it was not found in Exac, supporting its pathogenicity. All mutations found were primarily cumulated in the exon 2,7 and 8 of F10 gene.

A FEMALE PATIENT WITH SMITH-FINEMAN-MYERS SYNDROME

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OP51

Smith-Fineman-Myers Syndrome is a rare neurodevelopmental disorder which is inherited X-linked recessive. The characteristic findings are psychomotor retardation, seizures, speech delay (sometimes absence of speech), microcephaly, short stature and unusual facial appearance. The phenotype is caused by mutation in the ATRX gene.

We report a female patient at the age of 9 years, who was born with small for gestational age to consaguineous parents. The patient presented with severe speech delay, intellectual disability, psychomotor retardation, seizures, microcephaly, delayed closure of posterior fontanelle, unusual facial appearance with micrognathia, hypertelorism, downslanting palpebral fissur, widely spaced upper incisors and cafe au lait. The phenotype is consistent with the major findings of Smith-Fineman-Myers Syndrome. Smith-Fineman-Myers-Syndrome is an X-linked disease which is generally seen in male patients and we report this case because of the female gender. Molecular analysis is planned.

A RARE CASE OF DYSTROPHIC EPIDERMOLYSIS BULLOSA HALLOPEAU-SIEMENS TYPE WITH TYPE VII COLLAGEN DEFICIENCY AND COMPOUND HETEROZYGOUS COL7A1 MUTATION

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OP52

Recessive dystrophic epidermolysis bullosa Hallopeau-Siemens type is characterized by generalized severe cutaneous and mucosal lesions. The reported prevalence varies from 1/1,250,000 to 1/2,381,000 inhabitants. Lesions appear at birth/neonatal period and affect all the body as well as the oral and gastrointestinal mucosa. Healing of lesions occurs with scars. Complications such as corneal blisters that lead to visual loss and fusion of the tongue to the mouth floor (ankyloglossia) can occur. Excessive scarring can lead to adhesion of fingers and toes resulting to pseudosyndactyly, and to joint contractures (''mitten deformities''). Patients are at risk for squamous cell carcinoma.

The disesae is caused by VII collagen gene (COL7A1) that anchor the basement membrane to the dermis. Chronic malnutrition, growth retardation, delayed puberty, osteoporosis, refractory anemia, and hypoalbuminemia may also be observed. Diagnosis is confirmed by immunofluorescence antigen mapping and/or transmission electron microscopy on skin samples.

Here we present a four year-old male patient of DEB Hallopeau-Siemens type. He presented skin and mucosal lesions since birth. There was bilateral mitten hand deformity. Diagnosis was suspected at clinical examination and confirmed by skin immunofluorescence antigen mapping which showed lack of collagen VII. Family history revealed no consanguinity yet there were two similarly affected sibs, deceased. COL7A1 mutation analysis revealed a c.425A>G heterozygote splice site mutaton in exon 3 and a c.6781C>T p. R2261X heterozygote nonsense mutation in exon 86.

c.425A>G splice site mutation is the most common mutation in DEB Hallopeau-Siemens type (%12.16), resulting in prematüre termination codon and p. R2261X nonsense mutation results in prematüre termination codon. Severe phenotype in the present case could be due to co-occurence of these two mutations.

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UGT1A1 GENE MUTATIONS MAY CAUSE MYCOPHENOLATE MOFETIL INDUCED LEUCOPENIA AFTER RENAL TRANSPLANTATION: A CASE REPORT

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OP53

Mycophenolate is a immunosupresive drug used together with calcineurine inhibitor and corticosteroids after renal transplantation. Mycophenolate can induce bone marrow supression (anemia, leucopenia, trombocytopenia). Mycophenolic acid (MPA) is the active metabolite of mycophenolate. The primary metabolic pathway of MPA is glucuronidation. UDP-glucuronosyltransferases (UGTs) are an important class of diverse phase 2 drug-metabolizing and detoxification enzymes. The physiological importance of UGT1A is demostrated by mutations in this enzymes, which cause several diseases with varying degrees of hyperbilirubinemia. Within Caucasian and African American populations it is most commonly attributed to the UGT1A1*28 variant allele (rs8175347). This allele represents seven thymine-adenine (TA) repeats within the promoter region, as opposed to six that characterizes the wild-type allele (UGT1A1*1). These extra repeats impair proper transcription of the gene, resulting in decreased transcriptional activity of the gene by approximately 70%. UGT1A1*28 occurs with a frequency of 0.26 - 0.31 in Caucasians. We test UGT1A1 for wild, *28, *60 and *93 alleles with Real time PCR. Our case has heterozygous for three different low functional UGT1A1 polymorphisms but we test family and decided these alleles were cis position and he has one normal allel. We present one renal transplant patient and aim to remember that UGT1A1 gene mutations (either homozygote or heterozygote) may cause mycophenolate induced leucopenia.

PATERNALLY INHERITED PROXIMAL 22Q11.2 DELETION IN TWO SIBLINGS

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OP54

22q11.2 deletion syndrome (DiGeorge/Velocardiofacial syndrome) caused by a 1.5- to 3.0-Mb hemizygous deletion of chromosome 22q11.2. The phenotype is variable but commonly includes conotruncal cardiac defects, characteristic facial appearance, palatal abnormalities, immunodeficiency, endocrine dysfunctions, temporary neonatal hypocalcemia, urogenital abnormalities, and learning and behavioral problems. About 94% of the deletion is de novo whereas 6% have inherited the deletion from a parent. We report a 7 years old female patient with developmental delay, mild dysmorphic facial features, highly arched palate, missing teeth and learning difficulties with mild mental retardation. Karyotype analysis of the proband revealed an apparently balanced karyotype 46,XX,t(15;17)(q22p13). aCGH analysis (60K) and FISH confirmation showed 1292Kb deletion in the chromosome 22q11.2, including TBX1 and COMT genes. Because of the balanced translocation of the proband, cytogenetic/FISH analyses were performed in the family. Normal karyotype was detected in the mother but both 22q11.2 deletion and 46,XY,add(7)(q21) were seen in both the father and brother of the proband. They have similar dysmorphic features of the proband. a-CGH analysis showed an 3551 Kb amplification in 7q21.11. In conclusion, the clinical features of all cases are resulted from 22q11.2 deletions. However, further analysis are necessary for clarification of the extra band on 7q21.

A RECURRENT PREGNANCY LOSS CASE WITH T(1;7)(P26;Q36) TRANSLOCATION

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OP55

Recurrent Pregnancy Loss (RPL) is defined as the occurrence of two or more consecutive pregnancy loss before 20th week of gestation. Almost 5% of the population is affected. Chromosomal anomalies, single gene defects, anatomical abnormalities of the uterus, endocrinopathies, autoimmune / alloimmune causes and thrombophilia have been reported in the etiological factors of RPL. About 50-60% of first trimester abortions, 10-15% of second trimester abortions and 5% of third trimester still births are related with chromosome abnormalities. These chromosome abnormalities are mostly aneuploidies and 6.8% of chromosome abnormalities are derivative chromosomes inherited from balanced translocations of carrier parents. It is known that reciprocal translocations are the most frequent translocation type seen in RPL patients. Balanced reciprocal translocations occur in 0.2% of the population.

Here we present a 32 years old female, who was referred because of two times first-trimester pregnancy losses and found to have t(1;7)(p26;q36) in the karyotype. Her mother had a history of 10 pregnancy losses and one-year-old child who died at age one. This translocation was detected by GTG banding and confirmed by FISH. The aim of this report is to present a reciprocal translocation which has not been reported in the literature and which is easy to miss by standard banding techniques because of chromosomal size and localization.

CLINICAL AND MOLECULAR CYTOGENETIC (FISH) DIAGNOSIS OF WILLIAMS-BEUREN SYNDROME: RESULTS FROM 22 CHILDREN WITH WBS

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OP56

Introduction: Williams-Beuren Syndrome (WBS) is a rare contigious gene deletion syndrome which is associated with 7q11.23 region with a prevelance of 1/10,000-20,000 live birth. Clinical picture includes typical facial dysmorphism, developmental delay and congenital heart defects. The disease shows typical facial characteristics including broad forehead with bitemporal narrowing, low nasal root, bulbous nasal tip, long philtrum, stellate iris, full lips and widely spaced teeth. The most common cardiac defects are supralvular aortic stenosis (SVAS)(75%) and peripheral pulmoner artery stenosis (PPS)(50%). The deletion involves a region of 1.5-1.8Mb containing 26-28 genes, which is mainly sporadic. There are also a few reported familial cases.

Materials and Methods: This study includes 22 patients with WBS diagnosed at OMUTF Genetics Department between 2005-2015. The patients were evaluated with respect to clinical data, labaratory testing, cranial MR imaging, cytogenetic and FISH 7q11.23 results.

Results: There were 13 males and 9 females, totally 22 patients. Mean first referral age was 37 months (1-192 month). Average birth weight of 18 patients whose data was available was 2595 g, average birth length was 47.7 cm. Of these patients 7 had birth weight lower than 3rd percentile. All patients were dysmorphic and they showed develepmental delay of various severity. Echocardiography revealed 8 patients with aortic and pulmonary stenosis, 8 patients with peripheric pulmonary stenosis, 2 patients with aortic stenosis. Out of 20 patients 14 had either hypercalcemia or borderline calcium levels. 3 patients had undescended testis, 2 patients had hypospadiasis. Cranial MRI of 13 patients revealed several brain abnormalities including arachnoid cysts, chiary malformation, hypoplasic corpus callosum, hypoplasic pituitary gland, thickening of calvarium and brain atrophy. One patient showed extremely short stature. At age 11,5 years-old, his length was consistent with age 3,5 years and he had growth hormone deficiency in laboratory. Except 2 patients, 20 patients had normal karyotypes. One had rob (13;14)(q10;q10) and the other one had inv(7)(p11.2q11.23)dn. FISH analysis revealed 7q11.23 deletion in all patients. Parents of 13 patients were also analysed by FISH and found to be normal rendering the deletions to be de novo.

Conclusion: In parallel with literature data all patients in our study group presented congenital heart defects (100%) mostly as pulmonary or aortic stenosis. There was a high incidence of hypercalcemia. %59 of patiens presented remarkable brain abnormalities. An unusual case with severe short stature suggested the co-existence of growth hormone deficiency in association with WBS, a rare presentation of the syndrome. The patient with extreme short stature is an unusal presentation of WBS suggesting co-occurance of two different clinical entitities: growth hormone deficiency and WBS.

A NEW FACE OF INHERITED RECESSIVE CUTIS LAXA: ATP6V0A2 GENE MUTATIONS ASSOCIATED WITH METABOLIC DEFECTS

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OP57

Cutis laxa (CL) is a rare inherited disorder due to defective synthesis of elastic fibers and is characterized by lax skin, skeletal and developmental anomalies. Disease severity is variable. Several forms of CL have been described. ARCL2A (OMIM 219200) presents lax skin with persistent wide fontanels, downward slanted palpebral fissures, and reversed-V eyebrows. Intrauterine growth retardation, hip dislocation, scoliosis, and inguinal hernia are common.

A subgroup of patients with ARCL2A with ATP6V0A2 gene mutations have also metabolic problems mostly N- and O-glycan biosynthesis defect causing a unique glycosylation disorder (CDG type II).

Here we present two cases of ARCL2A both with homozygous ATP6V0A2 gene mutations, in one of whom, ethylmalonic aciduria was as well documented.

Case 1: A 6 year-old male patient from the 6th pregnancy of consanguineous parents was referred to our genetic center because of lax skin and a previous sib affected with CL. He showed normal growth parameters, a normal development yet a large fontanel and generalized lax skin was characteristic for CL. Mutation analysis revealed homozygous ATP6V0A2 gene mutations, (c.187C>T, p.R63X). No mutations were identified in the FBLN5 gene.

Case 2 was a 17 day old baby with facial dysmorphism, congenital hip dysplasia, a wide anterior fontanel, lax skin and pectus excavatum. Mutation analysis revealed homozygous nonsense ATP6V0A2 gene mutations, (c.187C>T, p.R63X). During follow up, an organic acid screening in urine tested because of developmental delay, revealed very high levels of ethylmalonic acaduria. A repeated analysis supported the same result.

Discussion: To the best of our knowledge no previous association of cutis laxa syndrome with ethylmalonic aciduria has been reported. Increased ethylmalonic acid in urine is a non-specific finding, and is observed in a number of inborn errors of metabolism, as well as in people with the SCAD coding region polymorphism. It is of interest that SCAD and ARCL2A are on the same DNA loci, 12q24.31.

We suggest that the finding of lax skin in a child with developmental delay should evoke detailed metabolic evaluation.

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3MC1 SYNDROME; REPORT OF THREE CASES AND REVIEW OF LITERATURE

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OP58

3MC syndromes are a group of rare autosomal recessive disorder characterized by short stature, variable degree of developmental delay or intellectual disability, umbilical anomalies and distinctive craniofacial features such as cleft lip and palate, hypertelorism, blepharophimosis, blepharoptosis and highly arched eyebrows. 3MC syndromes' phenotypic series are 3MC1 known as Michels (MIM 257920), 3MC3 known as Malpuech (MIM 248340) and 3MC2 known as Carnevale (MIM 265050) syndromes. There is remarkable overlap between all of the above phenotypes, because of the similarities in facial appearance and clinical features.

Here, we describe the clinical and molecular findings in 3 individuals with suspected 3MC1 syndrome from 2 previously unreported families. The exclusion of the COLEC11 gene in three patients from different consanguineous families, we described one novel mutation and one reported mutation in MASP1 gene. The p.(Gly665Ser) novel mutation in MASP1 cause severe mental retardation hasn't reported before, however p.(Trp3*) mutation cause mild developmental delay. Novel mutations and additional phenotypic features of the patients expand the genotypic and phenotypic spectrum of 3MC1 syndrome.

MICROGNATIA, FACIAL DYSMORPHISM, AORTIC VALVE PATHOLOGY, LOW WEIGHT, CHEST DEFORMITIES AND MENTAL RETARDATION: A CASE WITH WILLIAMS SYNDROME

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OP59

Objective and Aim: Williams Syndrome is a multi systemic disease and affects 1 in 10,000 people worldwide. 1,5-1,8 Mb hemizygous deletion on region chromosome 7q11.23 can be inherited from parents or occur as de novo. 7q11.23 chromosomal region contains 26 to 28 genes and ELN gene deletion was associated with supravalvular aortic stenosis. The distinctive facial features and mild to moderate mental retardation or learning problems are found in patients.

Methods: Chromosome analysis was performed with GTG banding from blood sample. Total DNA was isolated from peripheral blood-EDTA sample of patient and amplified by PCR. MR 1 panel were studied with MLPA method in the 3130 Genetic Analyzer instrument. MLPA results were analyzed with Coffalyser software. aCGH analysis was performed (Agillent) for confirmation.

Case: 17 years old girl referred from Pediatrics outpatient clinic because of micrognatia, thoraks deformity, aortic valve pathology and neuromotor retardation She has born from nonconsangiuneus healthy parents after non complicated term pregnancy. She has born 3500 gr but now her height is 10% and weight is 3%. Narrow nasal root (without a broad tip) also noted. Chromosome analysis was normal. MLPA and aCGH was planned for microdeletions.

Results: Heterozygous deletion was detected all three probes for ELN gene(Salsa MLPA MR1(P064-C1)) . 1.367Mb Loss from 7q11.23 and 134kb duplication at 10q26.3 was detected in aCGH analysis. Only CYP2E1 gene was in duplication region and considered as CNV.

Discussion: The patient was found compatible with Williams Syndrome in the results of clinical findings and molecular analysis.

A NOVEL BTD GENE MUTATION DETECTED DURING NEWBORN SCREENING

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P01

Biotinidase deficiency is an autosomal recessive metabolic disease. Biotin is a co-factor for carboxylases. Biotinidase enzyme plays an important role in biotin metabolism.

Profound biotinidase deficiency usually presents with severe neurologic abnormalities including seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous abnormalities like alopecia and skin rash while partial biotinidase deficiency causes milder symptoms such as hypotonia, skin rash, and hair loss, particularly during times of stress. The incidence of biotinidase deficiency is 1/50,000. However, this disease is seen more frequently in populations having a high rate of consanguineous marriages such as Turkey. To date, more than 150 mutations in the BTD gene known to cause biotinidase deficiency have been reported. In this study, we report a partial biotinidase deficiency case with a novel BTD mutation.

A two-month-old boy, detected to have suspicious biotinidase deficiency during newborn screening, was brought to the Medical Genetics department for molecular analysis. He was born to non-consanguineous healthy parents. Biotinidase activity was determined to be 27%. BTD gene mutation analysis was performed and p. P73L and p.D444H mutations were found. Mutations found in patient were confirmed by parental mutation analysis. P73L variant identified in this patient hadn't been previously reported. This variation was predicted to be "disease causing" with in silico tools. By itself, p.D444H considered a mild mutation but if combined with a severe mutation on the other allele results with partial biotinidase deficiency. Our patient's biotinidase activity and clinival findings are compatible with partial biotinidase deficiency.

HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

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P02

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disorder characterized by recurrent sensory or motor dysfunction and usually affects areas where nerves are liable to entrapment often following minor trauma or compression. Some affected individuals also have signs of carpal tunnel syndrome, peroneal palsy with foot drop and a mild to moderate peripheral neuropathy. Most patients with HNPP (90%) are found to have a contiguous gene deletion of chromosome 17p11.2 that includes peripheral myelin protein 22 (PMP22) gene which is allelic with CMT1A, but with duplication rather than deletion. The remaining 10% patients could have a point mutation at the allele of the (PMP22). A man at the age of fifty applied to our clinic with complaints of weakness, pins and needles with which he had been suffering for fifteen years. There was no family history. Clinical examination revealed weakness especially at the right side of the body and deep tendon reflexes were generally absent. Electromyography (EMG) revealed sensory-motor polyneuropathy. Based on the combination of clinical and EMG findings, the patient underwent the molecular analyses for PMP22 gene. Polymerase chain reaction was performed for analyze of 4 STR region of PMP22 gene. The patient displayed homoallelic for each analyzed locus and for the confirmation Agilent 8×60K array comparative genomic hybridization was performed and a 1412 kb deletion that include PMP22 gene at 17p12 was detected. Molecular analyses are helpful for differential diagnosis of neuropathies besides genetic counseling, prediction of prognosis, follow-up and therapy strategies.

FREQUENCY OF NEURAL TUBE DEFECTS IN SAMSUN PROVINCE AND RISK FACTORS FOR NEURAL TUBE DEFECTS

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P03

The study determined the frequency of neural tube defects (NTD) in Samsun province and investigated the relationship between NTD and sociodemographic properties of families and maternal eating habits. Maternal serum folic acid and vitamin B_{12} levels were also evaluated.

Between July 2007 and February 2008, 13974 alive and stillborn babies were officially recorded in Samsun region. 63 fetuses with isolated NTD were noted. The frequency of NTD in Samsun region was 3.4‰. Of 63 NTDs, 33 (52.4 %) were diagnosed with spina bifida, 27 with anencephaly (42.9%) and 3 (4.8%) with encephalocele. 34 (52.4%) fetuses were female and 29 (47.6%) were male.

In the study group, family incomes, maternal education level, consumption of meat, milk, egg, cheese, vegetable and legumes were lower than the control group ($p<0.05$). Sharing of the house with parents, unemployment rate, rate of febrile diseases, use of antipiretics and exposure to radiation were higher ($p<0.05$).

Maternal serum vitamin B12 and folic acid in NTD (group 1) were compared with normal pregnant women (group 2) and the female population (group3). The levels of both in group 1 were lower than group 2 and 3 ($p<0.05$).

The frequency of NTD in Samsun region was relatively high. NTD was more frequent in individuals with poor maternal education, low income and insufficient nutrition. Low serum vitamin B12 and folic acid levels posed an increased risk for NTD. The importance of the vitamin supplements during pregnancy is to be better appreciated by the health authorities as well as the families.

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A NEW CASE WITH MOSAIC TRISOMY 19Q

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P04

Supernumerary chromosome rings (sSCR) are usually a part of a mosaic karyotype of dysmorphic or mentally retarded patients. Chromosome 19 supernumerary rings, shown to cause obesity, developmental retardation, macrocephaly and facial dysmorphism, are very rare.

Here we describe a 3-year-old male patient with high birth weight and lenght, speech delay, articulation defect, facial dysmorphism and multiple linear hypopigmented areas along the lower extremities. Although the karyotype from the blood was normal, chromosome analysis of skin culture from hypopigmented areas showed a low level (15%) mosaicism for a ring chromosome. Array CGH study from the fibroblasts revealed the origin of the ring as 19q11-q13.31. As we reached from the literature, this is the third case with mosaic trisomy 19q. Our patient has a larger duplicated segment than those previously reported and has more dysmorphic features than previously described. Here, we report a genotype/phenotype correlation of this rare mosaicism between these three cases for further understanding of the impact of the genomic segment on the phenotype.

A RARE GENETIC DISORDER: GREIG CEPHALOPOLYSYNDACTYLY SYNDROME CASE

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P05

Greig cephalopolysyndactyly syndrome (GCPS) is an autosomal dominant, multiple congenital anomalies syndrome. Its real prevalence is unknown but it has been estimated 1-9/ 1,000,000. The typical findings are hypertelorism, macrocephaly with frontal bossing and polysyndactyly. Polydactyly is most commonly preaxial in the feet and postaxial in the hands called 'crossed polysndactility', with variable cutaneous syndactyly. Central nervous system (CNS) anomalies, hernias, and cognitive impairment are less frequent findings. The diagnosis of GCPS is based on clinical findings, family history and *GLI3* mutation/deletion analysis. Here we report a case of this extremely rare disorder.

We present a 8 month-old male patient, born of non-consanguinous marriage who was referred to us due to limb anomalies and corpus callosum agenesis. On the clinical examination; we detected macrocephaly, large fontanelle, frontal bossing, bilateral epicantus, hypertelorism, micrognathia, short neck, broad thumbs, in hands postaxial supernumerary digit with complete cutaneous syndactyly of digits 3-4 with fusion of the nails, preaxial polydactiliy in foot with complete cutaneous syndactyly of digits 2-5. His ophtalmological examination revealed retinal pigment atrophy. The milder end of the Acrocallosal syndrome phenotype can overlap with the severe end of the GCPS phenotype. So we performed *KIF7* gene analysis because of the differantial diagnosis, but it was normal. And then we planned performing *GLI3* gene sequencing analysis for Greig cephalopolysyndactility syndrome. This case report will provide contribution to literature because of its rarity and overlapped clinical findings with other syndromes.

EVALUATION OF PON1 GENE L55M POLYMORPHISM IN ABORTED FETUSES

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P06

Paraoxonase (PON1) is an esterase connected to the high dansity lipoprotein that hydrolyses lipid peroxides. Environmental factors, life style and toxin produced by cell material has an impact on oxidative stress.

Paraoxonase 1 (PON1) is an enzyme that specially allows the elimination of oil soluble free radicals in the body. The changes of PON1 activity, stems from the polymorphism in the gene that encoding this enzyme.

This study aimed to determine the relationship between PON1-L55M polymorphism in spontaneous abortion materials from the department of medical genetics in 2014-2015 years.

For this purpose DNA obtained from 40 aborted fetuses, PON1-L55M polymorphisms by PCR-RFLP method is applied in agarose gel electrophoresis was evaluated by UV transilluminator. In terms of the genotype distribution of abortion materials, 50% LL, 45% LM and 5% MM genotype was found.

At the result, it is believed that hyperhomocysteinemia's development and increase oxidative stress play a role in the pathogenesis of spontaneous abortion when compared with MTHFR C677T, MTHFR A1298C, PAI-1 4G/5G polymorphisms in the mother of abortion material.

PREVALENCE OF KLINEFELTER SYNDROME IN MALATYA BETWEEN 2014 AND 2015

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P07

Klinefelter syndrome is a genetic condition affecting males that is most often caused by an additional X chromosome (47,XXY karyotype). The syndrome is characterized by varying degrees of cognitive, social, behavioral, and learning difficulties and in adulthood additionally primary testicular failure with small testes, hypergonadotropic hypogonadism, tall stature, and eunuchoid body proportions. The aim of this study was to determine the prevalence and diagnosis rates of Klinefelter syndrome in Malatya. In this study, we investigated the karyotypes analysis of 1348 male patients admitted in Turgut Özal Medical Center and Research Hospital, Genetic Diseases Diagnosis Center Laboratory between 2014 and 2015 and retrospectively reviewed their clinical data. Chromosomes from cultured peripheral blood lymphocytes were analyzed using Giemsa Trypsin-Giemsa (GTG) banding. 47,XXY karyotype were detected in 21 (1.55 %) of 1348 male patients. The detected cases of Klinefelter syndrome were diagnosed at 13-50 years of age. Early detection of Klinefelter syndrome is recommended in order to offer treatment and intervention at the appropriate ages and stages of development for the purpose of preventing osteopenia/osteoporosis, metabolic syndrome, and other medical conditions related to hypogonadism. Accordingly, chromosome screening would be helpful, not only to diagnose Klinefelter syndrome but also other syndromes in which early treatment and guidance are beneficial for optimal development.

DISTRIBUTION OF PERICENTRIC INVERSION CHROMOSOME 9 AND ASSOCIATION WITH CERTAIN DISEASES IN CITY OF MALATYA AND AROUND

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P08

One of the most common structural balanced chromosome rearrangements is pericentric inversion of chromosome 9; also it is consider to be the variant of normal karyotype that has been found in both normal populations and patients with various abnormal phenotypes. The aim of this study was to determine the frequency of chromosome 9 rearrangement in Malatya and whether there is a correlation with certain diseases.

In this study, we investigated the karyotypes analysis of 2868 patients admitted in Turgut Özal Medical Center and Research Hospital, Genetic Disease Diagnosis Center laboratory between 2014 and 2015 and retrospectively reviewed their clinical data. Chromosomes from cultured peripheral blood lymphocytes were analyzed using Giemsa Trypsin-Giemsa (GTG) banding.

Pericentric inversion chromosome 9 were detected in 50 (1.74 %) of 2868 cases. 36 % (18) of cases with inv(9) for infertilty, 28% (14) for growth retardation, 8% (4) for multiple spontaneous abortions, 28 % (14) for other reasons has been referred to our laboratory. In this study, Malatya distribution of inv(9) shown and it is believed that these results contribute to the knowledge of inv(9) incidence in Eastern Anatolia Region and our country.

A CLINICAL REPORT OF AN INFANT WITH RUSSELL-SILVER SYNDROME

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P09

Russell-Silver syndrome (RSS) is characterized by intrauterine growth retardation accompanied by postnatal growth deficiency. Affected individuals typically have proportionately short stature, normal head circumference, fifth-finger clinodactyly, typical facial features with triangular facies characterized by broad forehead and narrow chin, and limb-length asymmetry that may result from hemihypotrophy with diminished growth of the affected side.RSS is a genetically heterogeneous condition and for most affected individuals represents a phenotype rather than a specific disorder. Hypomethylation of the paternal imprinting center 1 (IC1) of chromosome 11p15.5 is identified in 35%-50% of individuals with RSS. About 10% of individuals with RSS have maternal uniparental disomy for chromosome 7 (UPD7).

Here, we report the cytogenetic and molecular cytogenetic findings and clinical manifestations observed in a 14 months old male infant.The infant was delivered by Cesarean section at the 38th week of the gestation. The birth weight of the case was 1860 gr (<-1 sd) and height was 40 cm (<-2 sd). He had small triangular face, micrognathia, frontal bossing, minimal downturned corners of mouth, delayed fontanel closure, fifth finger clinodactyly, cafe-au-alit spots and developmental delay. Conventional cytogenetic analysis revealed 46,XY. In the light of clinical findings, we thought RSS for our case and did further analyses. With SALSA MPA ME030 BWS/RSS probemix method revealed methylation defect in the H19 region.

COCKAYNE'S SYNDROME-A CASE REPORT

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P10

Cockayne's syndrome (CS) is a rare, autosomal recessive disorder occurred with a frequency of 1/250,000 live births. It was characterized by growth deficiency, skeletal and neurological abnormalities, photosensitivity, loss of adipose tissue, mental retardation, short stature, microcephaly and pigmentary retinal degeneration. The patients commonly have hearing loss. Other features include cataracts, joint contractures, and a peripheral neuropathy. The syndrome is divided into four subtypes: three juvenile and one adult form. The juvenile variants include one severe, early onset form (previously known as CS 2), one intermediate (previously known as CS 1, classical form), and one mild form (formerly known as CS 3, atypical form). The fourth, adult form is a mild variant of the syndrome. It can be caused by mutations of two genes, the CKN1 or ERCC8, and the ERCC6, and also associated with mutations in XPB, XPD and XPG genes.

Here, we describe a rare case of Cockayne syndrome. He was a 3 year-old boy who was born from consanguineous parents at 40 weeks of gestation. He had craniofacial dysmorphism (enophthalmos, large and simple ears, microcephaly), postnatal growth and mental retardation, cardiac defect (PFO), kyphosis photosensitivity, ataxic gait, bilateral hearing loss, kyphosis and undescended testicles. Pigment epithelium atrophy revealed on his eye examination. His karyotype was normal. ERCC6 and ERCC8 genes exon analysis were requested.

Together with the findings of this patient, Cockayne's syndrome causing mutations and phenotypic effects discussed.

A LACK OF ASSOCIATION BETWEEN A COMMON CATECHOL-O-METHYLTRANSFERASE (COMT) SNP (RS4680) AND FIBROMYALGIA SYNDROME IN TURKISH PATIENTS

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P11

Fibromyalgia is a common chronic pain disorder affecting an estimated 2% of the general population. Approximately 90% of the affected individuals are female. There are some studies showing the association between common snp (rs4680) of Catechol-O-methyltransferase (COMT) gene and FMS. COMT is an enzyme which inactivates catecholamines. Rs4680 in codon 158 of the COMT gene (*val158met*) that affects COMT protein stability, results in reduced thermostability and activity of the enzyme. The aim of the study is to confirm the association between rs4680 and FMS in the group of the increased number of FMS patients in Turkish population.

Methods: 96 female patients diagnosed with FMS according to 2010 ACR criteria and 96 unrelated healthy controls were included in the study. DNA was extracted from peripheral blood leukocytes and screened by Sanger sequencing.

Results: Although the first study of Turkish population revealed significant association, we found that SNP rs4680 (Val-158-Met) is not associated with FMS ($p>0.05$).

Conclusion: The first study of rs468 revealed an association with FMS in 61 patient and 61 controls in Turkish population. Our study with the increased number of patient and controls showed that the association is not real. Other Meta analyses of rs4680 revealed the same result as in our study. Nevertheless, it needs to be confirmed with the increased FMS group.

ROLE OF ESM1 GENE IN CANCER

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P12

ESM1 is an proteoglycan secreted by endothelial cells and is expressed in various human cell types. Also it reveales directly effects on the tumor cell growth, metastasis and angiogenesis on many cancer types such as head and neck cancer and breast cancer.

The first step of our study was conducted using the head and neck cancercell lines UT-SCC 74A and its metastasis UT-SCC 74B. ESM1 gene expression in these cell lines is shown using immunofluorescence staining. Transfection efficiency of the cultured cells was determined via GAPDH-siRNA. Cells were then transfected with ESM1-siRNA. Knock-down was shown by q-RT-PCR. Efficient ESM1 gene knock-down was achieved using ESM1-specific siRNA.

In second step of our study we aim to identify whether mutations in the ESM1 gene may play a role in breast cancer. DNA samples were isolated from paraffin- embedded pateint tissue samples and the three exons of the ESM1 gene were sequenced to identify possible mutations.

In one of the samples, a previously identified silent mutation was found in exon two. In another polymorphism in exon two was identified. Based on the sequencing results, a polymorphism was identified in the polyA region of exon three in nine of the samples. As this is a region in which miRNAs are known to bind, this polymorphism could be important.

In conclusion the results suggest that with further studies new molecular treatment methods using ESM1 may be an alternative to currently available treatments.

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A CASE WITH CRI DU CHAT SYNDROME: CLINICAL AND CYTOGENETIC VARIABILITY

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P13

The Cri du Chat syndrome resulting from a deletion of variable size occurring on the short arm of chromosome 5 (5p-) was first recognized by Lejeune et al. in 1963. The incidence varies from 1:15,000 to 1:50,000 in live-born infants. The most recognizable phenotype is characterized by a high-pitched cry, dysmorphic features, poor growth and developmental delay. Here we reported on a seven months old boy who had clinically characteristic traits of Cri du Chat syndrome including microcephaly, hypertelorism, bilateral epicanthal folds, cup shape ears, microstomia, micrognathia and severe psychomotor and mental retardation. He had a relatively large deletion of chromosome 5p (5pter→p14) detected with high resolution banding and confirmed via fluorescent in situ hybridization technique. The present case study may contribute to a better definition and an improved comprehension of the correlation clinical and cytogenetic variability in Cri du Chat syndrome.

MECP2 DUPLICATION SYNDROME WITH ADDITIONAL FINDINGS

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P14

Rett syndrome (RTT) and Angelman syndrome (AS) are devastating neurological disorders that share overlapping clinical features with autism spectrum disorders (ASDs). It is reported that in addition to common mutations or deletions, individuals with chromosomal duplications including either the *MECP2* or *UBE3A* loci show clinical features related to those of RTT, AS, or ASDs. Here we report a 10-year-10-months old male patient having overlapping clinical features of RTT, AS and ASDs. He had mental retardation, lack of speech and developmental delay, and also dysmorphic features such as plagiocephaly, flat occiput, sparse eyebrows, high palate, retrognathia, malocclusion, uplift of ear lobule, fusiform fingers, fetal finger pads, hyperextensible joints in fingers and elbows, sandal gap between 1-2nd and 4-5th toes, broad great toe and three different sizes of cafe au laits. The X-ray revealed compound craniosynostosis. The cranial MRI at 3 month was normal, whereas at 10 years MRI showed delayed myelination. Cytogenetic analysis of the proband including high resolution GTG banding from peripheral blood did not reveal any microscopically visible chromosomal aberration. Due to the presence of his clinical features, we performed molecular karyotyping and found numerous genomic alterations ranging in size between 310 Kb and 4,8 Mb. Two of these genomic alterations including duplications of chromosome Xq28 and 15q11.2q13.11 were found to be compatible with his clinical findings. According to methylation analysis, duplicated *UBE3A* gene was not methylated. The present case study may contribute to a better definition and an improved comprehension of the overlapping pathways of *MECP2* and *UBE3A*.

AN INTERCHANGE TRISOMY 21 AS A RARE FORM OF DOWN SYNDROME

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P15

A thirteen months old girl referred to our department because of the suspected trisomy 21. The peripheral veneous blood culture was performed and besides two set of normal chromosome 21s, cytogenetic analyses revealed a balance reciprocal translocation between chromosome 17 and 21. As the mother who had suffered with the baby losses had balanced reciprocal translocation (17:21), this configuration was established as a 3:1 segregation of the unbalanced product of the translocation. The chromosomes of the carrier of the balanced reciprocal translocation pair with their matching homologous segments at meiosis I, a quadrivalent figure is formed and chromosomes segregate from this configuration. The final karyotype of the patient was 47,XX,+21,t(17;21)(q11.2;q22.1)mat and she had typical clinical feature of Down syndrome. The presented case is a reminder of the probability of the unbalanced products of the 3:1 segregation, rather than the common 2:2 segregation.

MOLECULAR CYTOGENETIC CHARACTERIZATION OF A SMALL SUPERNUMERARY MARKER CHROMOSOME DERIVED FROM CHROMOSOME 15

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P16

Small supernumerary maker chromosomes (sSMCs), defined as extra and abnormal chromosomes, while are found in ~0.043% of live births, seven times more prevalent in intellectually disabled patients. sSMCs are a major complexity in cytogenetic diagnostics and genetic counseling, because phenotypic abnormalities depend on several factors such as familial or de novo, chromosomal origin, chromosomal content, and structure of the marker. It's content cannot be distinctly determined by conventional chromosome banding techniques. We characterized sSMC present in a 15 years old male patient with dysmorphic features such as triangular faces, high and wide forehead, hypertelorism, deep set eyes, mild maxillar hypoplasia, broad columella, short philtrum, posterior rotated ears, prominent mandible, great toe and sandal gap, in addition to mental retardation and epilepsy. Chromosomal analysis according to standard cytogenetic methods by a peripheral blood lymphocyte revealed 47,XY,der(15).arr 15q11.2q13.3(22,765,628-32,416,311)X3 in all 20 cultured cells analysed. The origin of the der(15) in the progeny may be attributed to the 3:1 meiotic segregation with tertiary trisomy in the father. ArrayCGH revealed that sSMC included Prader Willi/Angelman Syndrome critical region. According to methylation analysis, *UBE3A* gene was not methylated in the patient. Although the sSMC(15) is the most common marker chromosome in humans, a clear description of the phenotype of the patients is restricted. It is important to investigate the critical regions of the marker chromosomes both for genetic counseling and revealing the role of the genes localized in this region that may have on effect on the phenotype.

CONFIRMATION OF THE PRENATAL MOSAIC TRISOMY 2 VIA FETAL USG AND CYTOGENETIC ANALYSES

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P17

Mosaic trisomy 2 in second-trimester amniocentesis is a very rare aneuploidy. Abnormal maternal serum screening, abnormal fetal ultrasound (USG) findings involving intrauterine growth restriction (IUGR) and various malformations may be associated with mosaic trisomy 2. The outcome of the pregnancies is quite variable, spontaneous abortions are frequent. The prognosis of the living fetuses are usually poor with growth and developmental delay. A 37 year old woman underwent amniocentesis at 18 weeks of gestation because of abnormal serum screening with single umbilical artery (SUA) and cardiac dextroposition in fetal USG, and the cytogenetic result was 47,XX,+2[12]/46,XX[73]. Repeated amniocentesis and simultaneously cordocentesis at 21 weeks of gestation were ended with the analyses of the same mosaic aneuploidy. In addition to SUA and cardiac dextroposition, diaphragmatic hernia was detected in USG examination that was confirmed by fetal magnetic resonance imaging. The pregnancy was terminated at 22 weeks of gestation. Prenatal diagnosis of two or more cells with trisomy 2 at amniocentesis with USG findings should alert the physician for clinically significant aneuploidy, and the presence of low-level trisomy 2 mosaicism at amniocentesis should be confirmed.

FREQUENCY OF *PSEN1* AND *APP* MUTATIONS IN EARLY ONSET ALZHEIMER'S DISEASE

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P18

Alzheimer's disease (AD) accounts approximately 60% of all dementia cases. Although neuropathological features are common in both early onset (age <65) and late onset (age >65) forms, intermittently atypical clinical courses and indications can be observed in early onset patients.

Lifetime risk for developing the disease is reported to be 10 to 12%. In general, the risk for the first degree relatives is found 2.5 times higher than in controls. Early onset forms account 1-6% of the AD, and 60% of this group underlies the familial forms. 13% of the familial forms display autosomal dominant (OD) inheritance. Presently, mutations in three different genes are associated with OD form and mutation frequency of these genes in all AD cases is 5 - 10%. 20 - 70% of the determined mutations are found in *PSEN1* and 10 – 15% are found in *APP* gene while *PSEN2* gene mutations are reported to be very rare. The studies show that ε4 allele contributes to clinical diagnosis and risk status of the disease, though it is neither specific nor sensitive for presymptomatic diagnosis. Genome wide association studies show 21 further loci related to the disease.

In our study, total of 59 early onset AD cases, 30 familial in which one atypical, and 29 isolated in which four atypical AD, referred to Department of Medical Genetics from Neurology Department of Istanbul Medical Faculty, between the years of 2013 – 2015, screened for coding exons of *PSEN1*, exon 16-17 of *APP*, and exon 4 of *APOE* genes by Sanger sequencing method. Four of the cases found to carry AD associated *PSEN1* gene mutations (6.7%), and one found to carry APOE-ε4 homozygosity (1.7 %) in the group.

Acknowledgement about the associated genetic mutations in early onset AD provides additional diagnostic benefit for the genetic counseling of the families. Genetic heterogeneity and unfavorable environmental factors cause molecular diagnosis challenging. Next generation sequencing technology, will grant screening of many associated genes in compact, quick, and cost effective manner, and besides will underlie the role of genetic factors more efficiently.

EVALUATION OF PRENATAL CYTOGENETIC DATA WITH IN-SITU CULTURE METHOD

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Aim: The rate of mosaic karyotypes detected prenatally is about 1-2% but 0.1-0.2 % of these cases are reported as true mosaicism. It is too difficult to distinguish pseudomosaicism from true mosaicism in prenatal diagnosis. For this reason, this discrimination was made by determining the level of detected mosaicism. It is possible to analyze too many cell colonies to identify detected mosaicism as level I (pseudomosaicism), level II (80% of these mosaicism are pseudomosaicism) or level III (true mosaicism). 5-15 colonies are obtained with in situ culture methods on a slide and these colonies are analyzed separately. Mosaicism levels of mosaic cases detected in 4000 amnion specimens were evaluated with in situ culture method in Mersin University, School of Medicine, Department of Medical Biology on between January 2007 and December 2015.

Material and Method: 4 in situ and 1 flask culture were performed from amniotic fluid cells. After colchisin, the cells are harvested and GTG banding was performed. Karyotypes were described according to ISCN.

Findings: Numerical, structural and gender abnormalities were detected in 277 of 4000 specimens (6.9%). 141 mosaic karyotypes were detected in 141 specimens (3.5%). There were gender mosaicism in 34 specimens (24.1%), otosomal mosaicism in 107 (75.9%) of these mosaic cases. %17.73 of gender mosaicism was pseudomosaicism and 6.8% was true mosaicism. True and pseudomosaicims rate of otosomal mosaicism was respectively 70.92% and 4.96%.

Results: It is limited to distungish true and pseudomosaicism. It is possible to analyse 20-60 colonies separately with in situ culture method. Due to shortness of the culture period and use of less materials, in situ culture method is an advantageous method.

PARTIAL TRISOMY 5P12-Q11.2 RESULTING FROM MARKER CHROMOSOME: A NEW CASE REPORT WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Partial trisomy of chromosome 5 was firstly described by Lejeune et al. in 1964 on the short arm. Vast majority of the partial trisomy 5 cases are composed of 5p duplications; but we reported as small supernumerary marker chromosome. General symptoms includes developmental delay, mental retardation, seizures, respiratory difficulties, congenital heart defects, abdominal muscle hypoplasia and dysmorphic features such as macrocephaly, enlarged anterior fontanelle, dolichocephaly, upslanting palpebral fissures, epicanthal folds, hypertelorism, abnormally modeled ears, midface hypoplasia, short nose, broad nasal bridge and microretrognathia. Arachnodactyly and club foot may be seen as cytoskeletal abnormalities and, hypotonia may be determined in neurological exam. Here we reported a case with developmental delay, attention deficit hyperactivity disorder, mild mental retardation and dysmorphic features, have a new small supernumerary marker chromosome, generating partial trisomy 5p12-q11.2. This small supernumerary marker chromosome has not been described previously, to our knowledge. Severe type of partial trisomy 5 includes seizures, congenital heart defects, hypotonia and failure to thrive. Previously reported partial trisomy 5 cases, who showed severe phenotype, had duplicated 5p13 region. Therefore, reported cases, did not include duplicated 5p13 region, showed mild phenotype. Also, duplication of the long arm of chromosome 5, may have contributed to the milder phenotype and the longer survival in partial trisomy 5 patients. Attention deficit hyperactivity disorder, which we described on the present case, may be a result of partial trisomy 5, because it includes ADHD4 gene. This case may help to better define the phenotype/karyotype correlation related to partial trisomy 5.

ISOVALERIC ACIDEMIA: A CASE REPORT WITH A NEW MUTATION

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Isovaleric acidemia is a rare, autosomal recessive, isovaleryl coenzyme A dehydrogenase enzyme deficiency disorder associated with an organic acid metabolism. There are two forms of the disease 1-) Acute form (approximately 50% of cases) appear in two weeks of life with lethargy, vomiting and dehydration. 2-) Chronic intermittent form occurs after stress or a high protein intake during later childhood (1-3). It is seen in 1/250,000 live births. Mutations in the IVD gene causes isovaleric acidemia. IVD gene is located in the 15q14-q15 region and has 12 exons. Up to now there is 25 defined mutation in IVD gene (4-9).

In this study, we present a 8-years-old-male who was brought to our emergency clinic with vomiting, fever and abdominal pain. The patient was hospitalized with acute pancreatitis. Two years ago he has been determined with same diagnosis. Cystic fibrosis whole gene sequence analysis was negative. Newborn screening of metabolic disorders was performed due to existing of refractory vomiting and abdominal pain, the absence of drugs or toxic agents ingestion, history of brother death. Due to diagnosis of isovaleric acidemia on tandem mass metabolic screening panel we made IVD gene whole exom sequence analysis. As a result we determine the patient p.E117K(c.349G>A)(Homozygous). The analysis of known mutations that are sent from the patient's parent and his healthy siblings were determined as p.e117k (c.349g> A) (heterozygous). We present this case because it is a new mutation in the IVD gene.

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CAN WE USE PIWIL2 GENE IN SCREENING PROSTATE CANCER AS A NEW MARKER?

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Aim: Piwil2, a stem cell protein and gene expression levels of this gene to determine whether correlated with serum PSA levels or not in prostate cancer.

Method: 60 patients admitted to our clinic between June 2012-May 2014 were included in the study. Three groups were formed, including one control group. None of the patients had malignancy or suspected malignancy except PCa. The first group was the control group, 20 patients whom pathology results had reported benign after TUR-P included this group and serum PSA levels were <4 ng/mL. The second group were included 20 patients whom pathology results were benign after TUR-P or needle biopsy and serum PSA levels >4 ng/mL. The third group also were included 20 patients whom pathology results were prostate adenocancer after TUR-P or prostate needle biopsy and serum PSA levels >4 ng/mL. RNA was isolated blood samples from patients and control groups. cDNA was obtained from RNA samples. The cDNA samples from piwil2 gene expression levels were determined by Real Time PCR. To compare the relationship between the groups T test, Oneway Anova, Man Whitney U and Kruskal Wallis were used to data analysis. P value of <0.05 was considered to be significant. This project supported by ERU BAP Coordination.

Findings: The average of age, PSA and piwil2 median levels for groups are shown in table 1. No significant difference was observed between the groups in terms of increase in PSA ($p<0.001$). Thus, consistent with the literature as known relationship between pathology was detected positive with an elevated PSA level. A weak correlation was observed between the groups in terms piwil2 expression levels ($p=0.029$). Therefore, in terms of the level of expression of pathology piwil2 from between positive and negative groups were whether there is a significant difference and there was no significant relationship between the two groups ($p=0.103$).

Result: Piwil2 serum levels of expression were found to be statistically insignificant in prostate cancer screening in this study. The small number of patients are thought to cause this situation. Today, still digital rectal examination and serum PSA levels in prostate cancer screening test is used as standard.

Table 1. Patient data

	The average age (year)	PSA (ng/mL) (median)	Piwil2 level (median)
1. group (n=20)	66.5 (±10.4)	2.4 (0.3-3.8)	1.17 (0.26-3.07)
2. group (n=20)	68.5 (±7.8)	8.89 (4.3-24.1)	2.27 (0.6-9.38
3. group (n=20)	68.4 (±10.1)	28.5 (4.6-98.1)	2.54 (0.28-9.27)

IDENTIFICATION OF ROLE OF IRISIN AND ITS SIGNALLING PATHWAYS IN OBESITY

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In 2012, Bostrom et al. discovered a new hormone which was given the name irisin that are released from muscle tissue (myokines) during or immediately after exercise. It was found that in subcutaneous fat it gave white fat tissue the characteristics of brown fat tissue. Brown adipose cells causes weight lose through transform a portion of energy to the form of heat. These cells contain a high number of mitochondria and uncoupling protein-1 (UCP-1) is highly expressed. UCP-1 is involved in the uncoupling of oxidative phosphorylation in mitochondria allowing a portion of energy to be produced in the form of heat.

Newly identified beige adipocytes are cells that are found within weight adipose tissue (WAT). The target of irisin is beige fat cells. Following exercise released irisin protein binds to a heretofore unidentified receptor and triggers a unique genetic program by a signaling pathway that is not yet fully understood and subsequently UCP-1 expression is increased.

Our aim in this project is to throw light on the effects of irisin at the molecular level. Firstly preadipose cells differentiated to adipose cells and then UCP1 expression of cells in which exposed to irisin and unexposed to irisin was evaluated by RT PCR. UCP1 expression levels of the adipose cells which exposed to irisin increased 4.5 times on the contrary those of the cells which unexposed to irisin. Microarray analyses were carried out from RNA of these cells.

According to Microarray results, 342 genes changed more than doubled. 246 of these genes as increased expression and 96 of them as decreased expression was analyzed. 3 each genes from both increased and decreased expression were selected and differences between their expression was verified by RT PCR.

After that genes with increased expression will be overexpressed and genes with decreased expression will be knockdown. Results from these experiments will indicate which effects are truly a result of irisin-mediated mitochondrial biosynthesis and energy regulation as well as the signalling pathways (such as MAPK, STAT, PI3K, TGFβ) that are involved in the observed effects.

A CASE OF CROUZON SYNDROME WITH MILD PHENOTYPIC FEATURES AND FGFR2 Y328C MUTATION

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Crouzon syndrome (CS) is a rare autosomal dominant fibroblast growth factor receptor (*FGFR*) *2* gene related craniosynostosis caused by premature closure of mostly coronal and sagittal sutures. Bony face deformity, hypertelorism, exophthalmos, strabismus, beaked nose, short upper lip, hypoplastic maxilla, malposed teeth and relative mandibular prognathism are the main clinical manifestations. No digital abnormalities are present. Visual and audiometric impairment may occur because of the intracranial hypertension. High intracranial pressure may even lead to death. The presence of a distinctive craniofacial appearance (hypertelorism, eye ball protrutism, prominent nose, and midface hypoplasia), and the absence of skeletal manifestations and dermatological features clinically differ CS from other *FGFR 2* related craniosynostosis. Clinical manifestations are variable and mild cases exist.

Here we presented a 2-year-old girl with cranosynostosis, hypertelorism, slight ocular proptosis, down-slanting palpebral fissures, midface hyoplasia and a parrot-like nose. She had no limb abnormalities. Audiometric and ophtalmologic examinations were normal. Craniosynostosis of all the sutures and hammered copper appearence were detected on X-ray imaging of the cranium. Her father had similar facial appearance and 11 more family members seemed to show the same phenotype. The patient was sequenced for *FGFR2* gene muatations and a heterozygous (c.983 A>G→ Y328C) missense mutation was detected.

The reason of the clinical variations in CS is not clear; gain-of-function mutations in FGFR2 that results in ligand-independent, disulfide-mediated, covalent receptor dimerization and activation may contribute the phenotypic variability. This should be a point to be discussed when providing genetic counselling for affected families.

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TWO TRISOMY 18 AND ONE ATYPICAL TRISOMY 21 CASE REPORT

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The majority of human chromosomal abnormalities occur in the autosomes. Aneuploidies especially the trisomies are the most common type of chromosomal abnormalities seen at clinical cases. The most common one of trisomies is Trisomy 21 (Down Syndrome).

Frequency is estimated to be 1 in 800 live births. Trisomy 18 (Edwards Syndrome) is the second most common autosomal trisomy after trisomy 21. Prevelance is approximately 1 in 6000-8000 live births. Some typical features characterised at trisomies. Trisomy 18 disorders tend to have much more severe clinical manifestations than trisomy 21, and only rarely do affected infants survive to one year of life.

Here, we summarisied three cases with atypical phenotypic features.

Our first case is a Trisomy 18 girl baby from 39-year-old mother's first pregnacy with prenatal ultrasound shows enlargement of lateral ventricles. After birth she had microcephaly, microphtalmy, large ventricular septal defect. Karyotype analysis resulted; 47,XX,+18 and due to heavy cardiac manifestations she died after five and half month later.

The other Trisomy 18 case also was from 39-year-old mother's fifth pregnacy an had anteriorly located ectopic anus. She had dolichocephaly, low set ears, high narrow palate, retromicrognathia, sacral hirsutism, patent foramen ovale. The patient is now ten months old and only has some type of recurrent upper respiratory tract infections.

The last one is a Trisomy 21 case with atypical presentation. A-four-year old girl with mental retardation and absence of speech admitted to our department with suspection of a genetic syndrome. We examine the patient and found: height and weight at low borders (3-10p), microcephaly (<3p) compared to standart development tables, low set ears, synophyrs, upslanting palpebral fissures, strabismus, high narrow palate, retrognathia, hirsutism at back, transverse palmar crease at only right hand, partial syndactly between second and third toes. Karyotype result is reported 47,XX, +21.

Eventually we can assume that trisomic patients may have unique features to themselves.

AN EPILEPSY SYNDROME: 16P13.11 MICRODELETION SYNDROME

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Microdeletions in 16p13.11 region can cause neuropsychiatric disorders such as schizophrenia, autism, mental retardation and epilepsy. In recent years it has been shown that 16p13.11 microdeletion syndrome is a rare epilepsy syndrome. The estimated prevalence of the disease is about 1/14000. In this report, a case having 16p13.11 microdeletion syndrome is presented.

Our case was referred to the hospital with afebrile seizures when he was 7 months old. He had been suffering afebrile seizure 3-4 times a day for a month. He had no history of other diseases. Physical examination was normal. His parents were not related. His mother had a history of abortion. It has been learned that, his mother and grandfather had hearing loss and his other grandfather had schizophrenia. The case's ocular fundus examination, hearing test, heart examination and echocardiography, abdominal ultrasonography, brain magnetic resonance examination was normal. The patient was diagnosed with infantile spasm considering EEG findings and he was treated. Chromosome analysis was performed on peripheral blood and the karyotype was 46,XY. Array- CGH analysis result was arr[hg19]16p13.11p12.3(15,404,452-18,669,725)x1. 3.265 kb deletion was determined in the p arm of chromosome 16. Genetic counseling was given to family. Array-CGH analysis was also planned for his parents. Some deletions and/or duplications are known to cause some sporadic epilepsy syndromes in the human genome.

An 16p13.11 microdeletion case have been presented here in order to emphasize the importance of the Array-CGH analysis in such cases.

A CASE OF TRISOMY 12P SYNDROME

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Trisomy 12p Syndrome is a very rare chromosomal abnormality. So far about 10 patients with whole chromosome 12p duplication are reported. Trisomy 12p Syndrome is characterized by craniofacial abnormalities, postnatal developmental delay, hypotonia and mental retardation. Clinical and dysmorphic features of the disease are similar to Pallister-Killian syndrome's (Mosaic Tetrasomy 12p).

Our case was referred to the hospital because of developmental delay, mental retardation and leukomalacia. Physical examination findings were round face, high frontal bossing, low set ears, hiperthelorism, epicanthus, strabismus, wide nasal bridge, short nose, long philtrum, thin upper lip and thick-everted lower lip. Audiogram, the heart and other system examinations were normal. He had been using antiepileptic drug due to epilepsy. He was born by C/S and his weight was 3100 gram. There were no significant feature in the analysis of pedigree. It was learned that all newborn metabolic disease tests performed and all of them were normal. The karyotype analysis results were evaluated as 47,XY,+mar. We proposed Array-CGH analysis. Array-CGH result was arr[hg19]12p13.33p11.1(230421-34756209)x3. We concluded that marker chromosome is consisted of chromosome 12's whole short arm. We diagnosed the patient as Trisomy 12p Syndrome. His parents' karyotype analyses were normal. Genetic counseling was given to family.

The case's clinical findings were similar to Pallister-Killian syndrome's (Mosaic Tetrasomy 12p). In the literature it is reported that trisomy 12p Syndrome and Pallister-Killian syndrome's facial appearance similarity is associated with the enhancement of gene dosage on 12p13.31 region. This rare disease is presented here in order to contribute to the literature.

A CASE OF NOONAN SYNDROME WITH COARCTATION OF AORTA

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Noonan syndrome (NS) is characterized by short stature, congenital heart defect, developmental delay of variable degree, broad or webbed neck, superior pectus carinatum or inferior pectus excavatum, cryptorchidism and characteristic facies. This disorder has an autosomal dominant inheritance pattern. The incidence of Noonan syndrome is estimated to be 1/1000-2500 live births. Despite being one of the most common seen in rare diseases, Noonan Syndrome can not be diagnosed with sufficient frequency.

Our case was referred to the hospital because of growth retardation. Physical examination findings were prominent-low set ears, high arched palate, downslanting palpebral fissures, epicanthal folds, low nasal bridge, upturned nose, bilateral ptosis, strabismus and pectus excavatum. Measurements of height, weight and head circumference were under 3 percentile. Nearly minimal coarctation of the aorta was defined in echocardiography. Neuromotor and endocrinological examination was normal. The result of karyotype analysis was 46,XY. The patient was diagnosed as Noonan Syndrome. PTPN11 gene mutation analysis was performed. Heterozygous mutations in 13.exon were identified [p.Pro491Ser (c.1471C>T)]. His father also had similar clinical findings. PTPN11 gene mutation analysis was planned for his father. Genetic counseling was given to family.

PTPN11 gene mutation was identified in %50 of affected individuals. PTPN11 gene mutations increase the risk of malignancy a threefold in Noonan Syndrome.

This case is presented here in order to emphasize that Noonan syndrome should be considered when the patient is male, short statured and suffering from coarctation of the aorta.

THE EXAMPLE OF A COHESINOPATHY: A CASE OF ROBERTS SYNDROME

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Roberts syndrome characterized by prenatal onset growth retardation, craniofacial anomalies and limb defects is a rare autosomal recessive genetic disease. 4 limbs are affected symmetrically in all cases. Mild-severe mental retardation, cleft lip-palate, micrognatia, hiperthelorism, microcephaly can be seen. ESCO2 gene mutation is known to cause the disease.

We presented here a case of Roberts Syndrome. She is 9 years old. She had mesomelic shortening in 4 limbs, thumb aplasia, joint contractures, hiperthelorism, epicantus, arc-shaped eyebrows, proptosis, strabismus, large nose wings, big mouth, facial telangiectasia and mental retardation. She had been using drugs for a year due to epilepsy. She had full-term but difficult birth story due to breech presentation. Her parents were not related but they were from the same village. Orbital magnetic resonance imaging made due to proptosis was normal. Opening on the sagittal suture vertex level and superior part of the coronal suture was determined in cranial computed tomography imaging. Asymmetric colposephalic expansion in bilateral occipital horn of the lateral ventricles was viewed. Karyotype analysis result was 46,XX. The patient was diagnosed as Roberts syndrome, so C-banding analysis was performed. The premature centromere separation known to be specific for Roberts Syndrome was shown with C banding analysis. ESCO2 gene mutation analysis is planned.

This rare disease being an example of the cohesinopathies is presented here in order to contribute to the literature.

IDENTIFICATION AND CHARACTERIZATION OF BXPC-3 CANCER STEM CELLS

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Pancreatic cancer has one of the poorest prognoses among all cancers. Advances in surgical and medical therapies have had little impact on the mortality rate of pancreatic cancer. Cancer stem cells (CSCs) are responsible for the growth and spread of pancreatic cancer. Studies on the cell surface marker expressions of CSCs, such as, CD133, CD44, CD24, and epithelial-specific antigen (ESA), have reported their involvements in solid malignancies of the breast, brain, prostate, and ovary. Human pancreatic CSCs Express high levels of CD44, CD24 and ESA.

Pancreatic cancer cell line, BxPC-3 was analyzed for the expression of CD44, CD24 and ESA by flowcytometry. Fluorescence-activated cell sorting (FACS) analysis was used to separate cancer stem cell population. We used sphere cultivation method to enrich the cancer stem cell population. The pluripotency maintenance factors (OCT-4 and BMI-1) were examined by immunofluorescence.

BxPC3, 68 % of cells expressed CD24, 99.6 % of cells expressed CD44 and 98 % cells expressed ESA. Pancreatic cancer CSCs showed self-renewal capacity.

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EXAMINING BORIC ACID EFFECT ON NECK AND HEAD CANCER CELL LINE PROLIFERATION AND TUMOR SUPPRESSOR GENE EXPRESSION

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Boric acid is a very common chemical used in a wide variety of industries and applications. Previous study related to boric acid effect on prostate cancer cell showed significant suppression on cell proliferation. In this study, the use of boric acid as a potential alternative cancer therapy was investigated by examining its effect on head and neck cancer cell line proliferation and tumor suppressor gene expression.

Head and neck cancer cell lines UT-SCC 6A, 6B, 9A, 16A, 16B, 24A, 54C, 74A, and 74B were treated with varying doses of boric acid, ranging from 200 ug/mL to 1800 ug/mL and XTT assay was used to measure the dose response. After optimizing effective boric acid doses, new cell culture cell treated with optimum boric acid doses. Subsequently, RNA was isolated from treated cells using the Trizol method. cDNA was made from the isolated RNA and then gene expression of P53, RB, ING1 and ING3 were analyzed with Real-time PCR.

RB, P53 and ING genes expression is significantly decreased varying amount (1.5 fold to 5 fold decrease) in different cell lines. The changes in gene expression levels were tested for statistical significance using Mann Whitney U test and the results are significant at $p \leq 0.05$.

In light of these results, boric acid appears to be a candidate alternative therapeutic agent for head and neck cancer.

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ISOLATION AND CHARACTERIZATION OF CANCER STEM CELLS IN YKG1 GLIOMA CELL LINES TO EVALUATE THE ANTI-TUMOR EFFECT OF THYMOQUINONE VS MITOXANTRONE

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In terms of treatment of tumors, surgery, chemotherapy and radiotherapy are not exactly efficient and recurrence could occur. It has been found that cancer stem cells (CSC) are resistant to chemotherapy and radiotherapy. Thymoquinone which had been isolated from Nigella sativa, investigated as antioxidant, anti-inflammatory and anti-cancer. We have proposed to reveal the role of thymoquinone on glioma cells by comparing with mitoxantrone and aimed to find more effective and less toxic treatment method.

YKG1 cell line has been thawed and proliferated. CSC has been successfully isolated by using Fluorescence Activated Cell Sorting (FACS) with the antibody CD133. Neurosphere formation has been observed and these spheres are well characterized by staining with Nestin. Various concentrations of thymoquinone (T1:40 uM, T2:80 uM, T3:160uM) and mitoxantrone (M4:0.5ug/mL, M3:0.05ug/ml, M2:0.005ug/mL, M1:0.0005ug/mL) were prepared by diluting in DMEM solution. The cells were exposed to thymoquinone and mitoxantrone alone and finally with both of mitoxantrone and thymoquinone series together.

Antiproliferative effect of thymoquinone was seen only at T3 doses while both M3 and M4 doses of mitoxantrone showed toxic effect to the cells. When combined use of mitoxantrone and thymoquinone were done, a significant antitumoral effect was seen in T2M4 combination.

The effect of T2M4 combination on the cell suppression was almost twice according to M4 doses of mitoxantrone. We thought this result shows synergistic effect of thymoquinone with mitoxantrone.

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A TURKISH FAMILY WITH A89T (P. ALA89THR, C.265G>A) MUTATION ON THE MEFV GEN

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Familial Mediterranean fever (FMF) is the most frequent hereditary inflammatory disease characterized by self-limited recurrent attacks of fever and serositis. MEFV gene mutations are responsible from the disease and its' protein product, pyrin or marenostrin, plays an essential role in the regulation of the inflammatory reactions. Until this time, more than 300 mutations and polymorphysms have been reported. A Turkish family with a total of three members clinically diagnosed as FMF are investigated. All exons of MEFV gene (1, 2, 3, 4, 5, 6, 7, 8, 9, 10) were amplified via PCR technic and complete exom sequencing analysis of MEFV gene was performed for three individuals. A single base mutation in the coding region of MEFV gene, named A89T (p.Ala89Thr, c.265G>A) heterozygot resulting in a mutated Pyrin/Marenostrin protein was detected. According to the Mutation Taster and PolyPhen-2 bioinformatics programs, this alteration seems to be pathogenic. Our examination showed that in addition to the proband, her mother had the same mutation, too. A89T is a rare mutation in exon 1 of the MEFV gene. To the best of our knowledge, this is the first report from Turkish family with A89T mutation. We thought this single base mutation may provide important information for further studies on FMF pathogenesis.

A TURKISH FAMILY WITH 761_764DUPCCGC (P.ASN256ARGFS70 ,C.761_764DUPCCGC). MUTATION ON THE MEFV GENE

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P34

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder which primarily affects Jewish, Armenian, Turkish and Arab populations. The FMF gene is the Mediterranean FeVer (MEFV) gene consist of 10 exon located on chromosome 16p13.3 is responsible for the disease. A Turkish family with a total of five members clinically diagnosed as FMF are investigated. All exons of MEFV gene (1, 2, 3, 4, 5, 6, 7, 8, 9, 10) were amplified via PCR technic and complete exom sequencing analysis of MEFV gene was performed for five individuals. A duplication mutation was identified in exon 2 of MEFV gene, named 761_764dupCCGC (p.Asn256Argfs70,c.761_764dupCCGC). Our results showed that in addition to the proband, his father, brother and sister have carried the mutation, too. His mother has not any mutation. The proband has abdominal pain, chest pain and no family history of FMF. This mutation has been previously described at HGMD (HGMD no: CI055758) and associated with FMF. Interestingly, excluding proband the others members of the family who carried this mutation has no clinical findings with FMF. According to the Mutation Taster and PolyPhen-2 bioinformatics programs, this alteration seems to be pathogenic. It was required that the additional works are needed to obtain more exact knowledge about the 761_764dupCCGC mutation. We thought that this mutation may provide important information for further studies on FMF pathogenesis.

A COMPLEX CHROMOSOMAL REARRENGEMENT BETWEEN CHROMOSOME 5 AND 8 IN A FEMALE WITH HABITUAL ABORTION

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P35

Cytogenetic abnormalities are considerable factors for spontaneous abortions and nearly 1-2% of spontaneous abortions occur due to structural chromosomal rearrengements including complex chromosomal rearrengements (CCRs). CCRs have been described as alterations between two or more chromosomes with at least three breakpoints. Balanced CCRs do not generally cause an abnormal phenotypic feature but some phenotypic effects may be seen in conception due to partial monosomy or partial trisomy in the fetus resulting in abortion. Here we report a 23-years old female with two first trimester abortions. A balanced CCRs involving chromosome 5 and 8 was detected by GTG banding and FISH analysis.

MBL2 GENE POLYMORPHISM AND RISK OF VITILIGO IN TURKISH PATIENTS

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P36

Mannose-binding lectin (MBL) plays a significant role in innate immunity. *MBL2* gene polymorphisms affect MBL serum levels. Therefore, this increases the risk of infection and may result in predisposition to autoimmune diseases. The aim of this study was to investigate whether there is an association between the *MBL2* gene codon 54 (allele B: rs1800450, c.161G>A; p.54Gly>Asp) polymorphism and vitiligo in Turkish patients. One hundred and one patients who were diagnosed with vitiligo and 101 control subjects were included in the study. The DNA was analyzed using the Kbioscience Competitive Allele-Specific PCR (KASP) technique. *MBL2* gene Codon 54 polymorphism frequencies were compared between the two groups. In statistical analysis, the level of significance was set at $p<0.05$. No significant differences in frequencies of A allele were observed between the patient and control groups. It was observed at similar rates in both groups ($p=0.890$). Our results suggest that the *MBL2* gene Codon 54 polymorphism is not associated with an increased risk for the development of vitiligo in our Turkish patients.

CLINICAL EFFECT OF A RARE MUTATION (P.GLU322ASP, C.966 G>T) IN PANK2 GENE IN A FAMILY WITH ATYPICAL PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION (PKAN) SYNDROME

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P37

Pantothenate-kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disorder caused by mutations in the pantothenate kinase 2 (PANK2) gene. Many different mutations in the PANK2 gene have been detected in association with PKAN. A 20 year old female patient who had been suffering from progressive gait disorder for 1 year was found to have the 'eye-of-the-tiger sign' from the brain magnetic resonance imaging (MRI). The same brain imaging findings were shown in the father and brother of the patient, whose parents arranged a consanguineous marriage. We found c.966 G>T (p.Glu322Asp) mutation in the PANK2 gene mutation analysis in the individuals from the brain imaging findings. Although individuals in this family who had a homozygous mutation in PANK2 gene analyses had the 'eye-of-the-tiger' sign and atypical disease, they were noted to have differing clinical findings.

CHROMOSOMAL TRANSLOCATION T(6;22) (Q13;Q11) IN AN INFERTILE MALE

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P38

Infertility is the failure to conceive after 1 year of regular unprotected sexual intercourse. It effects around 15-20% of reproductive-aged couples. In almost 30-50% of infertile couples, the problem is related to the male and it is frequently associated with impaired spermatogenesis. Several genetic and nongenetic conditions have been associated with male infertility. Chromosomal rearrangements are one of the most important causes of male infertility. Among infertile men with spermatogenic abnormalities, especially with severe oligozoospermia and azoospermia, the frequency of somatic chromosome anomalies can be estimated within the range of 5-15%. In this report we present a case of a 27-year-old male who was referred to our laboratory due to infertility. He had been married for 3 years but have no children. Semen analyses showed low volume oligozoospermia. The karyotype analysis and molecular investigation of AZF and SRY deletions were performed. The chromosome analysis revealed a nonrobertsonian balanced translocation t(6;22) with breakpoints at 6q13 and 22q11. This translocation confirmed by FISH analysis with 22q11.2 region probe. This region was observed on the chromosome 6. No microdeletions were found in AZF regions and SRY gene. We deduced that chromosomal rearrangement in this case was caused infertility due to the effect on spermatogenesis.

A CASE OF HABITUAL ABORTION WITH 46,XX,T(12;22) (Q13.2;Q13.3) TRANSLOCATION

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P39

Habitual abortion is defined as three or more consecutive pregnancy losses before 20 weeks of gestation, it is a major concern in the couples with reproductive problems.

A case with habitual abortion referred to our policlinic with three abortions, her mother and sister have abortion too.

With method of HRB (High Resolution Banding) blood culture, thirty metaphase chromosomes were karyotyped and 46,XX,t(12;22)(q13.2;q13.3) was identified in the case, also she had Factor V, MTHFR 677, MTHFR 1298, PAI-1 heterozygous in her thrombophilia panel. Then we invited her mother, father and doughter to our policlinic. With the same method we karyotyped their chromosomes, and we found the same translocation in her father.

At the result we suggested In Vitro Fertilisation and Pre-implantation Genetic Diagnosis method for her next pregnancies to them.

A RARE CASE OF 14Q31 DELETION: LOSS OF NRXN3 GENE IN PATIENT DIAGNOSED WITH AUTISM SPECTRUM DISORDER

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P40

There is a small number of reported cases with 14q31 deletion in literature. One of the significant genes located in this region is NRXN3. This gene's heterozygous deletion has been previously associated with autism spectrum disorder.

Previously diagnosed with autism spectrum disorder patient attended Medical Genetics department at Erciyes University. Developmental and speech delay were major complaints. Physical examination revealed the square face, protuberant cupped ears, deep-set eyes, hypodontia, short neck, spacing nipples, and tapering fingers.

Obtained 3 cc blood sample collected into a syringe with 0.3 cc heparin after 72 hours culture according to High-Resolution Banding and after Giemsa banding staining 20 metaphase cells were analyzed and reported as 46,XX,del (14)(q31). Parents' karyotype was also analyzed and reported to be normal.

The difference in phenotypes in reported cases can be explained by the quantity difference in lost genetic material. But similarities in phenotype in our and other reported cases shows the presence of a pattern in this pathology, especially relation of NRXN3 gene with ASD which is one more time demonstrated in this case.

In other family members, karyotype analysis must be performed because of a balanced translocation or even deletion possibility in parents with subclinical autism. Despite normal karyotype results from blood samples of parents, because of gonadal mosaicism possibility, parents should be advised of Preimplantation Genetic Diagnosis or at least Prenatal Diagnosis.

EVALUATION OF LABORATORY RESULTS IN CYSTIC FIBROSIS PATIENTS

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Objective: Cystic fibrosis is an autosomal recessive genetic disease whichis very common in Caucasians. CF reflects the clinical heterogeneity and characterized by the recurrentinfections of the respiratory tract, pancreatic insufficiency, intestinal obstruction, infertility in menContaining 27 exonsCFTR gene is located in theq22-31 region of the long arm of the chromosome 7 and encodes 230 kb length protein which is composed of 1480 amino acids. CFTR gene product Cystic fibrosis transmembrane conductance regulator (CFTR) proteinacts as a chloride channel. As a result of studies, in CFTR gene, more than 2000 mutations were identified. In this study, we aimed to determine the frequency of CFTR gene mutations in Kayseri region.

Methods: Between the years 2012-2015 in Erciyes University Medical Genetics Department samples of 120 patient were analyzed by Sanger sequencing method (exon 7, 10 and 11).

Results: ΔF508 mutation was found in 8 patients. 1677del T mutation was observed in 4 patients. I507del **in**2 patients and in 1 patient the R347H, I506V, R297Q, L327, R334W and L467F mutations were observed.

Conclusion: In this study as a most common mutation ΔF508 was observed which is compatible with literature. In studies conducted in recent years in our country, on cystic fibrosis, ΔF508 mutation frequency was found to be 24.5%. In our study, it was found to be 6.6%. Regional analyzes were conducted to determine the distribution of CFTR genemutation immigrants and in relatives throughout the community. These differences and the detection of rare mutations may be caused by some heterogeneity in Turkish society.

GENE EXPRESSION PROFILING AND FUNCTIONAL ANALYSIS OF CANCER STEM CELL IN HEAD AND NECK CANCER

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P42

Despite developments in surgical and chemo-radiotherapies in head and neck cancer, there has been no major change in the survival rates over decades. Cancer stem cells (CSCs) have been identified as rare cell populations in many cancers. CSCs are defined on the basis of characteristics such as high tumorigenicity, self-renewal, and differentiation that contribute to heterogeneity Understanding. In this study, we focus new CSC-targeted therapeutic strategies aiming to eradicate malignancies.

In this study we isolated CSCs (ALDH1+/cancer stem cells) from head and neck cancer cell lines (74A) and its metastasis (74B) cell lines using flow cytometric analysis. The mRNA expression profiles were analyzed using an Affymetrix GeneChip® oligonucleotide array and identified 2035 upregulated 2266 downregulated genes in 74A and 6350 upregulated 5322 downregulated genes in 74B. The differential gene expression profiles were confirmed at the mRNA level by quantitative RT-PCR. Five genes (SPRR1B, SPTSSB, SPC25, CTGF, FOS) were chosen according to their level of expression (Fold change in >10 or <-10) and effective on the cancer stem cell formation and expression plasmids formed and validated by sequence and western blotting. The head and neck cancer cell lines were overexpressed by transfection with these 5 genes to determine the effects on CSCs.

As a result more sphere formation was observed in transfected ALDH1 (+) and ALDH1 (-) cells with SPRR1B (small proline-rich protein 1B) and SPTSSB (serine palmitoyltransferase, small subunit B) comparison with control. In addition, 74A cells transfected with SPRR1B and SPTSSB genes showed increased proliferation.

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DETERMINATION OF DELETIONS WITH LACK OF AMPLIFICATION IN NEXT GENERATION SEQUENCING

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P43

With Next-Generation Sequencing (NGS) methods, we now obtain massive data that needs interpretation. Sometimes we face with unique situations that require different approach.

From the 28 male patients attended department of Medical Genetics at Erciyes University with suspicion of Duchenne Muscular Dystrophy blood samples were collected into tubes containing EDTA, after DNA isolation next generation sequence analysis of *DMD* gene were performed.

Results of 18 patients were normal, in 3 patient c.5637 CàA, c.4455 CàT, and c.10699 CàT hemizygous changes were observed that results in nonsense mutations. But in 7 samples there were observed the lack of amplification in some exons. There can be several reasons for this phenomenon but first we decided to check for deletions in this exons by Multiplex Ligation-dependent Probe Amplification (MLPA) method and in all cases (100%), deletions were determined in the exactly same exons. Because of a small number of cases we obtained differently but similar results described in the literature. In literature in 90%-95% lack of amplification cases, deletions were confirmed.

This results show that in male patients during sequence analysis of X-linked dominant diseases such as X-Linked Hypophosphatemia, Rett syndrome, Aicardi syndrome and X-linked recessive diseases such as Hemophilia A, B, X-linked ichthyosis, X-linked agammaglobulinemia and etc. if we see lack of amplification, first step of management must be checking for deletions by adequate methods.

PARTIAL TRISOMY OF THE LONG ARM OF CHROMOSOME 14 A RARE CASE OF PATIENT WITH PROGRESSING SEVERE OPISTHOTONUS

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P44

Major indications for karyotype analysis during the neonatal period is any dysmorphic syndrome, malformation, or neurological deficit.

Progressive back arching was a reason for a genetic counseling in a one-month-old infant. During physical examination syndromic face, sparse hairs, absent eyebrows, tall board forehead, premaxillary hyperplasia, hypertelorism, upslanting palpebral fissures, depressed nasal bridge, anteverted nares, micrognathia, barrel chest, normal male genitalia and bilateral cryptorchidism were observed.

The patient is prematurely (36 weeks; 1500 g) born the first child of non-consanguineous parents who have a history of spontaneous abortion in the first trimester. Birth performed via C-section, because of cyanosis and respiratory failure after the birth patient was referred to NICU. No abnormalities were found in MRI, ECG and abdominal USG.

In karyotype analysis revealed abnormality in the 8th chromosome which had additional unknown origin material on p arm and initially reported as 46,XY,der(8)add(8)(p23). Therefore parenteral karyotyping analysis was required. Karyotype analysis of father showed balanced translocation 46.XY,der(8)t(8:14)(p23,q24.3)del(14)(q24.3). So it means partial trisomy of the 14th chromosome presents in our patient. The identification of the parental origin of additional material is important because of imprinted genes in this region. There were reported cases with similar karyotype results which have clinical manifestation differences because of parenteral origin.

Because of spontaneous abortion and symptomatic child history family was referred to Preimplantation Genetic Diagnosis.

POLYMORPHISMS IN THE METHYLENETETRAHYDROFOLATE REDUCTASE GENE (MTHFR) ARE ASSOCIATED WITH ACUTE MYELOID LEUKEMIA IN A TURKISH POPULATION

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P45

Acute myeloid leukemia (AML) is a neoplastic disease of the hematopoietic stem cell which is characterized by the increased proliferation and decreased spontaneously apoptosis. In parallel with the bone morrow is invaded by the cells which are rapidly proliferated and differentiated. 5, 10-methylenetetrahydrofolate reductase is a flavoprotein and an essential enzyme in the metabolism of folate. It has also an important role in the DNA methylation. A mutation which occurs in the MTHFR gene decreases the enzyme activity. The relation between the MTHFR gene polymorphism and cancer is one of the most investigated issues in recent years. In this study we evaluated the relation between MTHFR polymorphism and AML. For this purpose the peripheral-blood samples has been collected into the tubes containing EDTA from 51 patients who applied to the Department of Medical Genetics in Erciyes University between the years 2014-2015. DNA was isolated by using genomic DNA extraction kit. Then, Real Time PCR protocol was realized by using NLM kit. The findings were evaluated by melting curve analysis. Our findings and literature have no significant differences, therefore results are concordant with the literature. For C677T polymorphism homozygote genotype (10.4%) and heterozygote genotype (29%) were found less frequent than the control group. For A1298C polymorphism was found that heterozygote genotype frequency is 44,7% and homozygote genotype frequency was found 21.3%. In conclusion these findings show that MTHFR polymorphism is related to acute myeloid leukemia patogenesis.

HOLOPROCENCEPHALY NOTED IN A CASE OF MOSAIC TRISOMY 9 SYNDROME

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P46

Mosaic trisomy 9 is a relatively uncommon chromosomal abnormality that has distinct clinical features involving cardiac, genitourinary, musculosceletal and CNS anomalies. Holoprocencephaly as a frequent finding of trisomy 13 and 18, is a rarely noted feature of mosaic trisomy 9 syndrome. Here, we report a mosaic trisomy 9 syndrome case with holoprocencephaly.

Besides holoprocencephaly, fetal ultrasonography and echocardiography revealed multiple anomalies like microphtalmia, absent nasal bone, tricuspit atresia and partial AVSD. At 39th week of the pregnancy, the fetus was delivered vaginally with low percentile (<5p) of weight, lenght and head circumference and soon after she died because of mentioned severe clinical defects. On postmortem fetal examination, brachycephaly, narrow forehead, hypotelorism, deeply set eyes, flat nose with single nostril, small mouth, posteriorly rotated ears, clenched hands with adducted thumbs and bilateral single transverse palmar creases were also noted. Fibroblast cultivation of the fetus ended with mosaic trisomy 9 (mos 47,XX, +9 [6]/46, XX[54]).

The present mosaic trisomy 9 syndrome case with holoprocencephaly would help to evaluate the clinical findings and the cytogenetic abnormality of the rarely noted syndomes.

APOPTOTIC EFFECT OF CROCETIN EXTRACTED FROM SAFFRON ON PRIMARY AND METASTATIC HEAD AND NECK CANCER CELL LINES

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P47

Head and neck cancer, an aggressive type of cancer, accounts for about 15% of all the cancers. Treatment includes classic methods such as radiotherapy, chemotherapy and surgery. The treatment of Head and Neck Cancer is difficult from other types of cancer if it is not early diagnosed. Due to its localization cancer itself and the treatment severely decrease the quality of life and cause serious physical and psychological problems. Thus, pursuit of finding alternative treatment methods directed scientists to investigate the potential plant and chemical sources.

Crocetin is a natural carotenoid dicarboxylic acid. Crocetin has been shown to have significant anti-tumor potential in both in vitro (cell culture) experiments and in animal models. Crocetin affects the growth of cancer cells by enhancing the anti-oxidant system, inhibiting the synthesis of nucleic acids, hindering growth factor signalling pathways and by inducing apoptosis. In our study, we investigated the effect of the crocetin on primary and metastatic head and neck cancer lines.

Crocetin inhibited proliferation of both primary and metastatic head and neck cancer lines according to MTT and xCELLigence assays we performed. Additionally, crocetin upregulated expression of a pro-apoptotic gene Bax, downregulated expression of an anti-apoptotic gene Bcl-2 and increased caspase 3 activity in both cancer lines. Our results suggest that crocetin can be used as potential therapeutics in head and neck cancer treatment.

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A CASE OF 1P36 DELETION SYNDROME DETECTED BY ARRAY-CG

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P48

Chromosome 1p36.1 deletion syndrome affects approximately 1 in 5,000 newborns and is the most common terminal deletion in humans. Clinical features are growth and developmantal delay, short stature, characteristic face, visual and hearing loss, epilepsy, brain anomalies, orofacial cleft, cardiac and renal anomalies. A 5-year old girl who has intellectual disability and epilepsy was reffered to the Ege University Pediatric Genetics Subdivision. She was born to healthy nonconsanguineous parents at the 39th week of gestation via caesarean section. Her neuromotor developmental milestones were delayed. She had hypothyroidism. On physycal examination, microcephaly, obesity, narrow and hairy forehead, depresed nasal bridge, long philtrum, thin lips and high arched palate were observed. Karyotype analysis was normal. Array-CGH analysis revealed a de-nova 198 kb delet, on at this (1p36.11) region. Although 1p36 deletion syndrome is respectively common, this case is the first case showing such a small deletion and mild clinical findings.

PARTIAL MONOSOMY 2Q AND PARTIAL TRISOMY 5Q IN A CASE WITH MICROCEPHALY, CONGENITAL HEART DISEASE AND GROWTH RETARDATION

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P49

Partial duplication of the long arm of chromosome 5 is a rare chromosomal disease characterized by growth and developmental retardation, microcephaly, dysmorphic facial features, low-set ears, brachydactyly, clinodactyly and heart defects.

Partial deletion of the long arm of chromosome 2 is also rare characterized by prominent forehead, thin high arched eyebrows, depressed nasal bridge, full cheeks, hypoplastic alae nasi, thin upper lips and minor anomalies of pinnae. One third of these patients have additional ocular, cardiac, central nervous system, gastrointestinal, renal and genitourinary anomalies.

A 3.5-year old girl who had mental retardation and dysmorphic features was reffered to the Ege University Pediatric Genetics subdivision. She was born to consanguineous parents. On physycal examination, microcephaly, short philtrum, low-set dysmorphic ears, thin upper lips, syndactyly of toes 2 and 3, sacral dimple were detected. Karyotype analysis was 46,XX. "Deletion of subtelomere 2q and duplication of subtelomere 5q" were detected by subtelomeric FISH analysis. The father was detected to be a carrier of t(2;5)(q37.1;q35.1).

This case is the second case carrying this chromosome abnormalities in the literature. As a conclusion, we want to emphasize the importance of the use of molecular cytogenetic techniques as complementary tests for undiagnosed specific cases with normal karyotypes.

46, Y,T(X;15)(P11.1;Q26) KARYOTYPE IN AN AZOOSPERMIC MALE

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P50

Approximately 15 percent of couples who were trying to conceive are infertile in Western countries. Male factor infertility forms about 50 percent of causes. In about 15% male subject have chromosome abberations and single gene mutations. The most common structural chromosamal abnormalities in humans are resiprocal translocations. These translocations are 6,5 times more frequent among infertile males. While most of resiprocal translocation involve two autosomes, a small part of them involve gonosomes (X or Y chromosome). Resiprocal translocations between a sex chromosome and an autosome are rare and most of the men who carrying these rearrengements are usually have azoospermia, although some of them show a severe oligozoospermia. Here we report a phenotypically normal 29- year old male patient who was refered to our department because of azoospermia. He had been married for 1.5 years but could not have children. The cytogenetic analyses revealed a 46, Y,t(X;15)(p11.1;q26) karyotype. The sequence-tagged-site (STS) analyses for the presence of Y-chromosome microdeletion showed an intact AZF region and the presence of SRY gene. Chromosomal analyses also had been done his parents and same karyotype with patient was found in his mother. X-autosome translocations are rare and usually inherited maternally or arising de nova. In general, female carriers continue normal reproductive function while male carriers are infertile.

In this report, we present a infertile man who has X-autosome translocation inhereted from his mother.

FUNCTIONAL ANALYSIS OF BONE MORPHOGENIC PROTEIN 9 (BMP9) IN HEPATOCELLULAR CARCINOMA

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P51

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. It is five times more prevalent between the ages of thirty to fifty and is more common in men than in women. Hepatitis B and C infection and liver cirrhosis are two known risk factors in the development of HCC. BMP is a member of TGF-beta family (a large family of growth factors). BMP9 was first identified as a hematopoietic, hepatogenic, osteogenic and chondrogenic factor. Analysis of BMP-9 expression has revealed that BMP9 is produced by hepatocytes and intrahepatic biliary epithelial cells. Studies have shown that BMP9 is a potential biomarker in especially liver, colon and prostate cancers so BMP9 could be a new target in the treatment of cancer cells. Studies have shown that BMP9 plays a significant role in hepatocellular carcinoma. In our study we transfected a hepatocelluler cancer cell line (HepG2) with BMP9-specific siRNA and examined subsequent gene expression of targets: ID1, ID2, p21, SMAD1, SMAD5, SMAD8 and SMAD4 by real-time PCR (RT-PCR) and western blot. We also examined BMP9 expression in HCC patient tissue samples by RT-PCR and immunohistochemistry. Most importantly, BMP9 knock-down resulted in a statistically significant reduction in cellular proliferation as determined by changes in cell index measured by xCELLigence real-time cell monitoring system. Obtained results suggested that BMP9 can be a potential therapeutic target in hepatocellular carcinoma treatment.

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DOWN SYNDROME COMBINED WITH KLINEFELTER SYNDROME: A RARE CASE REPORT

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Two chromosome abnormalities occurring in one individual is a very rare event. First double aneuploidy was reported by Ford et al. in 1959, in a patient with Down syndrome combined with Klinefelter syndrome. Chromosomal etiology of Down syndrome and Klinefelter syndrome were also described in the same year. Klinefelter syndrome is the most common aneuploidy combined with Down syndrome. It's frequency is 0.098%. This unexpected high frequency is explained by two theory. 1- Disomic ovum has more chance to fertilize by sperm carrying Y chromosome. 2- Sperm which carrying Y chromosome can promote nondisjunction in ovum. Here we described a three months old male patient referred to the department of medical genetics due to the dysmorphic facial features. He was born via C/S at 37 weeks of gestation. His birth weight was 3010 gr. In physical examination his head circumferences was 37.5 cm (<3. percentile), weight was 5750 gr (10-25. percentile). Dysmorphic features were hypertelorism, small mouth, and upslanting palpebral fissures. Systemic examinations, and radiologic investigations were normal. Cytogenetic analysis revealed abnormal karyotype, 48,XXY,+21, associated with combination of Down syndrome and Klinefelter syndrome.

FREQUENCY OF MVK GENE MUTATIONS IN MEVALONATE KINASE DEFICIENCY

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Mevalonate Kinase Deficiency (MKD) also known as Hyper IgD Syndrome (HIDS) is one of the periodic fever syndromes (PVS) which are the genetic disorders accompanied by recurrent episodes of fever and localized inflammations of serosal, synovial surface and skin. There are several autoinflammatory diseases with a different clinical spectrum which are caused by the mutations in the genes that encode inflammatory response regulatory proteins. Recurrent systemic inflammation signs such as rash, serositis (peritonitis, pleuritis), lymphadenopathy and arthritis and an increase of acute phase reactant levels are seen in PVS. Most common three diseases of this group are Familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS).

On DNA materials obtained from samples of 20 patients attended Erciyes University Medical Genetics department in 2015 with preliminary diagnosis of FMF performed MVK gene PCR analysis by using primers specific to exons of this gene. DNA sequence analysis was performed on the obtained PCR products by using automated DNA sequencing (Fluorescent Technologies) method.

The analysis result; in 20 patients 5 of them were detected with no mutation. 2 patients with c.52 G>A, Heterozygous; c.1129 G>A, Heterozygous effective mutations were detected. 1 patient with c.1129 G>A, Heterozygous symptomatic mutation has been identified. 1 patient with c.632-18 A>G, Heterozygous pathogenic mutation were identified. In the remaining patients c.155 G> A, Heterozygous, c.405 G> A Heterozygous; c.510 C> T Heterozygous; c.885 + 24 G> A, Heterozygous mutations with unknown effect were identified.

Evidence of efficacy and their reliability in MKD is still insufficient. That is why genetic diagnosis is very important in this patient group. It has been shown by studies from various centers in Turkey that it is possible to avoid complications of MKD by early diagnosis.

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