ERCİYES MEDICAL JOURNAL

Erciyes Medical Genetics Days 2017

11-13 May 2017 Erciyes University, Kayseri, Turkey

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11 – 13 May 2017, Erciyes University, Kayseri, Turkey

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Yusuf Tunca
Z. Oya Uyguner
Zafer Yüksel
Zerrin Yılmaz Celik

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Best Oral Presentation

First Place

Analyzing the relationship between liability to psychosis and telomere dysfunction: A sib-pair study
Güvem Gümüş Akay - Ankara University

Second Place

Two novel mutations in the *L1CAM* gene responsible for L1 syndrome
Esra Işık - Ege University

Prenatal gene therapy using Adeno-Associated virus serotyp-9 vectors in SMA mice
Ayça Aykut - Ege University

Third Place

Without the hotspot mutation, trismus-pseudocamptodactyly syndrome is possible?
E. Ferda Percin - Gazi University

Paternally inherited 18q deletion syndrome - Affected child and healthy father
Sinem Yalcintepe - Adana Numune Training and Research Hospital

Best Poster Presentation

First Place

Antioxidant effect of nesfatin-1 in alzheimer's disease model formed in astrocyte cells
Aysel Köse Yeter - Gaziantep Cengiz Gökçek Obstetrics and Pediatrics Hospital

Second Place

MECP2 gene analysis in children with Rett syndrome
Filiz Hazan - Dr. Behcet Uz Children's Hospital

Third Place

Prenatal diagnosis in single gene disorders: Ege university experience in 497 cases
Semih Aşıkovalı - Ege University

Student Special Incentive Award

General review of statistical data in FMF disease and genotype-phenotype correlation
Fatih Yavuz - Erciyes University

Statistical analysis of families with recurrent pregnancy loss and infertility applied between 2010-2013 and frequency of chromosome variants
Beyzanur Günsili - Erciyes University

OVERVIEW OF THE PRENATAL DIAGNOSIS AND INVASIVE TESTS

Meral Yirmibeş Karaoğuz

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

Through the date the first fetal karyotyping via amniotic fluid by Steel and Breg in 1966, "cytogenetic analysis" has still great value in prenatal diagnosis. Regarding the indication and time of gestation, chorionic villus sampling, amniocentesis and cordocentesis could be performed ideally in 11-14, 15-24 and 18-24 weeks of gestation, respectively. If necessary, all these invasive procedures could be applied till to term. For the accurate diagnosis of numerical and structural anomalies, direct preparation and cultivation procedures are performed by the usage of these materials. The quantitative fluorescence polymerase chain reaction and fluorescence in situ hybridization technique (FISH) screen the common aneuploidies (chromosomes 13, 18, 21 and XY) in affected foetuses. By obtaining the free fetal DNA from maternal blood circulation, the same aneuploidies could also be screened. Chromosome analysis after the long-term tissue culture of the relevant materials will not only confirm these results, but also make sure about the accurate karyotype of the foetus. Detecting the microdeletion syndrome by using FISH technique and detecting some single gene disorders are additional outputs of these prenatal genetic investigations. Nowadays chromosomal microarray analysis give the opportunity to detect the aberrations limited to kilobases rather than megabases and also accompanying by important challenges the other advances molecular test like next-generation sequencing can offer more detailed prenatal analysis. As a result, "cytogenetic analysis" is still gold standard test to detect the accurate karyotype of the foetus and this will allow parents to make an informed decision relating to the pregnancy.

PRENATAL GENETIC SCREENING METHODS IN THE CONTEXT OF UPDATED GUIDELINES

Zerrin Yılmaz Çelik

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

Prenatal genetic screening methods for chromosomal and monogenic disease rapidly change. Genetic screening practices are variable according to the regional and clinical experiences. Medical geneticists and perinatologists should be aware of the current practice for genetic screening. This presentation includes case reports with current molecular and molecular cytogenetic methods. New practice guides and algorithms will be discussed.

PRENATAL GENETIC COUNSELING

Hatice Ilgın Ruhi

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

Genetic counseling is a communication process that involves informing about the diagnosis of the genetic disease, the course of the disease, hereditary aspects and the risk of recurrence. When the individual is likely to come to the world with a genetic disease before birth, the meaning of this condition should be explained and test options for detecting the disease should be provided. Reliability of tests, risks of invasive procedures should be told. When the test results are received, information should be given according to the result and the options should be explained. This process is carried out by specialists in the field of medical genetics and counseling.

Genetic counseling indications in the prenatal period include advanced maternal age, positive maternal serum screening, Mendelian disease history, chromosomal disease in previous pregnancies, birth defect and/or mental retardation history, pathologic ultrasonographic findings, positivity in carrier screening, and/or teratogenic exposure. In addition, recurrent pregnancy loss and infertility, which are among the reasons for not having children, can be considered in this context. Furthermore, because of parental anxiety in the prenatal period, prenatal diagnostic tests and genetic counseling are on the agenda.

In the light of the genetic information that develops and changes day by day, the genetic counseling is an enormous field which the present genetic tests are suggested, the risks are evaluated and the test results are interpreted. Herewith, it is provided the direct contribution to the families for understand the risks of genetic diseases, cope with these and make important decisions.

TERATOLOGICAL COUNSELING: IMPORTANCE OF THE PREVENTION OF CONGENITAL ANOMALIES

Mehmet Buğrahan Düz[1], Selçuk Daşdemir[1], Emre Kırat[1], Aysel Kalaycı Yeğin[1], Mustafa Demir[2], Mehmet Seven[1]

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[2]Department of Nuclear Medicine, Istanbul University Cerrahpaşa Medical School, Istanbul, Turkey

Women exposed radiation without awareness during their pregnancies have often deep concern about possibility of having baby with the congenital anomalies. This situation leads families to make the decision for termination. "Teratological Counseling" provides information based on scientific data and without guidance to pregnant women with exposed to teratogens about the possible effects of the teratogens, potential for causing anomalies and what kind of anomalies the baby may have. To make best decision, the pregnant women need an effective, comprehensive, rationale and clear teratological counseling. Because, the pregnant women have no idea for potential harmful effect of radiation. Unfortunately, the physicians' anxiety may cause a potential biased guidance and it can lead to make a misperception for pregnant women.

More than 20.000 pregnant women who exposed various teratogens referred to our clinic for teratological counseling and 246 of the pregnant women who exposed to radiation were randomly selected and enrolled the study. Gestational ages were calculated based on the ultrasonographic measurements of the fetus by gynecologists. The risk of the congenital anomalies due to radiation exposure was calculated and the importance of "teratological counseling" was demonstrated.

Their radiation exposure weeks were 0.42-22.8 weeks (4.66±3.07) and fetal absorbed radiation dose ranged from 0.1 to 103 mGy (7.3±14.6). 228 of 246 (% 92.68) pregnancies gave birth to healthy children. 141 of 246 (% 57.31) pregnant women were suggested to terminate their pregnancy before teratological counseling. Following teratological counseling, only 9 of those women preferred to terminate their pregnancy, whereas remaining 132 pregnancies decided to continue the pregnancy and delivered healthy children. Teratological counseling has provided % 93.5 success of pregnant women who had the decision termination thanks to change their mind to continue their pregnancy after teratological counseling.

It is suggested that teratological counseling is not only necessary to reduce the anxiety of families but also the most effective method to prevent unnecessary pregnancy terminations.

MECHANISMS OF DNA REPAIR

Güvem Gümüş Akay

Ankara University Brain Research Application and Research Center, Ankara, Turkey

All DNA sequences are subject to changes that supply fuel for evolution, however they can also be pathogenic. The continuation of the DNA from one generation to the next depends on keeping mutation rates at low levels. Cells require the proper functioning of thousands of genes, each of which could be mutated in protein coding or regulatory sequences. There are two sources of mutations in the cell: i) DNA replication errors and ii) chemical/ physical damage to the DNA. The DNA replication machinery attemps to cope with the misincorporation of incorrect nucleotides through a proofreading mechanism, however some errors remain. Moreover, since DNA is a complex and delicate molecule, it suffers not only from spontaneous damage such as the loss of bases, but it is also attacked by chemicals and radiation leading to breakage of its backbone and alteration of chemical composition of its bases.

Replication errors and chemical/physical attack to DNA have two consequences. First, they can lead to permanent changes to the DNA, called mutations, that can alter the coding sequence of a gene or its regulatory sequences. The second is that some chemical altertions to the DNA avoid its use as a template for replication and transcription. In order to minimize the effects of these challanges, cells have effective DNA repair mechanisms that function in two steps. First, repair system scan the DNA to detect errors. Second, it restore the lesions as of original DNA sequence as much as possible. In this talk, I will explain the mechanisms of different DNA repair systems and try to answer the following questions: How is the DNA repair rapid enough to prevent errors from becoming fix in the genetic material as mutation? How does the cell distinguish the oiginal strand d from the newly synthesized strand during repairing of replication errors? How does the cell restore the proper DNA sequence when the original sequence can no longer be read?

ATYPICAL EXAMPLES OF TYPICAL SYNDROMES

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The clinically diagnosis of syndromes still remains valid despite the emerging new laboratory Technologies. Over time, the spectrum of clinical symptoms of the syndromes expanded, the genetic heterogeneity had been understood and, as a result; different types of them were found. New technologies were found to be very beneficial regarding in all these developments. Another benefit of new technologies is to enable diagnosis even though the presence of atypical clinical signs of well-known syndromes in which clinical findings are very well defined of their characteristic findings. Thus, it has been shown that there was a hope for the patients and their families who could not be diagnosed with classical methods. It also contributed to the science as including new clinical findings into the clinical signs of syndromes that we thought were well-known. In this talk, three different syndrome examples will be presented that is diagnosed in using two different new methodology. However, I would like to underline that these techniques should not lead to a misunderstanding such as clinical diagnosis solely depends on the laboratory results in all cases.

COMPLEX PHENOTYPE PUZZLE CAN BE SOLVED BY WHOLE EXOME SEQUENCING

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[3]Centogene AG, Rostock, Germany

Complex phenotypes arise from the co-occurrence of two or more genetic disorders with different modes of inheritance and origin, contributing to the clinical picture. Even the most experienced clinical geneticists cannot come up with a definite diagnosis and any unsolved case remains as a puzzle. Whole exome sequencing (WES), widely used for clinical diagnostic purposes after 2010, a powerful tool for the diagnosis of single-gene disorders, is useful in elucidating these complex, blended phenotypes which lack clinical diagnosis and there are several reports on WES cohorts showing 0.9-4 % of cases with dual molecular diagnosis.

In a cohort of clinically unsolved cases (n: 30) already karyotyped and SNP array performed, DNA samples were prepared using Nextera Capture System and exome libraries were sequenced using paired-end, 300-cycle chemistry on the Illumina NextSeq or HiSeq.

The first case with progressive developmental delay and ichthyosis was diagnosed as Sanfilippo syndrome and ichthyosis vulgaris with a novel mutation in *FLG* gene. Second case followed up due to dysmorphic features, developmental delay, Hirschsprung disease and intellectual disability, novel mutations in *PIGO* and *RET* genes confirmed diagnoses of Hyperphosphatasia with mental retardation and Hirschsprung disease. Index of the third family presented with renal tubular dysfunction, deafness and intellectual disability. Two pathogenic homozygous mutations were co-located in the proband, in *SLC5A2* and *MMAB* genes, rendering diagnoses of Renal glycosuria and Methylmalonic aciduria. The fourth proband had sparse hair, vision loss, ataxia and intellectual disability and mutations in *GRM1* and *CDH3* were revealed by WES, enabling diagnoses of Autosomal recessive spinocerebellar ataxia 13 and Hypothrichosis-juvenile macular dystrophy for the proband, as well as for his similarly affected siblings.

The study demonstrates the utility of whole exome sequencing in the context of complex phenotypes which would otherwise elude diagnosis and is the cohort with highest yield for dual molecular diagnosis (4/30; 13.3 %).

UTILITY OF NEXT GENERATION SEQUENCING IN DYSMORPHOLOGY

Ayça Aykut

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

The next generation Sequencing (NGS), which has been introduced in recent years, enables the development of personalized medical applications in diagnosis and treatment, with an accelerating pace. Whole Exome sequencing (WES) and whole genome sequencing (WGS), which are successful applications of NGS, have emerged as a very important technique in the molecular recognition of widely known diseases and in the identification of new genes in a wide range of unknown diseases. Another application of NGS is targeted next generation sequencing analysis which focuses panels contain a select set of genes or gene regions that have known or suspected associations with the disease or phenotype.

NGS has been an advancement not only for the diagnosis of Mendelian inherited diseases but also for dysmorphic diseases, as well as for use in all diseases in which polygenic and multifactorial etiologies are responsible and for all medical specialties likely to be used for all diseases in the future.

NGS completes the missing parts of dysmorphology in a very short period of time, as it has been seen, and has become applicable in clinical practice in the routine. NGS will likely become part of the standard assessment that facilitates, accelerates, and shortens the diagnostic process for the rarest dysmorphic syndromes in the future.

CONTRIBUTION OF ARRAY-CGH TO THE CLINICAL DIAGNOSIS

Gülsüm Kayhan

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Array-CGH is a widely-used method in genetic diagnosis in individuals with intellectual disability, autism spectrum disorders, and / or multiple congenital anomalies. With this technique, which has a much higher resolution than conventional cytogenetic analysis, the copy number variations (CNVs) in the genome can be defined up to 1kb. Some of the variants detected by this method are well-defined pathogenic or benign CNVs, while others are variants of unknown significance (VUS) which are the most challenging part of array-CGH analysis. Comparison of CNVs with internal and external databases and trio studies are recommended for the interpretation of the results. In addition, CNVs detected by array-CGH need to be confirmed by another diagnostic method. The laboratories that use the array-CGH in clinical diagnosis should pass the results through quality control and track their experience.

EXOME SEQUENCING WITH INTERESTING PATIENT SAMPLES

Kadri Karaer

Gaziantep Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Turkey

Since 2007, there have been tremendous advances in the development of diverse technologies for capturing arbitrary subsets of a mammalian genome at a scale commensurate with that of massively parallel sequencing. Exome is an example of parallel sequencing; just the protein coding content is the genetic code, about 1% -2% of the genome in all. Exome sequencing is often used in conjunction with two sampling strategies: family-based phenotypes (to use parent-child transmission patterns) and extreme phenotypes (to increase efficiency). In families where several individuals with a common trait are affected, one approach is to sequence the most distally related individuals: the more distant the individuals, the less genetic variants they share. However, even distant individuals share many variants that require further layering (e.g., functional layering) to identify a potentially causal allele. An alternative, family-based approach used to identify *de novo* variants involves the sequencing of parent-offspring trios in which only offspring are affected. This strategy was used to identify candidate genes for several complex features.

The combination of phenotype and genotype-based prioritization-strategies proved to be highly effective for detecting disease-causing mutations in high-throughput sequencing studies. However, the performance of these approaches also depends on the precision of the clinical description and requires some expert knowledge. Children with severe, undiagnosed developmental disorders (DDs) are enriched for damaging *de novo* mutations in developmentally important genes. We did exome sequencing about 2000 patients with DDs and here we presented some interesting samples.

FROM RARE PHENOTYPES TO COMMON DISEASES: DEFINING OF A NEW LYMPHEDEMA SYNDROME USING NEXT GENERATION TECHNIQUES AND POSSIBLE THERAPEUTIC RESEARCH

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[3]Department of Medical Genetics, Koç University Faculty of Medicine, Istanbul, Turkey

Mendelian diseases may act as models of simplified aetiology for the pathophysiology of complex conditions. The study of some Mendelian diseases has led to specific drug targets that are very effective in the general population. The best example is Familial hypercholesterolemia, the study of which led to the development of statins.

We report three individuals from two unrelated families, diagnosed with a new recessive syndrome presenting with prelingual sensorineural hearing loss, persisting lower limb lymphedema, short stature of prenatal onset, mild cognitive deficit, a recognizable facial dysmorphism comprising sparse eyebrows, upslanting palpebral fissures, prominent nasal bridge, broad nasal ridge, smooth philtrum, inverted thin upper lip, high palate, and borderline low-set ears. Whole-exome sequencing in the first family identified three distinct causative mutations segregating with the phenotype, including a protein-null allele, in CPD which encodes Carboxypeptidase D. We sequenced CPD in the affected from the second unrelated family, uncovering a homozygous distinct germline CPD mutation.

CPD is a circulating protease which hydrolyses proteins with a lysine or arginine at their C-terminus. To date, no endogenous substrates for CPD have been identified. Nitric oxide (NO) is a key molecule in mediation of lymphangiogenesis, and its synthesis is known to be stimulated by CPD. Using functional studies in patient-derived cells and zebrafish knockout animals, we aim to understand the pathogenesis of this new syndrome to further study the biologic mechanisms involving CPD and NO synthesis, and its role in lymphangiogenesis to develop CPD as a potential therapeutic for the treatment of lymphedema.

GENETIC CAUSES OF EARLY ONSET EPILEPTIC ENCEPHALOPATHIES

Derya Erçal

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Epileptic encephalopathies (EE) represent a heterogeneous group of epilepsy syndromes characterized by devastating recurrent clinical seizures that occur early in life with aggressive electroencephalographic paroxysmal activity, prominent interictal epileptiform discharges, cognitive, behavioral and neurological deficit, and often there is therapeutic resistance with early death. They are more often associated with structural defects, inherited metabolic disorders and defective genetic background.

Although very many pathogenic gene mutations may exist in the development of EE, there is still a great need for further studies to understand the neurobiology. Genetic studies also provided a better knowledge and understanding of the nature of EE for treatment options. The most common EE's are early myoclonic epilepsy, Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, West syndrome and Dravet syndrome with distinct and classifiable electroneurological features but the underlying causes may not be explained. Up to date more than 270 genes have been defined in epilepsy and several genes including *ARX, STXBP1, CDKL5, KCNQ2, SCN1A, SCN2A, SLC25A22, FOXG1 and PCDH19* have been found to be more associated with EOEE. In this presentation, a diagnostic approach to primary genetic causes of EOEE's has been aimed to help for the preparation of the mutation panels in clinical practice.

FORENSIC GENETIC ANALYSIS

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For the last 30 years, modern technological developments in molecular genetics have made important contributions in the field of forensic medicine. The DNA profiling was first discovered by Alec Jeffreys in the Department of Genetics at the University of Leicester in 1984 and the technique was named as DNA fingerprinting. Forensic genetic analysis can involve the analysis of material recovered from a crime scene, disasters, accidents, voluntary/court ordered paternity testing or the identification of human remains and etc. Molecular forensic genetic analyzes can be performed on biological samples such as blood, tissue sample taken from autopsy, abortus material, paraffin embedded tissue, urine, sperm, teeth, bone, buccal swap and saliva. In forensic genetic analysis, there is an international consensus to investigate 23 repetitive DNA sequences in microsatellite regions-also called a short tandem repeat (STR). Multiplex PCR using fluorescently labeled primers has been an essential method for the amplification of STR used in DNA profiling. In addition to the autosomal STR regions commonly used in human identification tests, the use of STR regions specific to Y or X chromosomes can be advantageous in some cases, for example in male-female DNA mixtures, etc. The use of mitochondrial DNA (mtDNA) in old or degraded biological samples has also become important since the number of circular mtDNA copies is about 100-1000 times that of the nuclear DNA and it is also resistant to adverse environmental factors because of the double membrane.

PERSONALIZED MEDICINE AND GENETICS

İlter Güney

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“Personalized medicine” can be described as tailoring medical treatment to the individual characteristics, needs and preferences of each patient. The concept of personalized medicine is not new: clinicians have long observed that patients with similar symptoms may have different illnesses with different causes and same medical interventions may work well in some patients with a disease but not in others with the same disease. Advances in a wide range of fields from medical imaging to regenerative medicine by using genomics especially with increased computational technologies have started a new era in medicine. For this reason, we are witnessing the existence of a period that passes from traditional medicine approaches to personalized medical applications.

Personalized medicine is much more successful than traditional medicine because it provides a sensitive and effective approach, equipped with unique clinical, social, genetic and environmental knowledge of each person. This approach is integrated, coordinated, and evidence-based, from health to illness.

Physiology, pharmacology and genetics are based on personalized medicine, and the knowledge gained through these disciplines is intended to be used for patients benefit. Today's first practices are largely in the field of oncology and are aimed at more effective, safe and cost-effective treatment. Because 60-80% of the variation in drug response based on genetic factors, the use of pharmacogenetic profiling has become important in routine practice. In addition to treatment, risk identification in patients and appropriate genetic testing for the prognosis of the disease are indispensable elements for more effective and safe personalized medicine applications. For this reason, it is undoubtedly one of the most important future goals of medical genetics units which especially provide routine genetic testing and genetic counseling services is to play a leading role in the practice of "personalized medicine".

COMPUTATIONAL APPROACH TO MOLECULAR MECHANISM FOR COAGULATION CASCADE AT AGÜ

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Coagulation disorders is the leading cause of death or disability in Turkey and around the world. We employ computational approach (*i.e.*, combination of molecular dynamics simulation and bioinformatics methodologies) to study the molecular mechanisms for the activation of coagulation cascade, which would lead to drug development against bleeding disorders. The key step in coagulation cascade is binding of coagulation factors to negatively charged areas of cellular membrane, minimizing degrees of freedom for coagulation factors to move. As a result, enzymatic activation of coagulation factors occurs not in the blood plasma but eventually only on the membrane surface. Coagulation factors are mostly peripheral membrane proteins; their membrane-binding modes are largely unknown, and are essentially inaccessible by all-atom molecular dynamics (MD) using current supercomputer power, due to slow dynamics of membrane lipids.

We are at the forefront of such formidable MD tasks with the HMMM model, a simple type of nano-scale biomimetics by replacing a part of acyl tails of membrane lipids with organic solvent. The bilayer-like model is self-forming and stable, keeping the right configurations of the membrane lipids. With this model included, Gla and C2 domains, two major membrane-binding domains of coagulation factors, exhibit membrane binding within a few to tens of nanoseconds in multiple independent MDs. For C2 domain of factor V, we repeatedly observe a phosphatidylserine headgroup interacting with K23, Q48, and S78, as originally suggested by the crystallographers, but in the opposite direction. The results provide a basis for further modeling the enzyme-cofactor-substrate complexes of coagulation factors.

CRISPR-Cas9 TRANSGENIC MICE FOR GENOME EDITING AND CANCER MODELING

Haydar Bağış

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In the last few years genomic editing technologies have been widely used in transgenic animal production.

Several classical methods have been used for gene transfer for many years. However, in recent years genomic editing techniques have been used. CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated9) genome editing technology has been developing rapidly in recent years. Conventional strategy for producing tissue-specific knockout mice is a time consuming and labor-intensive process that restricts the rapid functioning of the *in vivo* gene function. The CRISPR/Cas9 system is a simple and effective gene editing technique; this method ensures that knockout mouse lines can be obtained quickly by injecting CRISPR/Cas9 directly into the zygotes.

The CRISPR/Cas9 system has been widely adopted in life sciences. Genes have undergone desirable changes in many organisms, such as animals, humans, plants, bacteria, in order to correct important genes. Yeast, Drosophila, apes, rabbits, pigs, rats and mice were also used in this technique. In 2015, Chinese scientists used CRISPR/Cas9 technology to correct the diseased human beta globin gene in 3 nucleus human zygotes.

The CRISPR/Cas9 system of the designer nuclease systems currently available for sensitive genomic engineering appears to be the most perfect. Over the past four years, hundreds of transgenic animals have been produced easily, cheaply and quickly using the CRISPR/Cas9 system. The CRISPR/Cas9 system is currently under development to achieve the level of safety that can be used in clinical practice. I am foreseeing, these technics will be awarded soon the Nobel Prize

A FAMILY WITH TRICHORHINOPHALANGEAL SYNDROME, TYPE II (LANGER-GIEDION SYNDROME).

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[2]Child and Adolescent Psychiatry, Namık Kemal University Faculty of Medicine, Tekirdag, Turkey

[3]Ophthalmology, Tekirdağ Statement Hospital, Tekirdag, Turkey

OP-1

Trichorhinophalangeal syndrome Type II (TRPSII) or Langer-Giedion syndrome, is a contiguous gene deletion syndrome on 8q24.1, and characterized by its multiple dysmorphic facial features including large, laterally protruding ears, a bulbous nose, an elongated upper lip, as well as sparse scalp hair, skeletal abnormalities, and mental retardation. Most cases of TRPSII are sporadic although there are a few cases which are familial. Familial TRPSII is considered an autosomal dominant condition because one copy of the altered chromosome 8 in each cell is sufficient to cause the disorder. When the patient is referred for growth delay, we were diagnosed with typical facial and skeletal anomalies. In family inquiry, we found that his father and his two brothers resemble him. We present here a family with TRPSII and other finding.

DISTRIBUTION OF *ACE*, *CDKN2A*, *CDKN2A/B*, *KCNQ1* GENE POLYMORPHISMS IN TURKISH CYPRIOT POPULATION AND DETERMINATION THE METABOLIC DISORDER RISK FACTORS

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OP-2

Genetic risk scores are a useful tool for examining the cumulative predictive ability of genetic variation on metabolic disorders.

To determine the allele frequencies of clinically pathogenic variants and understanding the genetic makeup of metabolic disorders (MDs) in the island.

To investigate the MDs genetic risk score profile, we studied 250 healthy cross-sectional subjects. To genotype selective SNPs, PCR-RFLP technique is carried out. Allelic frequencies were estimated by genotypic distribution of polymorphisms and tested for Hardy-Weinberg equilibrium, by X^2 analysis.

rs4977574 (A/G) of *CDKN2A*, rs1333040 (T/C) of *CDKN2B/AS-1*, *ACE* D/I and, rs231361 and rs231359 *KCNQ1* variations are genotyped in our panel. 51% of the studied population are carrier for disturbing allele G for the SNP rs4977574 within *CDKN2A/B (p:0.790).* GG homozygosity frequency is calculated as 26% for *CDKN2A/B.* The frequency of T alelle of SNP rs1333040 might show correlation with MDs is 75% in Turkish Cypriot (TC) population *(p:0.967)* for the. TT homozygote genotype frequency is found around 56%. 47% of the studied TC population has deletion mutation (D) for ACE that increased the high risk of cardiovascular diseases *(p:0.07).* 23% of subjects are carrier for homozygote DD genotype.

Turkish Cypriots, who live in the island of Cyprus, have a unique mixture of allele distribution for each SNP to the other close by country neighbors. Thus, SNP-SNP interactions and also their relation with biochemical pathways might play critical role for developing MDs.

To conclude, this study will help for understanding the genetic profile of MDs in the Island and also will be great source and useful tool for prevention of MDs.

CAN VNTR VARIANTS IN *ENOS* AND *XRCC4* GENES CONTRIBUTE TO FORMATION OF RHEUMATOID ARTHRITIS?

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OP-3

Rheumatoid arthritis (RA) is a chronic, inflammatory disease of the joints that affects 0.5-1.0 % of the adult population. A VNTR in intron 4 of *eNOS* gene is responsible for production of more than 25% of basal plasma NO. *XRCC4* play a role in repair of DSBs. In present study, we aimed to investigate whether the VNTR variants in *eNOS* and *XRCC4* genes play a role in RA ethiopathogenesis.

Sixty-five patients with RA and 70 healthy controls (HCs) were examined for the VNTR variants in *eNOS* and *XRCC4* genes. All variants were genotyped by PCR and agarose gel electrophoresis.

The intron 3 VNTR variant in the *XRCC4* gene showed an association with RA patients while no association was identified between the *eNOS* and *RA*.

In conclusion, we suggested that the intron 3 VNTR variant in the *XRCC4* gene may be associated with the etiopathogenesis of RA as a marker of immune aging. Further studies with larger groups and different ethnicities are needed to determine the impact of *XRCC4*.

IS HYPOPIGMENTED SKIN PATCH A NEW SYMPTOM OF ROBERTS / SC PHOCOMELIA SYNDROME?

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OP-4

Roberts / SC phocomelia syndrome is a rare autosomal recessive disorder caused by mutations in *ESCO2* gene and characterized by prenatal growth retardation, craniofacial anomalies and limb malformations varying from symmetrical mesomelia to tetraphocomelia. We present here two affected sibling with Roberts / SC phocomelia syndrome.

Both patients, born from consanguineous marriage, had intrauterine growth retardation and similar facial appearance including epicanthic folds, hypertelorism, hypoplastic nasal alae, malar flattening, posteriorly rotated ears and mild retrognathia, and also multiple hypopigmented skin patches. The more severely affected boy had hypoplasia of tibia and symmetrical agenesis of radius, ulna, proximal carpal bones and fibula. The slightly affected girl presented with mild symmetrical mesomelic shortening.

Cytogenetic analysis showed the characteristic premature separation of centromeres, puffing of heterochromatic regions and varied aneuploidies. Further, sequencing analysis of the *ESCO2* gene identified homozygous mutation (NM_001017420.2) c.1111_1112insA p.(T371Nfs*32) in both patients.

To the best of our knowledge, there is only one patient previously reported with hypopigmented skin patches in the literature. Two independent studies of the *Esco2* gene in the zebrafish model mention from hypopigmentation in the embryo too. These findings led us to think that the hypopigmented skin patches may be a new symptom of syndrome and may present due to increased rate of the aneuploidies in these areas. More clinical reports and further studies are necessary to clarify this hypothesis.

WITHOUT THE HOTSPOT MUTATION, TRISMUS-PSEUDOCAMPTODACTYLY SYNDROME IS POSSIBLE?

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OP-5

Trismus-pseudocamptodactyly syndrome (TPS) (OMIM #158300) is a rare distal arthrogryposis (DA) inherited as an autosomal dominant trait with variable expressivity. It is characterized by decreased ability to open the mouth fully (trismus) and an unusual camptodactyly of the fingers that is apparent only upon dorsiflexion of the wrist (pseudocamptodactyly), short stature and foot deformities. To date only a single mutation, p.R674Q, in *MYH8* has been reported to cause TPS.

A 10-year-old girl presented with growth retardation, blepharophimosis, progressive ptosis especially for last two years, limited mouth opening and flexion of fingers when hand dorsiflexed.

Conventional cytogenetic analyses and array CGH (ISCA 8x60K) analyses were normal. Molecular analysis for the known hotspot mutation (p.R674Q) of TPS was performed and found to be normal.

The characteristic findings of this syndrome are trismus and pseudocamptodactyly. The blepharophymosis which was major complaint of our patient has been reported previously in another TRS patient. Although there was no mutation on the hotspot site, pseudocamptodactyly has only been reported in TRS within arthrogryposis types. So, we think that mutations in the other regions of the *MYH8* gene may be responsible for TRS. Reporting such a case is important due to they are one of the sources of data for calculating the prevalence of rare diseases and also form awareness for early diagnosis. Because of early diagnosis and management of this condition is important to prevent facial deformities in the patient.

EXPLORING/DEFINING THE ROLE OF A NOVEL HOMOZYGOUS NONSENSECAST MUTATION IN A PLACK FAMILY

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OP-6

The aim of this study was to assess the contribution of a novel homozygous nonsense mutation of *CAST* gene encoding Calpastatin, a protease inhibitor, to the autosomal recessive disease PLACK syndrome characterized by continuous shedding of the epidermis.

DNA was isolated from blood and whole genome exome sequencing was performed with Illumina system. Sequence alteration within the homozygous status of the patient and carrier status of other family members were identified by GenomeLab™ GeXP Genetic Analysis System. Calpastatin expression was assessed by immunoblotting in protein and one step RT-qPCR in mRNA level. *In vitro* Calpastatin activity was evaluated by fluorogenic calpain proteolysis assay. Confocal microscopy was used to determine localization of calpastatin in fibroblast cells of affected and healthy individuals.

Exome sequencing revealed a homozygous c.544G>T (p.Glu182*) nonsense mutation in the *CAST*. This novel stop-gain E182X variant produces a truncated protein lacking inhibitory domains II-IV. Immunohistochemistry results showed absent calpastatin staining in the proband compared to the epidermis in the control. Calpastatin activity assay revealed reduced calpain proteolysis in affected individuals. Immunoblot results showed tissue-specific expression of calpastatin, similar to RT-qPCR results. Confocal microscopy results confirmed the expression pattern shown in immunoblot results.

Recently, autosomal recessive loss of function mutations in CAST were described in PLACK syndrome. Treatment with calpain inhibitors could be used to reduce the unwanted complications in the clinics. Our findings might pave the way to explore new routes in proteolytic pathways in skin.

LETHAL MULTIPLE PTERYGIUM SYNDROME: A CASE REPORT

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OP-7

The multiple pterygium syndromes are phenotypically and genetically heterogeneous disorders and are divided into prenatally lethal and nonlethal types (Escobar Variant). Lethal multiple pterygium syndrome (LMPS) is a very rare autosomal recessive disorder characterized by multiple pterygia and flexion contractures, in association with cystic hygroma, hydrops, skeletal abnormalities, and facial anomalies. All patients with LMPS are either stillborn or die in early neonatal period. LMPS is caused by homozygous or compound heterozygous mutation in the *CHRNG*, *CHRNA1* or *CHRND* genes.

We present a case of lethal MPS. The stillborn fetus referred to our department was examined and found to have hypertelorism, short neck, multiple pterygia, joint contractures, scoliosis, pes equinovarus, rocker bottom feet and he was clinically diagnosed to have LMPS. Molecular analysis from fetal materials could not performed but sequence analysis from both of the parents have identified heterozygous c.1201C>T (p.Q401X) mutation in *CHRNG* gene.

Lethal multiple pterygium syndrome is a very rare and fatal disorder characterized with flexion contractures and multiple pterygia of joints. In addition, affected fetuses generally have cystic hygroma, hydrops and cleft palate. Here in this report, we present a new case of LMPS whose parents were carrier for c.1201C>T (p.Q401X) mutation in *CHRNG* gene.

A CASE WITH VASCULAR ANOMALIES: DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

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OP-8

Vascular anomalies include a wide spectrum of lesions. These anomalies may be isolated and may also be a secondary clinical expression due to localized or systemic influences of a recognized malformative association/syndrome and the differential diagnosis of the disease can be quite difficult for clinical geneticists. Vascular malformations have been historically treated with endovascular and operative procedures. But recently in the literature use of sirolimus, one of the best known mTOR inhibitors, for *PTEN* hamartoma tumour syndrome and Klippel-Trenaunay *syndrome (KTS)* has been reported. Here, we aimed to discuss the differential diagnosis of a patient who has a large AVM with skeletal and renal anomalies, such as *KTS*, Parkes Weber syndrome, CLOVES, Bannayan-Riley-*Ruvalcaba syndrome(BRRS).*

An 18-year-old female patient was referred to our medical genetic department when she was 11 years old, because of café au lait *spots(CALS)*, haemangiomas to be evaluated for *Neurofibromatosis(NF).* During following medical examinations, macrocephaly, aneurysmatic changes in iliac arteries and veins, a large arterio venous malformation in the abdomen, multiple CALS', haemangiomas on skin, unilateral renal hypoplasia and scoliosis have been determined. Karyotype was 46,XX and MLPA /FISH analyse for *NF* and *PTEN* gene sequence analysis were normal. But these results can't exclude the diagnosis for *BRRS* and CLOVES. Now we planned to perform *PIK3CA* gene sequence analysis.

The genetic evaluation of vascular anomalies with additional malformation is important for both disease management and genetic counselling. This case will contribute for differential diagnosis in patient having vascular, skeletal and renal anomalies.

MICRO RNA 373-3P SERUM LEVELS RELATED WITH CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION

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OP-9

MicroRNAs (miRNAs) are key regulators of gene expression and play important roles in the pathogenesis of human diseases. It has shown that miRNAs have role in macrovascular/microvascular (dys)function and they have potential as biomarkers for the early detection of cardiovascular disease(CVD). We aimed to test whether miR-373-3p has different expressions at coronary artery disease (CAD) patients.

In this study, totally 135 patients with angina or acute myocardial infarction(MI) who underwent coronary angiography were recruited and divided into 3 groups: 45 normal coronary arteries (coronary lesion<50% non-CAD), 45 obstructive CAD patients (≥50% stenosis) and 45 MI (complete stenosis or thrombosis). Serum obtained from blood samples which drawn before coronary angiography. Expression of miR-373-3p were detected by qRT-PCR after RNA isolation and cDNA synthesis. Statistical analysis of real-time PCR expression results achieved by using the $2^{-\Delta Ct}$ formula.

It showed that miR-373-3p was significantly up-regulated in patients with MI compared to non-CAD group ($p<0.01$) and also compared to obstructive CAD group ($p<0.05$). These alterations also detected at male patients and over 60 years old especially. MicroRNA-target interactions databases confirm that miR-373-3p has experimentally validated strong relation to *SIRT1* gene which has multiple cardioprotective functions.

SIRT1 gene also knowns as 'longevity gene', products a protein deacetylase that has been reported to suppress cardiovascular pathologies such as myocardial infarction via anti-apoptosis, anti-inflammation, or increasing mitochondrial biogenesis in model organisms. In addition to this, miRNAs are relatively recently discovered CVD biomarkers which have important implications for CVD early diagnosis, treatment and estimation of prognosis. These results suggest sirtuin related miR-373-3p have association with severity of CAD and may be a target for therapeutic intervention of CAD and also further evaluation by functional gene expression study recommended as the study is going on now.

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A REPORT OF TWO INFERTILE PATIENTS WITH ISODICENTRIC SHORT ARM OF CHROMOSOME Y

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OP-10

Isodicentric Yp (idic(Yp)), which is believed to occur during double-strand break repair of palindromes, can cause different phenotypes such as spermatogenic failure, sex reversal, Turner syndrome. Most idic (Yp) are not recognized or misidentified during cytogenetic studies. Here, we present two cases to draw attention to the genotype of idic (Yp) in infertile patients.

Two male patients aged 36 (P1) and 40 (P2) years with azoospermia were admitted. Patient 2 had TESE and no sperm was found.

Monosomy X mosaicism and der(Y) was found in both patients on chromosome analyzes. FISH analyzes revealed two copies of SRY, Ypter and centromere signals on der(Y) and lack of Yq12 signal, so der(Y) is defined as idic (Yp). Y deletion tests showed loss of AZFb and AZFc.

The mosaic status of the proband is assumed to be result of the loss of chromosome Y (idic) due to mitotic instability. The intact region of AZFa and the deletions of AZFb and AZFc in both patients suggest that the breakpoint was between AZFa and AZFb. The AZFb/c deletions may be thought to be the cause of infertility in these patients, but azoospermia have also been seen in patients with idic (YP), involving all Yq genes, with distal breakpoint. Therefore, during genetic counseling, it should be consider that mitotic instability and 45,X mosaicism contribute to spermatogenic failure.

ZELLWEGER SYNDROME: RARE DISEASE RARE MUTATION

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OP-11

Zellweger Syndrome (ZS) is a rare disease that takes a part in peroxisome biogenesis disorders. ZS shows autosomal recessive inheritance pattern. Identification of individuals carrying pathogenic mutations for the disease in countries such as Turkey where consanguineous marriages are frequent, prenatal and preimplantation genetic diagnosis are important in terms of preventing disease in newborns.

A 33-years-old father and a 24-years-old mother which are distance relatives consulted medical genetics outpatient clinic who had lost a daughter diagnosed with ZS. The physical examination and laboratory findings of the child (hypotonia, hypertelorism, pes equinovarus, renal cysts, pale optic disc, hypomyelination, epileptiform discharges in EEG, increased levels of VLCFA: C26:0, C24:0/C22:0, C26:0/C22:0) had been supporting ZS but genetic testing wasn't performed.

We performed *PEX1* gene with new generation sequencing for the parents. They have the same c.2085_2089delGATAA(p.M695Ifs*) deletion in exon 13 of *PEX1*. This mutation had been presented in compound heterozygous form at a patient who had c.2528G>A(G843D) in one allele and c.2085_2089delGATAA(p.M695Ifs*) in the other.

The deletion that found in parents have been accepted as a disease-causing mutation and we think the deceased child that diagnosed with ZS had this deletion in homozygous form. This mutation hasn't been reported in homozygous form in the literature. Although the child had no genetic testing, she could be accepted as the first case who had homozygous c.2085_2089delGATAA(p.M695Ifs*) mutation. It's important that the parents should be informed about the risks in new pregnancies, prenatal and preimplantation genetic testing.

THE EFFECT OF CATECHOL-O-METHYLTRANSFERASE (COMT) POLYMORPHISM ON ACUTE POSTOPERATIVE MORPHINE REQUIREMENTS: A CLINICAL PILOT STUDY

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OP-12

Genetic variability in the *COMT* gene may contribute to differences in pain sensitivity and response to opioid analgesics. The purpose of this study was to investigate whether *COMT* gene (VAL158/108MET) polymorphism contributes to the variability in response to morphine infusion used for acute post nephrectomy analgesia.

After having ethics committee approval and written informed consent, 25 patients were given intravenous morphine by Patient-Controlled Analgesia (PCA) device for post nephrectomy analgesia. Pain scores, sedation scores, the severity of nausea and vomiting, the incidence of pruritus, and the total intravenous morphine consumption were recorded for the first 24 postoperative hours. Genotyping of molecular variants (rs4680/rs6269) was performed by PCR-RFLP.

We evaluated VAL158MET in relation to the postoperative pain score. Demographic data were not significantly different between genotypes ($p>0.05$). Patients with GG genotype with VAL158MET had higher postoperative pain scores at the time of discharge from the post anesthesia care unit compared with the GA/AA genotypes ($p=0.041$). Total morphine dose requirement was also higher in patients with GG genotype (18.76±6.23 mg) compared with the GA/AA (17.50±5.52/15.54±6.68) genotypes. There were no differences in the severity of nausea and vomiting and the incidence of pruritus between all genotypes ($p>0.05$).

Genetic factors are involved in individual differences in sensitivity to pain and the use of analgesics. The present study demonstrated that VAL-158MET polymorphism is related with the amount of morphine required for pain control in the postoperative period. Further studies will be needed for patient specific pain control regimens in the future.

PUTATIVE ROLE OF CELL FREE DNA AND HMGB1 IN POSTMORTEM INTERVAL

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OP-13

Postmortem interval (PMI) determination is essential in criminal cases. Various methods have been used for PMI determination in present practice without certain results. Use of molecular technology is increasing in Forensic Medicine/Genetics lately. The objective of this study was to analyze the PMI by serum concentration changes of cell free DNA and HMGB-1 protein that raising especially after the cell necrosis.

The study was conducted on 96 Wistar rats whose weights ranging between 230- 260 g. After anesthesia and cervical dislocation, the rats were kept at 4°C and +24°C temperature Post-mortem blood samples were collected at the hours of 0, 3, 6, 9, 12, 24, 48 and 72. Serum cell free DNA was analyzed by luminometer after the nucleic acid staining protocol of SYBR Gold Nucleic Acid Gel Stain and serum HMGB-1 concentration was measured using HMGB1-ELISA kit. The results obtained in this study were converted to concentration with equations that obtained from standard samples.

Serum cell free DNA and HMGB-1 concentration were increased within the postmortem period at +4°C ($r=0.751$ $p<0.001$), ($r=0.698$ $p<0.001$), respectively. The negative correlation was found between postmortem period and the amount of cell free DNA at +24°C ($r=-0.213$ $p=0.15$), and the weak positive correlation was observed between the serum concentration of HMGB-1 and postmortem period at the same temperature ($r=0.313$ $p=0.030$).

Results of this study suggests that concentration of serum cell free DNA and the serum HMGB-1 can be used for determination of PMI at +4°C.

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PATERNALLY INHERITED 18Q DELETION SYNDROME-AFFECTED CHILD AND HEALTHY FATHER

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OP-14

The 18q deletion syndrome occurs in approximately 1/40,000 live births. This syndrome has a highly variable phenotype, although the size of the deletion and break points are variable, it does not correlate with the severity of clinical findings. In this report, we describe a female patient with a 18q22.3q23 deletion confirmed by microarray analysis, and dysmorphic appearance, hearing impairment, hypotonia, delay in white matter myelination.

The patient was born at 38 weeks of gestation, by sectio cesarean of a 37-yr-old mother, and had a birth weight of 3,000 g (25-50th percentile). This girl was the only child of non-consanguineous, healthy parents.

G-banded karyotype analysis performed on peripheral blood samples from the patient revealed the karyotype 46,XX,del(18)(q22.3q23). Mother showed normal karyotype, father revealed the karyotype 46,XY,inv(18)(p11.3q23). Subtelomeric FISH analysis of the patient showed ish der(18)(pter++;qter-)(VIJyRM2102++;VIJyRM2050-). Genomic DNA from the patient was analyzed by using the CytoScan750K Array (Affymetrix, Santa Clara, CA, USA) according to the manufacturer's instructions. Array analysis on the patient's genomic DNA revealed a 8,3-Mb (69,762,261-78,014,123) deletion in 18q22.3q23. Mother and father array-CGH analysis showed the deletion in patient was with paternal origin. However, the father has no clinical finding.

The phenotype of our case was relatively mild compared with other cases of 18q deletion syndrome having similar deletion sizes. Other factors could be correlated with the loss of genes on the 18q terminal region in order to explain various phenotypes.

3Q22.2-Q22.3 DELETION AND 16P11.2 MICRODUPLICATION SYNDROME IN A PATIENT WITH BLEPHAROPHIMOSIS, PTOSİS, EPICANTHUS INVERSUS SYNDROME

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OP-15

The patient, a girl, was born after an uncomplicated pregnancy by spontaneous vaginal delivery at 38 weeks of gestation to a healthy 25-year-old G1P1 mother. Her birth weight was 3140 gr. Parents are nonconsanguineous. The patient presented with complaints of flattened nasal root, bilateral epicantus and bilateral simian crease in Genetic Diseases Diagnosis Center who was 50 days old. The patient's physical examination revealed open anterior fontanelle and head circumference was 44 cm. Her dysmorphic features were brachycephaly, flat eyebrow structure, bilateral ptosis, blepharophimosis, epicanthus inversus, flattened and broad nasal root, bilateral simian crease and overlapping in the toes. The 15-month reevaluated patient's head circumference was measured as 45 cm. She could sit without support but she had walking and speech difficulties. Seizures were not reported.

Chromosomal microarray analysis was performed on the proband using Agilent Technologies 4x180K SurePrint G3 Human CGH+SNP Platform and Cytogenomics 3.0.4 software.

G-banding karyotype using peripheral blood was 46,XX. Copy number changes arr[hg19] 3q22.2-q22.3(135,067,196-138,663,953)x1 and arr[hg19] 16p11.2(29,656,684-30,190,568)x3 were identified in our patient.

To our knowledge, 3q22.2-q22.3 deletion and 16p11.2 microduplication has not been reported with together previously. The 3q22.2-q22.3 deletion we detected in our patient includes the *FOXL2* gene and supports blepharophimosis, ptosis, epicanthus inversus dysmorphic findings. Common characteristics that occur in people with a 16p11.2 duplication include a microcephaly and developmental delay, especially in speech and language. Affected individuals also have an increased risk of behavioral problems. 16p11.2 microduplication that we detected in our patient is followed in terms of intellectual and physical development.

UTILIZATION OF MULTI-GENE PANELS IN COLORECTAL CANCER: ANALYSIS OF CLINICOPATHOLOGICAL FINDINGS

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OP-16

Worldwide oncology field efforts to catalogue mutations in multiple cancer types are on the way. NGS (Next Generation Sequencing) based panel testing leads to new discoveries that will be translated to new diagnostic, prognostic and therapeutic targets. Therefore, we focus on emerging mutation-targeted therapeutic strategies, providing an outlook for personalized treatment and clinicopathologic findings in colorectal cancer patients.

Panel included comprehensive analysis of 12 genes (*KRAS, NRAS, KIT, BRAF, PDGFRA, ALK, EGFR, ERBB2, PIK3CA, ERBB3, ESR1* and *RAF1*). NGS were performed for all genes in 22 patients with pathologically confirmed malignity that underwent surgical treatment.

Positive rates were defined as the proportion of patients with a pathogenic variant(s) and were as follows; 56.25% (n=9) of 16 colon cancer samples in *EGFR, KRAS, KIT, ERBB2, KIT* and *PIK3CA* genes, and 50% (n=3) of the rectum cancer samples in EGFR, KRAS and ERBB2 genes. Most interestingly, three colon cancer patients had clinically significant variants in more than 1 gene who had distant metastasis. Moreover, one patient had locally-advanced cancer with novel clinically uncertain significant variant (c.2184+19GA>A) in *EGFR* gene.

Our data point to an important role of NGS where it is being considered for routine clinical use by allowing us to diagnose, determine the treatment strategy and cancer patient management.

NEXT-GENERATION SEQUENCING MULTI-GENE PANEL FOR LUNG CANCER IN CLINICAL USE: A PRACTICAL PERSPECTIVE

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OP-17

Early and precise delineation of therapeutic responses are key issues in lung cancer management. Conventional molecular cytogenetic and molecular genetic testing is currently used but exhibits limitations in sensitivity and specificity. As a result, next- generation sequencing (NGS) becomes a standard molecular diagnostic tool, and allows us to work with multi-gene panels. We evaluated a new system and multi-gene panel for the diagnosis of somatic mutations in lung cancer patients.

The test set is consisted of 99 FFPE tumor samples from lung cancer patients. *KRAS*, *NRAS*, *KIT*, *BRAF*, *PDGFRA*, *ALK*, *EGFR*, *ERBB2*, *PIK3CA*, *ERBB3*, *ESR1* and *RAF1* genes were next-generation sequenced (GeneReader NGS System).

99 FFPE lung tumor samples were analyzed. 48 (48.5%) of 99 patients had no clinically significant variants while 50.5% (n=50) of the patients had pathogenic variations in *BRAF*, *NRAS*, *KRAS*, *EGFR*, *ERBB2*, *ERBB3*, *KIT*, *PDGFRA* and *PIK3CA* genes. One (1%) patient had an uncertain significant variant in *PDGFRA* gene.

NGS systems became the most successful diagnostic tool, with improved turnaround time, decreasing costs and an expanding knowledge of the therapeutic and prognostic significance of the detected variants.

NEXT-GENERATION-SEQUENCING-BASED PANEL TESTING PLAYS A MAJOR ROLE IN THE MANAGEMENT OF PATIENTS WITH FOR HEREDITARY CHOLESTASIS

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OP-18

Familial intrahepatic cholestasis (FIC) comprises a group of rare cholestatic liver diseases associated with canalicular transport defects resulting predominantly from mutations in *ATP8B1*, *ABCB11* and *ABCB4*. Phenotypes range from benign recurrent intrahepatic cholestasis (BRIC), to progressive FIC (PFIC). Thus, molecular tests are required to permit a conclusive diagnosis and treatment. In this study, we examine the FIC patients for additional information to the diagnostic workup diagnostic panel of causative genes.

A panel of genes included *ABCB4*, *ABCB11* and *ATP8B1* genes. NGS was performed on MiSeq System, Illumina from leukocyte DNA from 35 cases of FIC. In-silico analysis for novel mutations was carried out using SIFT, PolyPhen2 and MutationTaster.

We detected disease-causing mutations in 6 out of 35 patients with FIC. More than that, while the identified mutations in 4 of 6 were in *ABCB11* gene, the other 2 were in *ATP8B1* gene. All the mutations were confirmed in the parents. Currently, first-line treatment includes ursodeoxycholic acid in patients with ABCB4 deficiency (PFIC3) and partial biliary diversion in patients with ATP8B1 or ABCB11 deficiency (PFIC1 and PFIC2).

In our PFIC case series, 6 different mutations in 2 different genes (*ABCB11* and *ATP8B1*) were identified. Our study showed clinical usefulness of comprehensive mutation analysis by NGS for intrahepatic cholestasis.

A NOVEL INDEL MUTATION IN THE TCOF1 GENE FOUND IN A NEWBORN WITH TREACHER COLLINS SYNDROME

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OP-19

Treacher Collins Syndrome (TCS) is a rare, autosomal dominant disorder characterized by hypoplasia of maxillary and mandibular bones, external ear abnormalities, preauricular hair displacements onto the cheeks, coloboma of the lower eyelid and absence of the lower eyelashes and conductive hear loss. *TCOF1* gene is located in 5q31.3-32 and responsible for 78-93% of the mutations related to TCS. Recently, autosomal recessive *POLR1C* and either autosomal recessive or dominant *POLR1D* gene mutations were also found to underlie the aetiology of TCS in 8-10% cases. *TCOF1* gene codes a protein called treacle which plays an important role in the development of facial bones in early embryonic period. We report a newborn with TCS. A 1-month-old male patient was referred to our clinics with abnormal facial features. He was the first live birth of the non-consanguineous parents. His neuromotor development was normal and hypertelorism, downslanting palpebral fissures, hypoplasia of right auricle, hypoplasia of the maxillary bones and narrow forehead were observed on his physical examination.

The *TCOF1* gene sequencing revealed a novel mutation c.4143_4144delGAinsTT (pLys1381Asnfs*2) (pK1381Nfs*2) (Heterozygous) (NM_000356.3) that is a frameshift mutation and expected to result in a premature stop codon. In addition, a heterozygous c.1552G>A (p.Val518Ile) (V518I) polymorphism in exon 11 of the *TCOF1* gene was seen in the case.

To date, about 200 different other pathogenic mutations have been reported in the coding region of *TCOF1*. The parents were normal for the mutation detected on the patient. Therefore, we concluded the patient's mutation was *de novo*.

A NEW MUTATION ASSOCIATED WITH BANNAYAN RILEY RUVALCABA SYNDROME

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OP-20

Bannayan Riley Ruvalcaba Syndrome (BRRS) is an autosomal dominant disorder characterized by macrocephaly, intestinal hamartomatous polyposis, hyperpigmented macules of the glans penis and devolepmental delay. *PTEN* gene mutations defined in approximately 60% of the patients and the disorder is classified as one of the *PTEN* Hamartomatous Tumor Syndromes. Here we report a 3 years old male patient who was referred to the department for macrocephaly and delay in walking. His developmental stages were coherent with his peers except the walking difficulty. Physical examination revealed that his weight was 18kg (95th percentile), height was 105 cm (>97th percentile) and head circumferance was 57cm (>97th percentile). He had pectus excavatum and there were multipl cafe au lait spots at lower extremities and hyperpigmented macules on the glans penis. The clinical findings of the case was opponent with BRRS and therefore, *PTEN* gene analysis was performed.

The molecular genetic analysis of *PTEN* gene sequencing revealed *de novo* p.N292Kfs*6 (c.872_873insA) heterozygosity. The mutation has already been reported in Cowden Syndrome (CS) that is another *PTEN* Hamartomatous Tumor Syndrome, but to our knowledge, this variant has not been reported previously for association with BRRS.

The in *silico* tools revealed the mutation as a pathogenic frameshift mutation that causes an early stop codon. We concluded that this frameshift mutation may also be associated with BRRS. Clinical follow-up of the case will be helpful for understanding the involvement of this gene mutation in clinical characteristics of the syndrome.

CHROMOSOMAL MICROARRAY EXPERIENCE OF 94 CASES: INITIATE DIFFICULTIES AND PROGRESSION

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OP-21

Chromosomal microarray analysis (CMA) or array based CGH technics are widely available molecular methods used for detecting unbalanced chromosomal rearrangements. SNP arrays are also capable of detecting loss of heterozygosity and haplotype analysis i.e. genome wide association studies. Here we present our initializing process of CMA and difficulties faced during the setup and analysis.

Various patients including recurrent pregnancy loss, multiple congenital anomalies, learning disabilities and known cytogenetic abnormalities are selected for CMA. We performed CMA from peripheral blood DNA, using CytoScan® Optima Suite (Affymetrix) platform which is SNP array designed for targeting common chromosomal abnormalities. Results are analyzed by Chromosome Analysis Suite (ChAS) 3.1 software. Variants are evaluated with databases (DGV and Decipher) for known copy number variations.

We could not detect any significant copy number changes in 47 out of 94 patients. The rest of the samples revealed at least one copy number (CN) change (gain/deletion). CN changes were varying from 50 kb to cytogenetic level (>3 Mb). Variants were reported to be benign, likely benign, likely pathogenic, pathogenic or uncertain significance.

Adapting microarray as a clinical routine test have some challenging points. Due to reimbursements and costs selecting right platform is important for effective testing. Choosing right resolution for the anomaly of interest plays an important role for array based analysis workflow. Wet laboratory and computational analysis are considerably time-consuming process. We would like to share our experience for laboratories that are planning to adapt chromosomal array tests.

THE PREVALENCE OF FAMILIAL MEDITERRANEAN FEVER (FMF) MUTATIONS IN PEDIATRİC PATIENTS WITH ASTHMA AND ALLERGIC RHINITIS

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OP-22

Some studies suggest that *MEFV* gene mutations may be protective against the allergic diseases. We aimed to compare the prevalence of FMF mutations in asthma and allergic rhinitis patients with controls in pediatric population and to analyse the effect of *MEFV* mutations in the development of atopy.

70 patients (45 allergic asthma, 11 allergic rhinitis and 14 both asthma and allergic rhinitis cases) and 72 controls were included in our study. The serum IgE levels of the patients were measured and the skin prick test panel was used to confirm the atopy. Total genomic DNA was extracted from peripheric blood using DNA isolation kit and patients and control group were screened for 12 *MEFV* gene mutations using reverse hybridization procedure.

There were 13 carriers (heterozygous mutation) (18.6%) in patient group. Controls had 23 carriers and 1 compound heterozygous (33.3%). It was not detected any homozygous mutation in both two groups. The most frequent mutation in both patients and controls was E148Q (38.4% in patients, 29.2% in controls). The number of individuals with mutation were higher in the control group ($p=0.045$) and the mutation ratio of the control group was also higher than patients ($p=0.046$).

According to the current study, FMF mutations are lesser in allergic rhinitis and asthma cases than in normal population. We thought that the negative association between allergic diseases and FMF mutations may originate from suppression of Th2 activity due to defective pyrin.

MLPA ASSAY IN THE MOLECULAR DIAGNOSIS OF COPY NUMBER ANALYSIS OF SURVIVAL MOTOR NEURON GENES IN TURKISH PATIENTS

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OP-23

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease characterized by degeneration of motor neurons in the anterior horn of the spinal cord that cause progressive muscle weakness and atrophy. Estimated incidence of SMA is 1/6,000-10,000 live births and carrier frequency is 1/40-1/60. SMA is mostly caused by deletion in the survival motor neuron 1 gene (*SMN1*). The *SMN1* gene, and its homologous *SMN2* gene are localized on 5q13.2. *SMN2* gene copy number can affect disease severity. The aim of this study to determine the copy number of *SMN1/2* using multiplex ligation-dependent probe amplification (MLPA).

MLPA analysis was performed for *SMN1* and *SMN2* genes in 135 cases between January 2013 and March 2017 who were referred for SMA and family history of SMA.

In *SMN1* gene, 39 out of 135 (28%) cases were found to have heterozygous and 19 out of 135 (14%) homozygous deletions by MLPA analysis. The *SMN2* copy number was 0, 1, 2 or 3 in the carriers, whereas it was 1, 2 or 3 in the patients.

MLPA is a simple and efficient method for copy number analysis of *SMN* genes. Here we report our *SMN1/2* data of the last four years and discuss our molecular results.

RING CHROMOSOME 3 IN A CASE WITH MICROCEPHALY AND GROWTH RETARDATION

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OP-24

Ring chromosomes are rare structural chromosome abnormalities that can occur in all human chromosomes. They result from two terminal breaks on both chromosome arms followed by fusion of the broken ends containing the centromere to form a circular structure leading to the loss of genetic material.

Ring chromosome 3, r(3), is a very rare abnormality which shows clinical heterogeneity. Common clinical features are growth retardation, intellectual disability, delayed psychomotor development, microcephaly, and dysmorphic facial features. Here we present a case with r(3) diagnosed after using cytogenetics and chromosomal microarray.

Fifteen months old boy was referred to outpatient clinics because of having microcephaly and growth retardation. He was born to a nonconsanguineous healthy parents. His weight, height and head circumference were 7,2 kg (<3 centile), 70cm (<3 centile) and 40 cm (<3 centile), respectively. On physical examination, microcephaly, prominent columella, long-flat philtrum and thin upper lip were detected. Biochemical tests, cranial imaging (MRI and 3d-CT), ophthalmological and audiological examinations were normal. Nephrolithiasis in the left kidney was detected by abdominal USG. Karyotype was 46,XY,r(3)(p26q29). Microarray analysis showed arr[hg19] 3p26.3p26.1(61.891-8.405046)x1.

To the best of our knowledge, this case is the 14th case of r(3) reported in the literature to date. Phenotypic features of our case were overlapping with other reported cases carrying ring chromosome 3 as well as cases of 3p deletion syndrome.

In conclusion, we would like to emphasize the importance of molecular cytogenetic tests in terms of showing losses and gains in cases carrying ring chromosomes.

MOLECULAR ANALYSIS OF A TURKISH FAMILY WITH ATAXIA-TELANGIECTASIA: THE IDENTIFICATION OF TWO NOVEL MUTATIONS

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OP-25

Ataxia-telangiectasia (A-T) is a rare autosomal recessive neurodegenerative disorder. It is characterized by early-onset, progressive cerebellar ataxia, oculomotor apraxia, choreoathetosis, conjunctival telangiectasias, immunodeficiency, and an increased risk of malignancy.

Herein, we report the clinical findings and genetic test results of an A-T siblings who presented with limb and truncal ataxia, immune deficiency, and telangiectasias of the eyes. The parents were consanguineous. In both siblings, sequence analysis of the *ATM* gene revealed two novel mutations: c.6108T>A (p.Tyr2036Ter) and c.26delT (p. I10SfX6). Segregation analysis showed that the mother and father were heterozygous for one of the mutations found in the siblings.

As a conclusion, despite there is consanguinity between parents in an autosomal recessive disease, compound heterozygosity could be present. Two novel mutations defined in this study may help to make phenotype genotype correlation in patients with A-T.

CONRADI-HUNERMANN SYNDROME IN A MALE AND FEMALE CASE WITH TWO NOVEL *EBP* MUTATIONS

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OP-26

X-linked Conradi-Hunermann-Happle syndrome (CDPX2) is a rare entity caused by 'sterol-Δ8-Δ7-isomerase' deficiency, encoded by *EBP*, comprising growth retardation, craniofacial dysmorphisms, epiphyseal calcifications, asymmetric rizomelic shortening, ichthyosis, ocular findings. Males display severe findings such as fetal demise, cerebral anomalies, and developmental delay. Affecteds have increased levels of 8(9)-cholestenol and 8-dehydrocholesterol levels in sterol profiling. We here present clinical, biochemical and molecular findings of a male and a female with CDPX2.

Both patients were karyotyped prior to sequencing of *EBP* in DNA from lymphocytes and buccal mucosa. Fibroblast sterol analysis was performed in Amsterdam Center for Metabolism, AMC, Netherlands.

At age 2 months, the boy had flat facial profile, hypotonia, ichthyosis, cataracts, asymmetric rhizomelic shortening, aortic coarctation, marked generalized stippled calcifications, vertebral segmentation defects, developmental delay and moderate hydrocephaly requiring shunt. Mild 8-lathosterol accumulation was detected in fibroblasts. The 5-year-old female was diagnosed due to flat facial profile, scoliosis, aysmmetric risomelic shortening, ichthyosis, cataracts and epiphyseal stipling. Both patients had normal karyotypes, and *EBP* sequencing revealed two novel *de novo* mutations, heterozygous c.388G>C (p.Gly130Arg) in the female, and heterozygous c.338 + 3A> T in the boy, suggesting mosaicism.

Milder findings in the female can be attributed to differences in expression of the mutated allele caused by skewed X-inactivation. Somatic mosaicism in the boy was supported by 8-lathosterol accumulation being less than expected in affecteds. This study adds to the literature on phenotypic and mutational spectrum of the very rare CPDX2 phenotype.

PRENATAL GENE THERAPY USING ADENO-ASSOCIATED VIRUS SEROTYPE-9 VECTORS IN SMA MICE

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OP-27

Intrauterine (IU) correction of survival motor neuron (*SMN*) gene expression seems can be critical in the treatment of spinal muscular atrophy (SMA) disease. In this study, recombinant adeno associated virus serotype-9 carrying SMN gene (rAAV9-SMN) was delivered into mice embryos. The symptoms related to disease and histopathological findings were then investigated.

In this study, 180 and 165 mice fetuses received 4 x 10^{10} vgc of single-stranded (ss) AAV9-SMN and self-complementary (sc) AAV9-SMN via IU-Intracerebroventricular (ICV) injection, respectively. In the first group (180 mice), 44 mice were homozygously affected with the SMN deletion. From the second group (165 mice), 39 mice were homozygously affected with the same deletion. After Birth, affected mice were investigated in relation to the SMN protein expression, survival rate, and improving of disease symptoms.

The live birth rate was 69.4 % in all the mice received ss or scAAV9-SMN via IU-ICV injections. However, live birth rate was only 43.8 % in homozygously affected mice. Prenatally delivery of both ss and scAAV9-SMN vectors lead to an increased lifespan of injected SMA mice fetuses, 63±30 ve 105±50 days respectively. The muscle pathology and number of the motor neurons have been improved in both study groups. We determined a greater efficiency from scAAV9-SMN vector when compared to ssAAV9-SMN vector.

As a conclusion, intrauterine administration of rAAV9-SMN via ICV injection may provide an alternative therapeutic approach for treating SMA disease. However, further studies are needed to fully investigate potential safety implications of this method.

1P/19Q STATUS AS A DIAGNOSTIC AND PROGNOSTIC FACTORS IN GLIOMAS: A SINGLE CENTRE STUDY

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OP-28

Gliomas are the most common primary intraparenchymal tumours of the central nervous system and are a genetic and phenotypic heterogeneous group. Gliomas with oligodendroglial component are relatively rare and associated with longer survival than astrocytic gliomas. The cellular morphological distinction between oligodendroglioma and astrocytic glioma can be subjective with inter-observer variability. Large multi-institutional studies have provided firm insights into the basic genetic drivers in gliomas. The main genetic markers routinely applied to evaluate gliomas include *MGMT* promoter methylation, *IDH1* or *IDH2* mutations, and 1p19q status. Many of these markers have become standard of care for genetic testing and prerequisites for clinical trial enrolment.

In this study, we present 1p/19q status of 215 glioma cases from a single centre. Formalin fixed paraffin embedded samples are examined by using interphase FISH. Fifty of these 215 cases showed codeletion, 5 of 215 showed only 1p or 19q deletion and 40 of 215 showed polysomy of 1p/19q.

Previous studies suggested that gliomas with 1p19q-codeleted gliomas are the most favourable molecular status- with prolonged survival and better response to chemotherapy- than 1p or 19q deletion alone or polysomies of 1p19q. However, 1p/19q status is not a diagnostic marker for gliomas alone, but it supports the diagnosis and it could be a prognostic biomarker for gliomas.

TWO NOVEL MUTATIONS IN THE *L1CAM* GENE RESPONSIBLE FOR L1 SYNDROME

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OP-29

L1 syndrome is a rare X linked recessive disorder. It is characterized by hydrocephalus, intellectual disability, adducted thumbs and spasticity of the legs. Molecular defects in L1 cell adhesion molecule (*L1CAM*) gene are responsible for L1 syndrome. The gene encodes a protein which plays important roles on neuronal development. In this study, two unrelated L1 syndrome cases with two novel mutations in the *L1CAM* gene are presented.

Following DNA isolation from peripheral blood, molecular analysis of *L1CAM* gene (NM_000425) was performed using a targeted next generation sequencing panel (the TruSight Inherited Disease® panel). Mutations found in that gene confirmed by Sanger sequencing.

Two patients with global developmental delay and hydrocephalus were referred to pediatric genetics subdivision for genetic counseling. Bilateral adducted thumbs and spasticity in the lower extremities was observed in both patients. Taking into consideration the clinical features, they were diagnosed to have L1 syndrome. Molecular analysis revealed two novel hemizygous mutations in the patients: a deletion mutation (c.749delG; p.Ser250Thrfs*51) and a splicing mutation (c.3166+1G>A). Segregation analysis in the families was planned.

When a comprehensive physical examination, including the defining of dysmorphological features, of a child with mental retardation is the most important step of diagnostic evaluation. In patients with mental retardation and hydrocephalus, L1 syndrome should be considered if adducted thumbs are present.

ANALYZING THE RELATIONSHIP BETWEEN LIABILITY TO PSYCHOSIS AND TELOMERE DYSFUNCTION: A SIB-PAIR STUDY

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OP-30

Compared to the general population individuals with Schizophrenia (Sz) experience a higher number and an earlier onset of chronic medical disorders, resulting in a reduction in their life expectancy by an average of 15-25 years. Recently, it has been hypothesized that the Sz is a syndrome of accelerated aging. One of the best biomarkers of cellular aging is considered to be the telomere length (TL). We have investigated TL in sib- pairs discordant for Sz to test the hypothesis that the relationship between psychosis and TL would be paralleled in first-degree relatives. Relationship between detailed clinical and neuropsychological variables and TL has been evaluated. In addition, the effect of lifelong psychological stress on TL has been analyzed in each group.

Sz patients (n=100), their discordant siblings (n=100) and healthy controls (n=100) were enrolled in this study. TL was measured by a TL-qPCR.

Shorter TL in patients has been found supporting the hypothesis of Sz is a premature ageing syndrome (P<0,001). Surprisingly, we have found that the nonschizophrenic siblings have longer TL compared to both patients and controls (P<0,001). Significant negative correlation has been observed between psychotic symptoms and TL (r=-0,208; p=0,001). Childhood experiences of care and abuse had negative effect on TL (P<0,05). In accordance with longer TL, higher education level, better cognitive function and better metabolic profile has been determined in the sibling group. This is the first study in which the relationship between TL and detailed clinical variables and the effect of psychological stress on TL in Sz have been investigated. To clarify the biological pathways underlying the shorter TL in patients and longer TL in sibs, longitudinal and additional studies at the cellular level are warranted.

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THE PREVALENCE OF BRCA1/BRCA2 MUTATIONS AMONG BEFORE AGE 60 WOMEN WITH TRIPLE-NEGATIVE BREAST CANCER. SIGLE CENTER EXPERIANCE

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OP-31

Molecular screening for *BRCA1* (BReast CAncer 1) gene and *BRCA2*(BReast CAncer 2) gene mutations is now an established component of risk evaluation and management of familial breast cancer.

We studied 33 women who were diagnosed with triple-negative invasive breast cancer at or before age 60. *BRCA1* and *BRCA2* screening was performed using a combination of fluorescent multiplexed-PCR analysis.

Thirty-three female patients with triple negative breast cancer under 60 years of age were included in the study. The average age was 45.9 (range 30-60), 12 of the patients were between 50-60 years, 11 were between 40-50 years, and 10 were under 40 years old. BRCA1 / *BRCA2* positivity was detected in 8 patients (24%) from 33 patients. *BRCA1* mutants were found in 6 (18.1%) patients and *BRCA2* mutants were found in 2 (6%) patients. There was no statistically significant difference between *BRCA1/BRCA2* mutation positive patients (n = 6/2) and *BRCA1/BRCA2* negative patients (n = 27/31) according to age groups, menopausal status, tumor in right or left breast, histologic type of tumor.

Both *BRCA1* and *BRCA2* mutations in breast cancer patients were more common in triple negative patients under 40 years of age. However, there was no statistical significance. We think that the reason for this is due to the small number of patients. We recommend the absolute *BRCA* mutation in patients with triple negative breast cancer below 40 years of age.

CIRCADIAN CLOCK-REGULATED DNA REPAIR GENE XPA IS DOWNREGULATED IN METASTATIC OF LUNG CANCER

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OP-32

Lung cancer is rarely detected in the early stages of the disease and 60-70% of patients have advanced or metastatic disease at diagnosis. Metastatic spread to other organs is the main cause of death in lung cancer. However, the underlying mechanisms of metastasis remain unknown and therefore further systematic studies are necessary on the possible differences in expression of markers in primary and metastatic tissues. The DNA repair capacity, which is directly involved in tumorigenesis, is controlled by circadian clock through XPA oscillation. Morever, overexpression of DNA repair genes has been suggested to be associated with metastasis. Therefore, we examined the expression of XPA at different stages of carcinogenesis from primary tumors to metastasis in patients with lung cancer.

The purpose of this study was to compare the expression of XPA in the primary tumors and metastatic lymph nodes of 21 lung cancer patients. We have analyzed the expression of XPA in 21 formalin-fixed paraffin-embedded (FFPE) specimens derived from primary non-small cell lung cancer tumors and lymph node metastasis as well as normal lung tissue. FFPE specimens were used to isolate RNA from samples, which were classified as normal lung tissue, primary tumors, and lymph-node metastases according to pathological confirmation.

Our results indicate that XPA had significantly different expression metastatic lymph nodes rather than primary tumors of patients with lung cancer. Against the general expectation that XPA levels would increase in metastatic samples, XPA levels are significantly downregulated in metastatic lymph nodes as compared to normal lung tissue

Targeted chemotherapy of lung cancer is currently based on sensitivity of the primary tumor to specific drugs. These results provide an initial step toward the improvement of lung cancer therapy that is based on measurement of the expression of genes in the metastatic lymph nodes.

EVALUATION OF PHENOTYPIC SPECTRUM IN A 18P DELETION SYNDROME CASE

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OP-33

18p deletion syndrome is a chromosomal disorder characterized with mild mental retardation, cerebral malformations, short stature, psychomotor problems, cardiac defects and specific facial feature such as round face, ptosis, epicanthus, short protruding philtrum, ears with detached pinna. Although the prevalence of this syndrome is 1:50.000 live-born infants, about 150 cases have been reported. Clinical manifestations of these cases show great variability. Here, we report a female infant with *de novo* 18p deletion syndrome associated with severe cardiac defects and milder cerebral malformations. Our patient may be helpful to point out wide phenotypic spectrum of this syndrome.

Metaphases obtained from peripheral lymphocyte culture were analyzed after GTG banding. 18p subtel, 18q subtel probes and TUPLE1 probe for differential diagnosis of DiGeorge syndrome were used to perform FISH analysis.

Firstly, karyotype analysis was reported as 46,XX,del(18)(p11.1). To confirm this deletion, FISH analysis was performed and there were two signals of 18q subtelomeric region and single signal of 18p subtelomeric region. In addition, FISH analysis for DiGeorge syndrome was normal. Her parental karyotype analyses were performed and found as normal. As a result, her karyotype was reported as 46,XX,del(18)(p11.1).ish 18pter(D18S552x1)18qter(pVYSs250Ex2)22q11.2(TUPLE1x2)

Phenotypic features of our patient are generally consistent with previously delineated cases of 18p deletion syndrome. Cardiac defects are observed in about 10 percent of previously reported cases. Unusually, this feature is major manifestation of our patient. It presents a tangible evidence of wide phenotypic spectrum of 18p deletion syndrome.

FILTERING, ANALYZING AND CLINICAL REPORTING ISSUES IN ARRAY KARYOTYPING

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OP-34

Aim is to review the important issues in array karyotyping in clinical laboratory practice.

Array karyotyping is a new technology that has enabled genome-wide detection of genomic imbalances. Especially single-nucleotide polymorphism arrays (SNP-A) give promising results because of their high resolution advantage from the usage of very large numbers of allele-specific probes. This methodology is now the first tier test in autism spectrum disorders, multiple congenital anomalies and developmental delay. SNP-A karyotyping also allows genome-scale detection of absence and loss of heterozygosity (AOH, LOH) or uniparental disomy (UPD), which is widely observed in cancer genomes. This also allows the analyzer to focus on the homozygosity blocks whenever a genome sequencing experiment is performed for the patient.

Here, we will review the the filtering, analyzing and clinical reporting issues of SNP-A. karyotyping in the window of current status and its applications.

IL-17F RS763780 VARIANT IS NOT ASSOCIATED WITH CLL AND MM SUSPECTIBILITY IN A TURKISH COHORT

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OP-35

Chronic lymphocytic leukemia (CLL) is a hematologic malignancy which is characterized by accumulation of tumor cells in the peripheral blood, bone marrow and lymph nodes. Multiple myeloma (MM) is a malignant proliferation of monoclonal plasma cells. Interleukin-17 (IL-17) is involved in the development of autoimmunity, inflammation, and tumors. This study aimed to investigate the relationship between IL-17F rs763780 variant and CLL/MM susceptibility in a Turkish cohort.

The study included 37 CLL/21 MM patients and 100 healthy controls. IL-17F rs763780 variant was analysed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The frequencies of the alleles and genotypes in patients and controls were compared by the χ^2 test.

The distributions of genotypes and allele frequencies were compared among all groups. No significant differences in genotype and allele frequencies of IL-17F rs763780 existed between patients and controls ($P > 0.05$).

This results do not support any major role of IL-17F rs763780 in CLL and MM pathogenesis. Further large-scale and well-designed studies are needed to confirm these results.

MYOCLONUS-DYSTONIA SYNDROME: A NOVEL SGCE MUTATION

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OP-36

Myoclonus-Dystonia (M-D) is a rare autosomal dominant inherited disorder caused by heterozygous mutations in the epsilon-sarcoglycan gene (*SGCE*). M-D typically features a variable combination of dystonia and non-epileptic myoclonic jerks.

We describe here a large dominant pedigree of Turkish origin.

We identified a novel heterozygous STOP-gain mutation in exon 3 of *SGCE* (c.272T>G; p.Leu91*).

We show an exceptionally large variability of the clinical symptoms, even between members of the same family. We hereby report this case series with a discussion of the literature.

GENERAL REVIEW OF STATISTICAL DATA IN FMF DISEASE AND GENOTYPE-PHENOTYPE CORRELATION

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OP-37

FMF is most commonly diagnosed in Mediterranean-based nations that characterized by recurrent fever episodes, arthralgia and abdominal pain. Turks, Arabians, Armenians and Non-Ashkenazi Jews have the most frequency with nearly %20 of public carrying mutation. Disease related to *MEFV* gene and most likely inherited in autosomal recessive manner.

Our aim is to investigate the most frequent mutations and correlate mutation with symptoms of patients with FMF.

We reviewed files of 1006 patients from our clinic pre-diagnosed with FMF between 2016 and 2015 years. We created a profile for each patient with their symptoms and history of appendectomy, kidney failure-cases and FMF in family history. We obtained results from Computation and Administration System of Hospital. Tests were performed by using Qiagen Pyrosequencing Q96 ID Systems (Biotage, Uppsala, Sweden).

We observed pathogenic variants in %53 of our patient and female: male ratio was 1:3. Abdominal pain, arthralgia, fever and chest pain are the most frequent symptom in mutation-detected patients. M694V, R202Q, E148Q, M680I and V726A are the most frequent variants. K695R mutation is the 4th most frequent variant in patients with the abdominal pain.

Despite we detect that the consanguinity ratio was %24, homozygote variants were detected in %9 patients. Our 2nd most frequent mutation, R202Q, has a lower ratio against the allele frequency in ExAC database.

STATISTICAL ANALYSIS OF FAMILIES WITH RECURRENT PREGNANCY LOSS AND INFERTILITY APPLIED BETWEEN 2010-2013 AND FREQUENCY OF CHROMOSOME VARIANTS

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OP-38

Infertility is the failure to achieve a clinical pregnancy after 12 months of regular sexual intercourse (www.who.int) and according to the American Society of Reproductive Medicine (ASRM) recurrent pregnancy loss (RPL) is two or more pregnancy losses. In this work, we evaluated files of 517 couples with infertility and 2239 couples with RPL and described some parameters.

Most of couples with infertility applied to clinic between 2.5-3.5 years of marriage, but there are also many couples who applied to clinic after 6 month of marriage. In three patients 47, XXX karyotype were found witch is consistent with literature. 46XX, t(6;15); 46XX, t(5;9); 46XX, t(7;9); 46XX, t(11;21); 46XX, t(10;18); 46XX, t(13;14) translocations each were observed in one female and 45XX,t(13;14) were observed in two females with RPL (males were not evaluated at time of presentation). The frequency of observed chromosomal variants are described in table where we can see inv (9) is the most observed.

Observed Chromosomal variant	%
14ps+	0.18
15ps+	0.04
16 qh+	0.04
21ps+	0.04
1qh+	0.04
22ps+	0.27
9qh+	0.22
9ph+	0.04
inv(9)	0.36
inv(12)	0.04

20 percent of couples with infertility and 25 percent of couples with RPL had a consanguineous marriage which makes us suspicious about relation between RPL and consanguinity. While we analysed the consanguineous marriage frequencies and years of marriage between 1988-2012 years we observed significant decrease which proves the importance and benefit of consciousness-raising of population.

THE FUNCTIONAL VARIANTS OF *TNF-α*, *MPO*, *MIF*, *ENOS* AND *XRCC4* GENES IN RHEUMATOID ARTHRITIS PATIENTS: NO ASSOCIATION WITH *TNFα* (-238), *MPO* (-463), *XRCC4* (-1394), BUT *ENOS* (+894), *MIF* (-173) *TNF-α* (-857 AND -308) VARIANTS ASSOCIATED WITH THE DISEASE ACTIVITY IN TURKISH PATIENTS

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PP-01

The aim of this study was to explore the association among functional variants in tumor necrosis factor α (*TNF-α*), myeloperoxidase (MPO), macrophage migration inhibitory factor *(MIF)*, endothelial nitric oxide synthetase *(eNOS)*, X-ray repair cross-complementing group 4 *(XRCC4)* genes and clinical parameters (anti-TNF-α therapy) in rheumatoid arthritis (RA) patients.

We compared seven single nucleotide polymorphisms (SNPs) (-308, -238 and -857 in *TNF-α* / -463 in MPO / -1394 in *XRCC4* / -173 in MIF / +894 in *eNOS*) genes in 65 patients with active RA who were treated with DMARD or anti-TNF therapy and and in 70 healthy controls. The genotyping were performed by the PCR-RFLP method. Clinical responses were compared by using disease activity score, VAS and health assessment questionnaire after 6 months of treatment.

A significant positive association was observed at *TNF-α* (-857) CC genotype / *MIF*-CC genotype and *eNOS*-TT genotype in RA patients (p=0.046, p=0.038, p=0.029 respectively). At the six months the mean VAS, HAQ and DAS 28 improvement was not significant among groups. Improvement in DAS was significantly better in *TNF-α* (-308) GG genotype than AG genotype in anti-*TNF* subgroup (p<0.05). Conclusions: Our results suggest that *TNF-α* (-857) CC genotype / *MIF*-CC genotype and *eNOS*-TT genotype may be associated with susceptibility to disease and that *TNF-α* gene (-308) polymorphisms might have an effect on RA patients and response to treatment.

PARTIAL TRISOMY 3Q AND VAN DER WOUDE SYNDROME DUE TO THE COMPLEX CHROMOSOMAL REARRANGEMENT CONSISTING MATERNALLY INHERITED UNBALANCED RECIPROCAL TRANSLOCATION AND INVERTED INSERTION

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PP-02

Van der Woude syndrome (VWS) is the most common cleft disease characterized by cleft lip/palate and pits of the lower lip. VWS-1 is caused by heterozygous mutation in the *IRF6* gene localized at chromosome 1q32.2. Partial 3q duplication is a rare disease with a broad clinical spectrum according to the band region it contains. We present a patient with a complex chromosomal rearrangement resulted in these two entities.

A 13-year-old male patient had intellectual disability, speech defect, operated cleft palate, strabismus, cryptorchidism and some other facial findings. His mother had also operated cleft palate.

Maternal unbalanced reciprocal translocation and inverted insertion was detected in the proband [46,XY,t(1;15)(q32.2;q25),rec(15)ins(15;3)(q23; q25.3q25.1)]. Array-CGH analysis revealed two deleted segments on the long arm of chromosome 1 (3 Mb and 476 kb deletions in the 1q42.13 and 1q32.2, respectively) in the proband and the mother, and a duplication of 8.6 Mb in the 3q24q25.31 region in the proband.

The presence of cleft palate in both the proband and the mother suggests that this finding may be associated with IRF6 gene located in the deletion region 1q32.2. The remaining clinical findings were thought to be related to the duplication of the 3q25.1q25.3 region. Although the larger partial 3q duplications consisting the 3q25.1q25.3 region have been previously described, the duplication containing only this region has not been reported. We think that the patient presented here will be a significant contributor to the literature in terms of partial dup(3q) syndrome.

INFERTILE MAN WITH 46,XX TESTICULAR DISORDER

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PP-03

Infertility which affects about 15% of couples, is a failure to achieve spontaneous pregnancy in one year of regular sexual activity. 46,XX testicular disorder is a rare cause of male infertility . Clinical features can be variable from phenotypically male to sexual ambiguity and hermaphroditism. Approximetly 90 % of males with this syndrome are known to carry *SRY* (sex-determining region on the Y). The *SRY* plays an important role in sex determination . The presence of Y chromosome material on the paternally derived X chromosome is usually due to an abnormal X-Y interchange during the obligatory X-Y crossing over that occurs during male meiosis. Here, we reported a man with *SRY* positive 46,XX testicular disorder.

A 38 year-old married man was consulted to our department with a history of male infertility. He was externally male. There is no pathological findings in our first physical examination. Semen analysis revealed azoospermia. Hormone profile was FSH:42.51(H), LH:14.9(H), Prolactine:15.1(N), Total testesterone: 4.42(N).

Y chromosome microdeletion analysis (ZFY, SY84, SY86, SY127, SY134, SY254, SY255) and *SRY* was investigated. The SRY section was intact but whole section of AZF region was deleted. The karyotype analysis was then performed and karyotype was 46,XX.

46,XX testicular disorder is a rare genetic abnormality and the diagnosis is necessary for counseling and management of this entity. This case emphasized the importance of evaluation and genetic analysis for infertility.

A CASE PRESENTATION WITH WOLF-HIRSCHHORN SYNDROME

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PP-04

Wolf-Hirschhorn syndrome (WHS) is a rare genetic disease approximately 1 in 50,000 births. Wide nasal roots, microcephaly, hypertelorism, arcuate eyebrows, micrognathia are main dysmorphic features. Intrauterine postnatal growth retardation, developmental mental retardation, seizures, congenital heart defects and urinary anomalies are common in affected individuals. The cause of the disease is heterozygote deletion on chromosome 4p16.3, with *de novo* mutations in the majority of cases. We present A 1.5-year-old girl WHS patient with cleft palate, cardiac and renal anomaly.

Baby born from the sixth gestation of 34-year-old mother who had no consanguineous relationship with her husband, had horseshoe kidney and broad secundum ASD at birth. Patient also had seizures resistant to anticonvulsant treatment. Physical examination included microcephaly, hypertelorism, epicanthus, Greek warrior helmet-like nose, arch-shaped eyebrow, incomplete cleft palate. Karyotype was 46,XX and 4p16.3 deletion detected FISH.

Many individuals who have WHS survive to adulthood. Clinical findings in WHS are quite variable such as antibody deficiencies, hearing loss, ALL, hepatic adenoma and HCC. Also there is a correlation between the size of the deletion and the severity of the clinical findings. It has been reported in the literature that deletions greater than 3 mb increase the frequency of heart defects and cleft palate. The presence of cleft palate and ASD suggests that the deletion may be larger than 3 mb, although FISH analysis not gives information about the size of the deletion. Genetic counseling provided to family in details.

WAARDENBURG SYNDROME TYPE 1: A NOVEL MUTATION IN *PAX3* GENE

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PP-05

Waardenburg syndrome type 1(WS1) is an inherited autosomal dominant disease characterized with congenital sensorineural hearing defect and loss of pigmentation at iris, hair and skin. Its prevalence is about 1/40,000. Mutations in the *PAX3* gene that encodes the PAX3 paired box protein with 10 exons localized on chromosome 2q36.1 are the cause of the disease. PAX3 paired box protein, composed of 128 amino acids, is a necessary transcription factor at the regulation of neural crest cells. We have examined a novel mutation in *PAX3* gene.

A 19-year-old female patient, whose parents were secondary cousins, had a cochlear implant at 5 years of age. She could neither hear nor speak. Physical examination revealed piebaldism, synophysis, hypertelorism, light blue eyes, high and wide nasal root. Sequence analysis of *PAX3* detected p.Asn287Glnfs*123(c.857insT) heterozygous variant in the 6th exon that was not reported before at the literature. It is predicted that this variant may be the cause of disease in bioinformatics analysis programs. So these clinical findings and heterozygous mutation suggest WS1 diagnosis.

WS1 has penetrance about 85% and the genotype phenotype correlation could not be shown between cases and mutations. Rarely WS1 cases may have cleft palate, spina bifida, alveolar rhabdomyosarcoma. At that case, since there is no individual with similar findings in the pedigree, the change in the patient is thought due to a *de novo* mutation or germline mosaicism. Genetic counseling provided to family in details.

MYC REGULATED LONG NON-CODING RNAS IN BREAST CANCER: A PRELIMINARY DATA

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PP-06

MYC plays critical roles in breast tumorigenesis and progression. Several genetic targets have been identified by activation or repression of MYC. c-myc gene is a hormone responsive gene in breast cancer. Previous studies have observed that endogeneous c-myc expression is very low in MDA-MB-231 cells compared to MCF-7 cells which are hormone responsive. Deregulated expression levels of lncRNAs have also been observed in breast cancer. In this study we aimed to compare the expression levels of lncRNAs related to MYC expression in breast cancer cells.

In this study MYC expression is supressed by lentiviral shRNA vector in MYC amplified non-metastatic MCF-7 cells and MYC expression is overexpressed by lentiviral overexpression vector in MYC non-amplified metastatic MDA-MB-231 cells. LncRNA cDNA is transcribed from total RNA samples and 90 lncRNAs are evaluated by qRT-PCR.

According to qRT-PCR results the expression levels of 7SK, ANRIL, GAS5, MEG3, lincRNA-p21 and NEAT1 are found to be related with deregulated expression levels of c-myc.

According to our preliminary data we have observed some lncRNAs correlated with deregulated levels of c-myc. Some of these lncRNAs have tumor supressor (GAS5, MEG3, lincRNA-p21) and some of them have oncogenic roles (PVT1,HOTAIR) in breast cancer. These preliminary data will give us a light to identify molecular mechanisms related to MYC-lncRNA regulatory pathways.

UNBALANCED CHROMOSOMAL REARRANGEMENT IN FETUS WITH CONGENITAL ANOMALY: A CASE REPORT

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PP-07

The balanced chromosomal translocation carriers have increased risk for pregnancy losses or having children with mental or physical abnormalities because of unbalanced segmental chromosomal losses and gains. The purpose of this case is to show an unusual segregation identified at the amniocentesis material.

Amniotic fluid of a 27-year-old healthy 19 w pregnant women was referred for prenatal diagnosis because of prosencephaly detected at ultrasound screening. Conventional cytogenetic analysis of the amniotic fluid revealed

46, XY, add(7)(q32?) inv(7)(p12?p21?) .arr[hg19]2p25.2p22.2(12,770_37,592,568)x3,

7q36.3(155,295,853_159,119,707)x1 for the fetus and substantial parental karyotyping was performed which resulted in maternal balanced 46, XX, t (2; 7) (p13?; q32?), translocation. To understand the maternal chromosomal rearrangements while maternal subtelomeric and whole chromosome Fluorescence *in Situ* Hybridization (FISH) analysis were ongoing we performed molecular karyotyping to amniotic fluid which showed a segmental duplication of the 2p25.1p21 region and partial deletion of the distal arm of 7q on 7q36.3. Maternal whole chromosome FISH analysis detected reciprocal translocation between the p arm of chromosome 2 and q arm of chromosome 7 while there was an extra signal belonging to chromosome 7 on the long arm of chromosome 2 showing an insertional translocation. Finally, karyotype of the mother was designated as 46, XX, t (2;7)(p13?; q32?), ins (7;2)(q22?;q?q?), inv (7)(p12p21).ish t(2;7)(p13?; q32?), (wcp7+;wcp2+),ins(7;2)(22q;q?q?)(wcp2+), inv (7)(p21)(TWİST1)(p11)(ELN).

Unbalanced segregation of balanced chromosomal rearrangements causes neurodevelopmental anomalies in the fetus, while carriage of balanced translocation does not lead to any phenotypic effect on the prospective parents.

FETUS WITH PARTIAL TRISOMY 4 AND T(2;16) DUE TO MATERNAL COMPLEX REARRENGEMENT INVOLVING THREE CHROMOSOMES: A CASE REPORT

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PP-08

Complex chromosome rearrangements (CCRs) are structural chromosome anomalies involving two or more chromosomes and more than two breakpoints. These can be balanced rearrangements (BR) not causing a chromosomal gain/ loss or unbalanced rearrangements (UR) that result in loss/gain of genes at the breakpoints. These gene changes can cause fetal anomalies. It is important that URs can be *de novo* or occurring because of BRs of parents.

Here we report a foetus with partial trisomy 4 and t(2;16) due to maternal complex rearrangement.

A couple, a 22-year-old female and a 32-year-old male, both in good health, was referred for genetic counselling following an abnormal fetal sonogram. This was the couple's second pregnancy following one first trimester miscarriage. They were nor consanguineous parents. In the family history, mother's parents have had an ex-preterm infant. An ultrasound study performed at 26 weeks' gestation revealed craniosynostosis and anencephaly. At this time, the patient was counselled about the high risk of a fetal chromosome abnormality. Karyotype and multiprobe FISH analyse of the cord blood sample was performed and 47,XY,+der(4)del(4)(q13.2?).ish t(2;16)(q33;q22)(wcp16+;wcp2+),add(4)(?;q13.2?)(wcp4+) was detected. Parental karyotyping revealed a chromosomally normal father and the mother was carrying 46,XX,t(2;16)(q33;q22),ins(2;4)(q31?;q21qter?).ish t(2;16)(q33;q22)(wcp16+;wcp2+),ins(2;4)(q31?;q21?)(wcp4+). The pregnancy was terminated.

Although CCRs are rare, they are often associated with multiple congenital abnormalities, recurrent spontaneous abortions and infertility. Therefore, genetic counselling for CCR carriers is very important and can be offered before and after pregnancy.

SPASTIC PARAPLEGIA TYPE 11 IS ONE OF THE RARE TYPE SPASTIC PARAPLEGIA

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PP-09

The hereditary spastic paraplegias (HSP) are clinically and genetically heterogeneous disorders characterized by lower extremity spasticity and weakness. HSP can be inherited in autosomal dominant (AD), autosomal recessive (AR), X-linked or mitochondrial manner. Among these, the most common form is AD inheritance. AR types can rarely be detected. We describe a patient with a homozygous mutation in the *SPG11* gene, showing an AR inheritance pattern.

A 32-years-old patient was counseled to the genetic polyclinic with suspect of HSP. When the patient was 16 years old, findings such as fall in school success, walking at the tip of finger appeared, speech was gradually deteriorating. She'd lost her ability of walking. Now the patient is bed dependent, can't sit without support and use her hands, can talk with single words. She has mild Intellectual disability and incontinence. In physical examination; Prominent muscle weakness, atrophy, decreased DTRs distal, proximal elevated, positive palmomental reflex, bilaterally positive Hoffman reflex were determined. The corpus callosum hypoplasia /agenesis is noted in the cranial MRI.

The most common type of HSP with corpus callosum agenesis is SPG type 11 and *SPG11* gene was studied with Sanger sequencing in this case and homozygosity was determined for the p.Ser412*(c.1235C>G) mutation.

HSP is large group of diseases with different inheritance patterns, many of which are responsible for many genes, some of which are accompanied by systemic and neurological findings. In countries where consanguineous marriages are frequent, such as in our country, the disease is promoting genetic counseling.

DIABETES MELLITUS CASE RECORDS (2005-2014) IN PREGNANCY : A PRELIMINARY STUDY

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PP-10

Enviromental and genetic factors play roles in pregnancy diabetes mellitus (PDM). Maternal age is the most important factor for prevalance of PDM. PDM is important with regards to complications as macrosomy, increasing risk for intrauterin death, congenital malformation, hyperbilirubinemia, polistemia, hypocalcemia. Our aim to generate a database to set the light to genetic researches and identify some risk factors by analysing pregnancy diabetes mellitus records on hand.

This is an illustrator and retrospective study. Data were obtained from records. 456 cases with PDM diagnosis according to the ICD 10 coding from Denizli Public Hospital, Servergazi Public Hospital and Pamukkale University Medical School Hospital between 1 August 2005- 9 January 2014, compose the cosmos of the study. Dependent variable of the study is to have PDM. Independent variables are group of age, application year to the hospital, age of diagnosis, medicational status.

Mean age of study group (n=456) is 36,41±7,41. 31,8% (n=145) of cases are between the age of 20-29; 66% (n=311) of them are at the age of 30 and above. 80,0% (n=365) of pregnants have an outpatient treatment, 20,0% (n=91) have an in-patient treatment. Only 3,3% (n=15) of cases are identified as "O24.0-Pre-existing diabetes mellitus, type 1, in pregnancy, childbirth and the puerperium".

31,8% of cases are between the age of 20-29; 66% of them are at the age of 30 and above. At present time , genetic background of the individuals with PDM are still not clear. Further studies are needed.

MOLECULAR AND CYTOGENETIC CHARACTERIZATION OF CHROMOSOME 4P AND 22Q13.3 DUPLICATION IN A HYPERACTIVE 10-YEAR-OLD GIRL WITH SHORT STATURE, ATTENTION DEFICIT AND INTELLECTUAL DISABILITY

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PP-11

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The chromosomal 4p duplication results in recognizable clinical findings of mental retardation and congenital anomalies. Here we present clinical, molecular and cytogenetic data on a 10-years-old girl with 4p duplication.

The clinical symptoms for the current presented case were clinodactily of the fifth digit, triangular face, bicuspid aortic valve, myopia, high palate, short stature, attention deficit, intellectual disability and convulsion attacks.

The chomosome dup(4p) was detected by standard cytogenetics karyotyping, MLPA and aCGH techniques. 22q13.3 duplication was detected by FISH and aCGH technique.

She was diagnosed as 46,XX,der(15),t(4;15)(p15.2;p11.2), invdup(22)(q13.3) after karyotype and aCGH genotype analyses.The aCGH analysis showed arr(hg19)4p16.3-p15.2(45,882-27,428,268)x3 and arr(hg19)22q13.3(51,062,707-51,067,384)x3 profiles. Her mother was normal but father was in 46,XY,t(4;15)(p15.2;p11.1) karyotypes after peripheral lymphocyte cell cultures analysis.

Here we present a case with complex t(4p;15p) and invdup(22)(q13.3) chromosomal rearrangements and some clinical findings of affected case report. Duplication *ARSA* gene on 22q13.3 have no significant phenotype there by deletion of the gene results OR Metachromatic leukodystrophy. On the other hand 4p duplications results various phenotypes depending on which genes including the duplicated region Results confirmed the complicated gene duplication syndrome of the intellectual disability.

A STUDY ON THE ASSOCIATION BETWEEN *PON1* (PARAOXONASE 1) 55L/M (RS854560) POLYMORPHISM AND PSEUDOEXFOLIATION SYNDROME AND PSEUDOEXFOLIATIVE GLAUCOMA

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PP-12

Pseudoexfoliation syndrome (PES) is a disorder of the extracellular matrix characterized by the progressive accumulation of abnormal fibrillary material in many ocular tissues. Pseudoexfoliation material accumulates into canals providing drainage of aqueous humor fluid and results in raised intraocular pressure and pseudoexfoliative glaucoma (PEG). Deficient antioxidant protection mechanism can have important roles in the pathogenesis of PES. Paraoxonase 1 *(PON1)* is an important antioxidant enzyme that is found in the aqueous humor fluid and tears. *PON1* gene has several genetic polymorphisms. 55L/M (rs854560) single nucleotide polymorphism (SNP) is found in coding region and leads to amino acid change from Leucine to Methionine, which affects the stability of the enzyme. Aim of this study was to investigate if there is any association between *PON1* 55L/M SNP and PES and PEG diseases.

Study population consisted of 50 patients with PES, 50 patients with PEG and 50 controls. Blood samples were collected by Gülhane Medical Faculty, Department of Ophthalmology, Ankara. Genomic DNAs were isolated from whole blood samples using a salting-out manual DNA isolation protocol. Genotypes were assigned by PCR followed by restriction fragment length polymorphism analysis.

The frequency of *PON1* 55L/M polymorphic allele M was 0.360 in controls, 0.360 in PES patients (OR=1.016, P=1.000) and 0.350 in PEG patients (OR=0.957,P=0.883). Statistical analysis showed that there is no significant relationship between PON1 55L/M SNP and PES or PEG.

This work did not point out a role for *PON1* 55L/M SNP in the risk for PES or PEG.

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ANALYSIS OF THE RELATIONSHIP BETWEEN *PON1* (PARAOXONASE1) 192Q/R (RS662) POLYMORPHISM WITH PSEUDOEXFOLIATION SYNDROME AND PSEUDOEXFOLIATIVE GLAUCOMA

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PP-13

Pseudoexfoliation syndrome (PES) is an age-dependent systemic disorder, characterized with progressive accumulation of abnormal fibrillary material in ocular tissues. Pseudoexfoliative Glaucoma (PEG) occurs when pseudoexfoliation material blocks the canals responsible for the drainage of aqueous humor, increasing intraocular tension. Glaucoma is the second most common factor leading to blindness and possibility of a PES patient to develop glaucoma is 34.3%. Since PES is thought to be related with a deficiency in the antioxidant protection mechanisms, a well-known anti-oxidant enzyme, Paraoxonase1 *(PON1)* is chosen to be investigated in this study. *PON1* gene is known to have several genetic polymorphisms. 192Q/R (rs662) single nucleotide polymorphism (SNP) is located in coding region and alters enzyme activity. Aim of this study was to investigate if 192Q/R polymorphism of *PON1* gene is associated with PES-PEG diseases.

Study population included 50 PES patients, 50 PEG patients and 50 controls. Blood samples were collected by Gülhane Education and Research Hospital, Department of Ophthalmology, Ankara. Genomic DNAs were isolated manually from whole blood samples. Genotypes were determined by PCR followed with restriction fragment length polymorphism analysis.

The frequency of PON1 192Q/R polymorphic allele R was 0.270 in controls, 0.280 in PES patients (OR=1.051, P=0.874), 0.250 in PEG patients (OR=0.901, P=0.747). Statistical analysis showed no significant relationship between *PON1* 192Q/R SNP and PES/PEG.

These are the preliminary findings of an ongoing research project. This work did not indicate a role of *PON1* 192Q/R in the risk for PES or PEG diseases.

Acknowledgment: This study was supported by TUBITAK (315S190)

PRENATAL DIAGNOSIS OF A COMPLEX CHROMOSOMAL REARRANGEMENT BY THE USAGE OF CONVENTIONAL AND ARRAY KARYOTYPING

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PP-14

Complex chromosomal rearrangement (CCR) due to the reciprocal translocation consisting three nonhomolog chromosomes is a rare condition with the negligible or remarkable clinical findings. Here we present a fetus with CCR diagnosed via prenatal conventional and array karyotyping because of high aneuploidy risk in double screening test.

The chorionic villus sample (CVS) of 33-year-old primiparous woman at estimated 13 weeks of pregnancy was admitted to our clinic for karyotyping because of combined risk of 1/206 for trisomy 21 in double screening test.

Fetal cytogenetic analyses revealed *de novo* reciprocal translocation consisting chromosomes 5, 17 and 20 [46,XX,t(5;17;20)(q22;q23;q13.1)]. No deletion was detected as the fluorescence probes dyed all three relevant chromosomal segments. A deletion between 51.6 and 52.9 Mb (hg19) was detected in 20q13.2 region via array-CGH. The fetal ultrasound in 21 week revealed no extraordinary finding.

The deletion of a part of a chromosome can cause more severe clinical conditions than the duplication of the same part. Lack of any case reported in the literature, the deletion of the 20q13.2 region is obscure while the duplication of the relevant region is related with intellectual deficiency, facial dysmorphism, cardiac malformation and skeletal anomalies. Approximately the 1.3 Mb deleted region in our case whose ultrasonographic findings was normal, consist six genes and one of them especially expressed in brain (BCAS1). Hereby, the relationship between intellectual deficiency and the deletion was not excluded with these restricted findings.

PATHOGENIC VARIATIONS OF *BRCA1* AND *BRCA2* GENES IN THE BREAST AND/OR OVARIAN CANCER PATIENTS LIVING IN TRAKYA REGION OF TURKEY

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PP-15

The role of *BRCA1* and *BRCA2* gene mutations in breast cancer and/or ovarian cancer risk is supported by a great number of studies worldwide. In this study, we aimed to present the results of breast/ovarian cancer patients who were found to have pathogenic variations in *BRCA1/BRCA2* genes at Genetic Diagnosis Center of Trakya University between 01.09.2014 and 01.03.2017.

DNA samples isolated from peripheral blood cells of 30 nonconsanguineous female breast/ovarian cancer patients (25 breast cancer, 4 ovarian cancer and 1 ovarian-and-breast cancer cases) were used for downstream applications. Pathogenic variations in the coding regions of *BRCA1* (NM_007294.3) and *BRCA2* (NM_000059.3) genes were determined using Next Generation Sequencing (NGS) method (Ion Torrent PGM and Illumina MiSeq systems). Gross deletions and duplications of BRCA1 and BRCA2 genes were investigated by Multiplex ligation-dependent probe amplification (MLPA) method (MRC Holand).

Pathogenic variations in the BRCA2 gene were identified in 12(40 %) out of 30 patients whereas 18(60%) out of 30 patients have pathogenic variations in *BRCA1* gene, including a gross deletion. Three novel pathogenic variations (c.3626T>A in *BRCA2*; c.536_537insT and c.1885A>T in *BRCA1*) were identified. The c.5266dupC (p.Gln1756Profs) variation was the most frequent (50 %) *BRCA1* pathogenic variation whereas c.67 + 1G> A variation was the most frequent (33.3 %) *BRCA2* variation.

BRCA1 pathogenic variations were found to be more frequent than *BRCA2* pathogenic variations in our patient population. Screening of all the exonic regions allows determination of novel variations as well as common variants.

A NOVEL MISSENSE MUTATION OF *COL1A1* GENE IN A PATIENT WITH OSTEOGENESIS IMPERFECTA

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PP-16

Osteogenesis imperfecta (OI) is a genetic disorder characterized by bone fragility and osteopenia. OI or brittle bone disease, is a fairly common rare disorder (1/ 15-20 000 births). Clinical manifestations are variable but commonly include: increased fracture risk, deformities and short stature, blue-gray color of sclera, loose joints and early loss of hearing in some cases. Disease classification comprises 4 subtypes based on clinical and radiological features: OI Types I (mild OI with bone fragility and blue sclera), II (perinatal lethal), III (progressive deforming), and IV (normal sclera and mild deformity). We aim to present a novel mutation in *COL1A1* gene in a pediatric patient. Methods: About 90 % of the mutations are related to alterations in the *COL1A1* and *COL1A2* genes, located at chromosome 17q21.33 and 7q21.3, respectively. Targeted exome sequencing was performed to delineate the mutation. Results: The patient presented with recurrent bone fractures, and mildly short stature. We reported a novel mutation (c.662G>T) in the *COL1A1* gene. This mutation is not present in human genome variation databases or in disease-causing mutation databases. In silico analysis revealed a deleterious effect of this mutation on protein function. Conclusion: Osteogenesis imperfecta is associated with high genetic heterogeneity. To date, mutations in 16 different genes have been found to cause OI phenotypes of varying severity. Genotype-phenotype correlations are important to predict clinical course of the disease. This novel mutation reveals a mild phenotype.

MAIN MODULATOR OF EPITHELIO-MESENCHIMAL TRANSITION IN BLADDER: TGF-B3 VS CTGF

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PP-17

The process of epithelial-mesenchymal transition (EMT) is a complex biologic event involving an alteration of distinct characteristics of an epithelial cell enabling it to show mesenchymal cell phenotype with increased expression of extracellular matrix markers. Bladder remodeling seen as a part of some diseases like multiple sclerosis, diabetes mellitus or bladder outlet obstructions is induced by many biochemical pathways. CTGF is a matricellular protein with known biological functions of fibrosis, wound healing, development and EMT. Transforming growth factor β (TGF-β) is expressed ubiquitously and involves signaling pathways regulating a series of cellular processes including proliferation, differentiation, migration, and wound healing as CTGF. TGF-β is a potent inducer of EMT. It also promotes CTGF expression in a feedback fashion. The aim of this study was to evaluate the main mediator of bladder remodeling on bladder epithelial cells *in vitro*. Recombinant TGF-β3 and CTGF treatments on bladder cell lines were performed. Alpha SMA, E-cadherin, S100A4, vimentin, fibronectin 1 and mCOL1A1 expressions were evaluated via RT-PCR. Results: Expressions of aSMA and vimentin were primarily induced by TGF-b3, whereas s100A4 expression was boosted by CTGF. E-cadherin and fibronectin-1 expressions were evoked equally by the both growth factors. mCOL1A1 expression did not change against the treatment. Although both EMT-drivers work together in coherence, and their effects are related to one another, individual effect of each protein gives rise to different impact on EMT markers in bladder epithelial cells.

A RARE COMBINATION OF MOSAIC RING Y CHROMOSOME AND *SHOX* DELETION IN AN INFERTILE MALE

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PP-18

Genetic evaluation of the infertile man with azoospermia and short stature with normal body proportions.

Chromosome analysis and Y chromosome microdeletion analysis were performed from peripheral blood sample. Fluorescent in situ hybridization (FISH) and polimeraze chain reaction (PCR) were performed to analyse specific Y chromosome regions.

Chromosome analysis revealed a mosaic 46,X,r(Y)[13]/45,X[11] karyotype with ring chromosome Y. Y origin of the ring chromosome and mosaicism confirmed by FISH analysis with X and Y alpha satellite probes. FISH analysis with SHOX gene probe detected that ring chromosome did not have the *SHOX* gene signal. No microdeletions were found in AZF regions and *SRY* gene.

Structural rearrangements of the Y chromosome are frequently associated with testicular dysfunction. Patients with ring Y chromosome can present a wide spectrum of sex phenotypes, including Turner syndrome, ambiguous genitalia, short stature, infertility because of azoospermia, oligospermia and high gonadotropins. Ring Y chromosomes are known to be unstable during mitosis therefore mosaicism with a 45,X cell line is detected in most patients. Infertility because of azoospermia in the presented case can be explained that Y chromosome anomalies can affect X/Y pairing during meiosis resulting in breakdown in spermatogenesis. Short stature in this case may be associated with the presence of 45,X cell line and/or *SHOX* gene deletion.

A FAMILY WITH HOMOZYGOSITY FOR A ROBERTSONIAN TRANSLOCATION (13Q;14Q)

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PP-19

Robertsonian translocations are the most common structural chromosomal anomalies in humans and are observed in about 1 in every 1000 livebirths. Although majority of Robertsonian translocation carriers are phenotypically normal, reproductive risks such as children with trisomies, abortion, stillbirth and infertility may be expected. Homozygosity for Robertsonian translocations are very rare. In literature, all mentioned cases were fertile.

A 33 year old male patient was referred to medical genetics outpatient clinics for primary infertility. The couple have had one failed IVF (*in vitro* fertilization) attempt. Chromosomal karyotyping for peripheral blood lymphocyte culture, Y-chromosome microdeletion screening and PCR (Polymerase Chain Reaction) analysis for *SRY* (Sex-determining region of the Y chromosome) were performed.

The patient's semen analysis revealed azoospermia. Levels of FSH (follicle-stimulating hormone) and LH (luteinizing hormone) were high (29.5 and 16.9 mIU/ml, respectively) and total testosterone level was subnormal (1.83 ng/ml). No microdeletions were observed in AZF (azoospermic factor) regions. *SRY* gene was showed to be existing. Cytogenetic analyses of patient and his wife showed 44,XY,der(13;14)(q10;q10)x2 and 46,XX, respectively. The parental karyotypes were found 44,XY,der(13;14)(q10;q10)x2 and 45,XX,der(13;14)(q10;q10), respectively. Patient and his father had same abnormal karyotype.

Infertility occurred in our patient, although this chromosomal abnormality did not cause reproductive problems in his father. As far as we know this is the first case of infertility seen in male with homozygosity for Robertsonian translocations. Robertsonian translocation homozygosity can not be a possible speciation mechanism in humans as claimed.

A CASE WITH HETEROZYGOTE N540K HYPOCHONDROPLASIA-CLINICAL FEATURES

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PP-20

Autosomal dominant mutations in fibroblast growth factor receptor 3 (*FGFR3*) cause achondroplasia, hypochondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) and thanatophoric dysplasia. Hypochondroplasia is a skeletal dysplasia which is characterized by short stature, macrocephaly, brachydactyly, limited range of motion at the elbows, lumbar lordosis and bowed legs. Radiological features of hypochondroplasia are flared metaphyses, narrowed interpedicular distance, square ilia, and short femoral necks.

The patient was a 1 year and 2 months old boy, who was born at full term after an uncomplicated pregnancy and delivery. There was no consanguinity between parents. His height was 80 cm (-0.4 SDS), his weight was 8,5 kg (-2.9 SDS) and head circumference was 51 cm (99p). He had frontal bossing, macrocephaly, a mildly flattened nasal bridge, and short limbs, café-au-lait spot on the skin which measured 1,5x0,5 cm. The serum concentrations of bİochemİcal values and thyroid hormone were normal.

Genomic DNA was extracted from peripheral blood leukocytes by standard procedures. PCR amplification of exons 7,10, 13, 15 and 19 of *FGFR3* was performed. We found N540K (c.1620 C>A) heterozygote mutation in the *FGFR3* gene in our patient.

A heterozygous c.1620C>A mutation was identified in exon 13 which is a major hotspot of the *FGFR3* gene. This mutation leads to aminoacid substitution; asparagine to lysine (p.N540K). 1620C>A and 1620C>G mutations are determined in approximately 50-70% of hypochondroplasia patients. This case represents the importance of evaluating the shortness in childhood and genetic counseling in cases for hypochondroplasia.

PRENATAL DIAGNOSIS OF A FETUS CARRYING inv(12): CASE REPORT

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PP-21

Inversions are intra-chromosomal rearrangements that occur as a result of two breakpoints, turns 180 degrees reversing and rejoining with fracture points. Here, we present a pregnant women who underwent amniocentesis (AFS) for advanced maternal age and diagnosed as inv(12) in prenatal karyotype analysis.

A healthy 39-year-old woman who has a healthy male child was referred to outpatient clinic at 10 weeks of gestation because of advanced maternal age. Her physical examination, biochemical screening test and USG findings were normal. There was no history of abortion and no significant finding in the pedigree analysis. Karyotype analysis was performed following AFS.

Fetal karyotype revealed 46, XX, inv (12)(p11.2 q15). Chromosomal analysis of the family showed that father had the same inversion and the mother was 46, XX. Prenatal USG findings and prenatal follow-up were normal. Pregnancy is still ongoing normally.

Although inv(12) in the literature does not generally produce a clinical effect, empiric recombination risk due to unbalanced gamete formation in couples with inversion carriers is about 6% depending on the size of the inversion. Therefore, microarray analysis was suggested to the family as a part of genetic counseling but family decided to continue pregnancy without additional testing. This case is important to show follow-up pregnancies, genetic counseling and risk assignment of prenatal diagnosis.

PRENATAL DIAGNOSIS IN SINGLE GENE DISORDERS: EGE UNIVERSITY EXPERIENCE IN 497 CASES

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PP-22

Prenatal genetic testing is used to detect a broad range of genetic disorders. Although analysis of cell-free DNA from maternal plasma has been introduced for non-invasive prenatal testing recently, still invasive techniques are considered to be gold standard screening methods. Genetic molecular tests are applied for DNA analysis of single gene disorders by using invasive sampling techniques.

The aim of our study is to examine the results of 497 cases between 2009-2016 referred for invasive prenatal diagnosis of known single-gene disorders.

Proper molecular methods were applied for the genetic diagnosis. The results were confirmed with at least 2 different methods. Maternal contamination were excluded in all samples. Amniocentesis in 303 cases, chorionic villus sampling in 185 and fetal blood sampling in 9 cases were used.

The most referred single gene disorder was thalassemia. (289 cases, 58%). Cystic fibrosis was the second (132 cases, 26%) and spinal muscular atrophy (SMA) (42 cases, 9%) was the third most common referral reasons for prenatal diagnosis.

Of 497 cases studied in total, mutation was found in 90 (18%) cases in which half of the cases comprised CVS and the other half AFS. A total of 80 pregnancies were terminated.

Here we report our experience of prenatal diagnosis in single gene disorders and discuss our findings.

IDENTIFICATION OF A NOVEL HOMOZYGOUS DELETION OF THE TYROSINASE GENE IN A TURKISH FAMILY WITH OCULOCUTANEOUS ALBINISM TYPE 1

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PP-23

Oculocutaneous albinism (OCA) is a group of genetically heterogeneous autosomal recessively inherited disorders characterized by decreased or absent pigmentation in the hair, skin, and eyes. OCA type 1 (OCA1) is the most severe and common form of OCA, and is caused by mutations in the tyrosinase gene (*TYR*).

Our patient is a 2-month-old boy born at term by normal delivery with normal physical parameters. His parents were consanguineous (second cousin). In his physical examination, length was 55 cm (10-25P), weight 5 kg (10-25 P), and head circumference 37 cm (3P). He had milky white skin, white hair, white eyelashes and eyebrows, decreased pigment in the iris and nystagmus. His audiologic examination was normal.

TYR gene sequence analysis using Sanger sequencing method was used.

We found a novel homozygous c.1037-13_1038delTTTTAATGAACAGGA (p.G346Vfs*3) mutation in intron 2 and exon 3 in *TYR* gene. Her parents are heterozygous state for the same mutation.

This frameshift mutation resulting in a truncated protein is also likely to disturb normal splicing and exon skipping. We reported our patient to contribute to genotype-phenotype correlations in OCA.

BBS10 FRAMESHIFT MUTATION IN A TURKISH GIRL WITH BARDET-BIEDL SYNDROME

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PP-24

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder characterized by retinitis pigmentosa, rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, renal dysfunction and hypogonadism. BBS is a defined ciliopathy notable for extensive allelic and genetic heterogeneity and oligogenic inheritance.

Our patient is a 2-year-old girl born at term with normal physical parameters to consanguineous parents. Postnatally she was hypotonic. In her physical examination, length was 78 cm (<3P), weight 14 kg (90-97P), and head circumference 47 cm (25P). Her dysmorphic features were a broad face, narrow forehead, hypertelorism, narrow palpebral fissures, mild synophrys, dry rough hair, long eyelashes, broad and depressed nasal root, broad nasal ridge, long and smooth philtrum, small mouth, thin upper vermillion, small ears, microdontia, short neck, atypical palmar crease, truncal obesity, postaxial polydactyly of hands and feet and pes valgus. Her eye examination showed retinal pigment epithelial degeneration. Her pelvic and renal ultrasonography, echocardiography and cranial MRI were normal. Her high resolution banded karyotype was normal.

BBS1, BBS2 and *BBS10* genes were sequenced via Sanger sequencing.

We found homozygous c.270_271insT (p.Cys91Leufs*5) mutation in *BBS10* in exon 2 resulting in a highly truncated protein. Her parents are heterozygous for the same mutation.

Our patient has typical clinical features of BBS. The mutation found is the most common mutation in the *BBS10* gene. We reported our patient to contribute to genotype-phenotype correlations in BBS.

EVALUATION OF BRCA1/BRCA2 TEST RESULTS FOR TURKISH BREAST CANCER FAMILIES

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PP-25

Inherited mutations of *BRCA1* and *BRCA2* genes are the most common cause of hereditary breast and ovarian cancer (HBOC) in Turkish women. In this retrospective study we report the outcomes of BRCA clinical testing in Turkish individuals with personal and familial history of breast/ovarian cancer.

55 breast cancer patients and 51 at risk individuals undergoing *BRCA1* and *BRCA2* full sequencing in Marmara University, Medical Genetics Laboratory from 2015 to 2016 were included in this study. Clinical information, including demographic and personal/family cancer history data were obtained.

67% (37/55) of breast cancer patients and 100% (51/51) of individuals at risk reported breast/ovarian cancer familial history. While mutations of *BRCA1* and *BRCA2* were detected in five and five breast cancer cases respectively, they were one and two in individuals at risk. So, while mutation rate in these selected breast cancer cases was 17.5% (10/57), it was 5.7% (3/52) in the risk group.

Our results show a high frequency of mutations in our breast cancer patients. We can conclude that the criteria of the patient selection was successful. Although NGS is an efficient method for *BRCA1* and *BRCA2* mutation screening, many other genes need to be detected in HBOC cases. Besides this, increasing the number of analysed genes will increase the number of variants of uncertain significance in clinical testing.

A MALFORMED CHILD WITH A RECOMBINANT CHROMOSOME 1 RESULTING FROM A MATERNAL LARGE PERICENTRIC INV(1)(P36.3Q43)

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PP-26

Pericentric inversions are structural chromosomal abnormalities resulting from two breaks on both sides of the centromere followed by the 180° rotation and reunion of the segments between these breaks. Although most pericentric inversion carriers have normal phenotype, reproductive risks may occur in the form of infertility, spontaneous abortions or chromosomally unbalanced children.

Chromosome analysis was performed by standard lymphocyte karyotype with Giemsa staining. Fluorescence in situ hybridization (FISH) analyses were carried out using the Vysis ToTelVysion probe panel.

A 10-month female was referred to genetic department because of hypotonia and dysmorphic features. On physical examination, she had metopic ridge, periorbital fullness, nystagmus, blue sclera, bulbous nose, flat philtrum, thin lips, preauricular skin tag on the right side, short neck, unilateral simian line, overriding second toes. She was within normal limits in height, weight and head circumference but neurodevelopmentally delayed. Cranial MRI showed slight thinning of the corpus callosum, minimally dilated ventricular system. Echocardiography revealed ventricular septal defect and patent foramen ovale. Chromosome analysis of the patient revealed 46,XX,del(1)(q43) karyotype. The maternal karyotype was 46,XX,inv(1)(p36.3q43). Both the deletion and inversion was confirmed by subtelomeric FISH analysis.

Pericentric inversions are associated with a risk of aneusomy for the offspring. Production of a significant level of unbalanced gamete needed the inversion of at least 50% of the chromosome length and a minimum size of 100 Mb. In our case, the length of the inverted segment was the largest one reported in other pericentric inversion cases published to date.

FANCONI ANEMIA IN A INFANT WITH EARLY HEMATOLOGICAL MANIFESTATION

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PP-27

Fanconi anemia (FA) is an autosomal recessive disease characterized by congenital abnormalities, bone marrow (BM) failure, and increased risk for malignancy. Common clinical manifestations are short stature, abnormal skin pigmentation, limb malformations, microcephaly and genitourinary anomalies. Hypersensitivity to DNA-crosslinking agent like diepoxybutane (DEB) or mitomycin C (MMC) is often used as a diagnostic test.Progressive BM failure typically presents in the first decade.Hematologic manifestations in early infancy is rare.

Here we report a patient with FA who presented cytopenia in early infancy.

A 10-month old boy was referred to our clinic because of cytopenia which was noticed due to his complaint of epistaxis and physical abnormalities.He was born to uneventfull pregnancy at term.His motor milestones were proper with his age.His parents were consanguineous.On physical examination, he had microcephaly, mild dysmorphic features like hypertelorism, retrognatia and antevert ears, unilateral bifid thumb, cryptorchidism and hypopigmented macule.He had additionally ectopic right kidney and secundum ASD.On complete blood count there were mild anemia, thrombocytopenia and neutropenia.HbF and AFP was elevated.Normal cellularity and morphology was shown on bone marrow examination.Chromosomal instability test with MMC was performed and found as positive.

Patients with FA are diagnosed generaly in the first decade.Rarely, BM failure can present in infants and small children.Butturini report that the age of initial hematological abnromalities ranges from birth to adult.Our patient first manifested at 10 month with pancytopenia and an MMC test confirmed the diagnosis of FA.

FA should be considered at any age in a patients with unexplained cytopenia accompanying any congenital abnormalities.

A NEW MUTATION IN THE *WISP3* GENE (c.935_936insT;p.C314Lfs*7) IN A PATIENT WITH PROGRESSIVE PSEUDORHEUMATOID DYSPLASIA

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PP-28

Progressive pseudorheumatoid dysplasia (PPD) is a rare autosomal recessive genetic disease which presents progressive swelling without inflammatory context, deformities of multiple joints, limitation of motion, widened epiphyses, platyspondyly, narrow joint spaces, and osteoporosis.

We here report a patient of PPD disease with a novel frame shift mutation in *WISP3* gene.

A 27-year-old woman presented with skeletal dysplasia. She had hip (bilateral total hip prosthesis) and knee operations. After the age of one the patient showed growth retardation and bowing of the legs. Physical examination revealed flexion contractures, progressive swelling and stiffness of the interphalangeal joints. Limitation of motion was progressive. She had kyphoscoliosis in addition to growth retardation, pectus carinatus, O-bain deformity.

Biochemical parameters were normal. X-ray images showed platyspondyly, narrow joint space, kyphoscolios, wide epiphyses and metaphyses. MRI showed narrowing of spinal canal and increasing of anteroposterior diameter of the vertebral body. PPD was the clinical diagnosis. Sequencing of the relevent *WISP3* gene revealed a novel homozygous frame shift mutation in exon 5 (c.935_936insT;p.C314Lfs*7).

PPD is caused by mutations in the *WISP3* gene and most common mutations are missense (41%) and frameshift mutations (36%). In our patient, a novel frame shift mutation was detected in exon 5. Mutation was pathogenic with the prediction programs. Our patient's symptoms appeared earlier(at age one) than reports in the literature (at three to eight years) and all joints were involved yet a definite genotype-phenotype corelation could not be ruled out.

ASSOCIATION OF DEVELOPMENTAL DELAY, CONGENITAL ADRENAL HYPOPLASIA, DUCHENNE MUSCULAR DYSTROPHY AND GLYCEROL KINASE DEFICIENCY: A RARE Xp21 CONTIGUOUS GENE DELETION SYNDROME

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PP-29

Chromosomal microdeletions and duplications are one of the major causes of congenital malformations and developmental delay.Lately by the effect of array-CGH,many new syndromes are defined in patients with congenital malformations and developmental delay.Xp21 contiguous gene deletion syndrome is one of the rare microdeletion syndromes.This syndrome is characterized by developmental delay,congenital adrenal hypoplasia, DuchenneMuscularDystrophy (DMD) and glycerol kinase deficiency.

7 years old boy was hospitalized due to dehydration,hyponatremia and hypoglycemia on postnatal 20th day and diagnosed as congenital adrenal hypoplasia. His twin died with the same diagnosis when he was 1 month old.On further examinations,it was noticed that he had neuromotor developmental delay,hypotonia,lethargy and elevated triglyceride and creatinine kinase (CK). He was consulted to our clinic due to coexistence of developmental delay, congenital adrenal hypoplasia, glycerol kinase deficiency and *DMD*.Chromosomal analysis was 46,XY. On array-CGH a 7 Mb deletion (>1500 probes) in Xp21.1p21.2 was detected.

Xp21 contiguous gene deletion is a microdeletion syndrome with intellectual disability,congenital adrenal hypoplasia,glyserol kinase deficiency and dystrophinopathy.It is a rare disease, reported in around 100 boys and 8 girls in the literature to date.In Xp21 locus,there are dystrophin, *GK,DAX1 (NROB1)* and *IL1RAPL1* genes which are related with dystrophinopathy,glycerol kinase, congenital adrenal hypoplasia and intellectual disability, respectively.In our patient,there was Xp21 deletion including dystrophin,*GK,DAX1* and *IL1RAPL1* genes.

In this report,we aim to emphasize that according the deleted genes in contiguous gene deletions there might be coexistence of more than one disease and by the array-CGH it is possible to identify related genes.

A NEW GENE RESPONSIBLE FROM MOLAR TOOTH SIGN AND CLEFT PALATE: PYRUVATE DEHYDROGENASE PHOSPHATASE REGULATORY SUBUNIT *(PDPR)*

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PP-30

Recently array CGH technique has been proven to be a method of gene discovery.

To detect a region of microdeletion/duplication in a case of mental reterdation and dysmorphism which could yield to the discovery of a gene responsible for the disease.

8-day old male baby was referred to or center because of complete median cleft palate and facial dysmorphism. He was shown to have right eye retinal coloboma in association with right eye pitosis. A brain MRI showed severe vermis hypoplasia, molar tooth sign, agenesis of corpus callosum, retrocerebellar enlargement (variant Dandy Walker syndrome?) and colpocephaly. His echocardiographic examination was normal and no other malformation was observed. On clinical grounds he was diagnosed as Joubert or Joubert like syndrome. However Ciliome sequencing with a panel of genes relevant to Joubert syndrome revealed no pathogenic variation.

An array-CGH was performed and a microdeletion of 136kb at chromosome 16q22.1 was detected. The deleted region involved a new gene that could be responsible for the clinical manifestations including cleft palate and Molar tooth sign, pyruvate dehydrogenase phosphatase regulatory subunit *(PDPR). PDPR* is involved in the regulation of pyruvate dehydrogenase (PDH) complex which is crucial for glucose conservation when glucose is scarce. Adequate PDH activity is required to allow both ATP and fatty acid production from glucose.

We suggest that *PDPR* is a new gene responsible for cleft palate and molar tooth sign and possibly presents a variant of Joubert syndrome.

A CASE WITH 2q37.3 DELETION AND 9q34.1-q34.3 DUPLICATION

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PP-31

2q37 microdeletion syndrome is characterized by mild-moderate developmental delay/intellectual disability, brachymetaphalangy of digits 3-5 (often digit 4 alone) (>50%), short stature, obesity, hypotonia, characteristic facial appearance, autism or autism spectrum disorder (30%), joint hypermobility/dislocation, and scoliosis. Duplications in long arm of chromosome 9, including the segment q34.1-q34.3, have been rarely described in the literature. It is associated with various manifestations, including mental retardation and congenital abnormalities. Dolichocephaly, fascial asymmetry, deep-set eyes, microphthalmia, prominent chin, microstomia, retrognathia, arachnodactyly, camptodactyly are commonly described features. Here we report a 10 months old boy with 9q34.1-q34.3 duplication and 2q37.3 deletion. He has frontal bossing, hypoplasic nose wings, midfacial hypoplasia, microstomia, down turned corners of the mouth, microretrognathia, arachnodactyly and a global developmental delay. His father, grandfather and uncle's high resolution (HRT) G-banding karyotype analysis are 46, XY,t(2;9)(q37;q34.1). Deletion and duplication syndromes must be searched in patients who have distinct dysmorphic features and global development delay and array-comparative genomic hybridization (array-CGH) should be performed. Balanced translocation carriers may have offsprings with unbalanced genomic constitution also should be kept in mind.

THE DETERMINATION OF RELATIONSHIPS BETWEEN THE BIOCHEMICAL PARAMETERS WITH THE RATE OF STARVATION BLOOD GLUCOSE

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PP-32

It was aimed to determine the relationships between the other biochemical parameters that may be related to the elevation of fasting blood glucose (Glucose) in 150 patients and 50 control groups of different age ranges.

The collected blood samples from patients and healthy control group were studied in the biochemistry autoanalyzer which works based on spectrophotometer. Serum fasting glucose, urea, creatinine, triglyceride, total cholesterol, HDL (High Density Lipoprotein) cholesterol, ALT (Alanine Aminotransferase) and AST (Aspartate Aminotransferase) concentrations were analyzed by this photometric method. The results were recorded as an Excel file and the data file and related parameters were transformed into column charts to determine whether there was a meaningful change in the parameters depending on the increasing starvation sugar. The results were transformed into a data matrix and subjected to Student's t test, ANOVA and Pearson correlation tests. $p<0,05$ was considered significant. Covariate parameters were evaluated.

It was determined that when fasting blood glucose value increased, triglyceride levels increased.The triglyceride levels of diabetic patients were significantly higher than the control group ($p<0,001$). There was no significant difference between the groups in terms of other parameters.

We found similar but not identical results with previous national and international studies, in this study done. Triglyceride levels was adversely effected in diabetic patients having high fasting blood glucose.

Fasting blood glucose, Diabetes mellitus, Triglycerides

Acknowledgments: This work is produced from a master thesis entitled "Investigation of Muscle Glikogen Synthase Gene (GYS-1) Polymorphism in Type 2 Diabetes Patients''

CLINICAL UTILITY OF PHARMACOGENETIC TESTING: CURRENT EVIDENCE OF HLA-B57 POSITIVITY

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PP-33

Most recently, significant strides have been made in the area of pharmacogenomic research and its effect from bench to bed side, with the discovery of associations between certain geno/haplo-types and drug-response phenotypes. In this study, we present the scientific evidence for diagnostics within infectious diseases example as in HIV-infected (Human Immunodeficiency Virus - infected) patients whom have HLA-B57 (Human Leukocyte Antigen B57) can experience life-threatening adverse events in response to latest treatment option: Abacavir.

Peripheral blood samples were collected from 45 HIV-infected patients. HLA-B57 positivity was determined by Real-Time PCR (Real-Time Polymerase Chain Reaction).

Our results showing that the presence of HLA-B57 allele occurs in 28.9% (n=13) in HIV infected patients. Interestingly, the incidence of HLA-B57 allele in Turkish population is higher than the other reported populations.

This study describes the evidence supporting the clinical utility of pharmacogenetics testing and presents the cases to demonstrate use in everyday practice.

A NOVEL *CREBBP* GENE MUTATION IN A TURKISH GIRL WITH RUBINSTEIN-TAYBI SYNDROME

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PP-34

Rubinstein-Taybi syndrome (RSTS) is a rare autosomal dominant hereditary disorder characterized by intellectual disability, postnatal growth retardation, typical facial features, microcephaly, broad thumbs and halluces. It has been shown that mutations in the genes encoding the cyclic-AMP-regulated enhancer binding protein (*CREBBP*) on chromosome 16 and its homolog E1A-binding protein p300 (*EP300*) on chromosome 22 contributed to the development of RSTS. It was also determined that; both of the genes involved in a number of basic cellular activities, such as DNA repair, growth, differentiation, apoptosis of cells, and tumor suppression. This can explain the symptoms variety. The aim of this study is to report clinical and molecular findings in a child with Rubinstein-Taybi Syndrome.

An affected girl applied to our clinic with the complaints of mental retardation, growth deficiency, microcephaly, broad thumbs and halluces, and dysmorphic facial features include; highly arched eyebrows, long eyelashes, downslanting palpebral fissures, broad nasal bridge, highly arched palate and mild micrognathia. She had an operation for tetralogy of fallot and for polydactily and broad thumbs. For mutation analysis, the coding region of *CREBBP* gene was sequenced.

Mutational analysis revealed a novel heterozygous mutation, p.Q1194X, in exon 18 of the *CREBBP* gene.

Although most RSTS cases are currently diagnosed based on clinical features, genetic tests are also useful for the diagnosis of RSTS. It is also important to identify new mutations to clarify their clinical importance and helpful for providing data to be used in genetic counseling.

MECP2 GENE ANALYSIS IN CHILDREN WITH RETT SYNDROME

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PP-35

Rett syndrome (RTT) is an X-linked dominant neurodevelopmental disorder which is primarily seen in girls. In 80% of the patients with RTT, mutations are present in the methyl CpG-binding protein 2 gene (MECP2). More than 700 pathogenic *MECP2* mutations have been reported. Deletions in the *MECP2* gene have been reported in 10% of affected patients. The most common mutations are found in exons 3, 4 of this gene. In about 70% of RTT patients mutation is in the form of nucleotide transition from cytosine to thymine (C > T) . The most common eight mutations are 473C>T (12.2%), 502C>T (11.9%), 763C>T (10.7%), 808C>T (9.6%), 880C>T (8.2%), 916C>T (6.4%), 397C>T (5.4%), 316C>T (4.8%).

We revealed 10 patients who have RTT. PCR amplification, sequence and MLPA analysis were employed to analyze MECP2 gene.

The four common mutations (473C>T, 502C>T, 763C>T and 808C>T) were detected in 6 patients. Two patients had exon deletions (exon3,4) and c.G1189A (p.E397K) and c.1157-1198del41 (p.Leu386fs) mutations were noted in two patients.

The most common mutations and deletions of *MECP2* were detected in the 8 of 10 patiens. Our results compatible with the literature. Williamson et al suggested that PCR-based screening analysis of exon 3 and exon 4 is the first step for genetic diagnosis of RTT because of the majority of mutations are seen in these regions. As a result, we would like to emphasize that the analysis of the most common mutations of *MECP2* can be the first step to molecular genetic diagnosis.

PREIMPLANTATION GENETIC DIAGNOSIS FOR T(2;5)(q37.1;q35.1): CASE REPORT

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PP-36

Carriers of structural chromosomal rearrangements such as Robertsonian or reciprocal translocations have an increased risk of spontaneous abortion and having children with congenital anomalies. Preimplantation Genetic Diagnosis (PGD) enables the selection of balanced/normal embryos for transfer and gives an opportunity to the families to have a healthy child. We reported a case of a girl with trisomy for the distal part of the long arm of chromosome 5 (5q35.2-->qter) and a concomitant monosomy 2 (2q37.1-->qter) last year. The chromosomal abnormalities resulted from a paternal balanced translocation involving chromosomes 2 and 5 t(2;5)(q37.1;q35.1). The inheritance of the translocation was ascertained by familial cytogenetic and FISH studies. The aim of this study is to present the prenatal genetic diagnosis of this family after PGD.

After controlled ovulation induction, 10 oocytes were recovered by means of transvaginal follicular punction. In total, 6 were fertilized, and all of them were biopsied successfully on day 3 of culture. Only one blastomere was biopsied from each embryo.

Of the tested embryos, 4 were unbalanced and 2 were balanced. The balanced embryos were given at day 4. At 16th pregnancy week, amniocentesis was performed. Subtelomeric FISH was applied to detect the cryptic anomaly which was not visible by standard cytogenetic banding because of translocation size. After metaphase FISH analysis, balanced karyotype was confirmed.

Pregnancy obtained after PGD was confirmed by prenatal diagnosis and balanced translocation carrier was shown.

INVESTIGATION THE EFFECT OF Thr399Ile CONVERISON ON THE RHEUMATOID ARTHRITIS

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PP-37

Rheumatoid arthritis (RA) is a chronic and inflammatory disease characterized by synovial inflammation that causes cartilage and bone destruction as well as systemic defects, including cardiovascular, pulmonary, psychological, and skeletal disorders. The etiology of RA is unclear, but it has been suggested that the inflammatory and autoimmune activities take important roles in the development of the disease. Toll-like receptors (TLRs) are trans membrane glycoproteins that recognize pathogen-associated molecular patterns (PAMPs) produced by microbial agents. TLRs are related to inflammation via synthesis of proinflammatory cytokines as TNF-α, IL-6, and IL-1β and inflammatory enzymes including inducible nitric acid synthase and cyclooxygenaase-2 by NF-Kb way. In this study, *TLR4* polymorphism was studied because of the effect of *TLR4* on chronic inflammation and autoimmunity and the important role of inflammation and autoimmunity in rheumatoid arthritis.

DNA extraction was realized by salting out method from peripheral blood lymphocytes of 110 rheumatoid arthritis patients and 146 healthy controls. PCR amplifications carried out with F: 5´-GGTTGCTGTTCTCAAAGTGATTTTGGGAGA A-3'; and R: 5´-ACCTGAAGACTG-GAGAGTGAGTTAAATGCT-3' primers and polymorphisms detected by the cleavage of amplicons with Hinf1 restriction endonuclease enzyme.

According to the results obtained from 110 rheumatoid arthritis patients and 146 healthy controls, Thr399Ile (rs4986791) conversion has not shown any statistical difference.

Including the other polymorphisms of TLR family into this type studies, will give more information about the role of TLR family in rheumatoid arthritis.

ANTIOXIDANT EFFECT OF NESFATIN -1 IN ALZHEIMER'S DISEASE MODEL FORMED IN ASTROCYTE CELLS

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PP-38

Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disease caused by irreversible loss of neurons in the hippocampus and cortex areas of the brain. Aim of this study is investigation antioxidant effects of nesfatin-1, which is newly defined anorexigenic hormones, closely related to diabetes, obesity, anorexia, nervosa, psychiatric disorders and neurogenic diseases, on cell viability in AD model that is formed in astrocyte cells with amyloid Beta (Aβ).

Catalase (CAT), glutathione peroxidase (GSX-Px), superoxide dismutase (SOD), malondialdehyde (MDA) were measured using method of enzyme linked immunosorbent assay (ELISA). Cell viability was assessed in AD model for the different doses of Aβ, nesfatin-1, Aβ + nesfatin-1.

In the model formed by adding amyloid beta, cell viability value was 100% compared to the control group, but decrease in cell viability value with the increase of doses of Aβ is observed. Cell viability was decreased by 28.5% at 5 µM, 28.93% at 7.5 µM, 29% at 10 µM, and 30.9% at 12.5 µM. When the effect on nesfatin-1 on cell viability was examined, there was a decrease in cell viability at low dose (1uM), an increase in cell viability up to a certain dose (10µM), and cell viability started to decrease after this dose. The cell viability decreased by 41% with addition of Aβ. When nesfatin-1 was added, cell viability increased by 10.3%, and when Aβ and nesfatin-1 were added together, cell viability decreased by 6.8%.

The results show that decreased values of CAT, GSX-Px, and SOD antioxidant enzymes by Aβ are balanced with the addition of Nesfatin-1, and the increased value of MDA bioactive aldehyde with Aβ decreases with addition of Nesfatin-1 and Aβ together. The results will help to prevent neurodegenerative changes associated with Aβ.

COMPARISONS OF CALCULATED ALLELE FREQUENCIES OF ALL VARIANTS DETECTED WITH THE NGS IN TURKISH POPULATION WITH THE ExAC DATABASE

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PP-39

We are confronted with problems such as the multiplicity and the interpretation of the data obtained with the NGS methods. Although the different guidelines are prepared, the most popular and widely used is "American College of Medical Genetics and Genomics" and "Association for Molecular Pathology". According to this guideline variants are classified into five categories: Benign (B), Possible Benign (LB), Unknown Variant (VUS), Possible Pathogen (LP) and Pathogen (P). One of the most important criteria for determining these is the allele frequencies with international databases such as the Exome Aggregation Consortium (ExAC), 1000 Genome and ESP6500 are used. For example, if a variant is above 5% of the allele frequency, it is a sufficient criterion for evaluating that variant as benign. There is no adequate population database specific to Turkey in which allele frequencies can be assessed for our country.

DNA samples from patients referred to our clinic with NF preliminary diagnosis patients were sequenced by using the "TruSight Cancer Target Genes and SNPs" panel and MiSeq Illumina platform. Observed variants in *NF1* gene were classified according to ACMG guidelines and benign variant allele frequencies were compared with EXAC database, pathogenic variants were checked for novelty by using the ClinVar archive. Chi-squared test was used for detection of possible differences between our center benign allele variant frequencies and EXAC database.

We have found four novel and two previously reported pathogenic variants, and fourteen exonic and intronic benign variants. While comparing benign variants' allele frequencies with ExAC database, no significant differences were observed.

Until there will be genome database for Turkish population there is not any disapproval in the clinical use of comprehensive databases such EXAC, at least for *NF1* gene.