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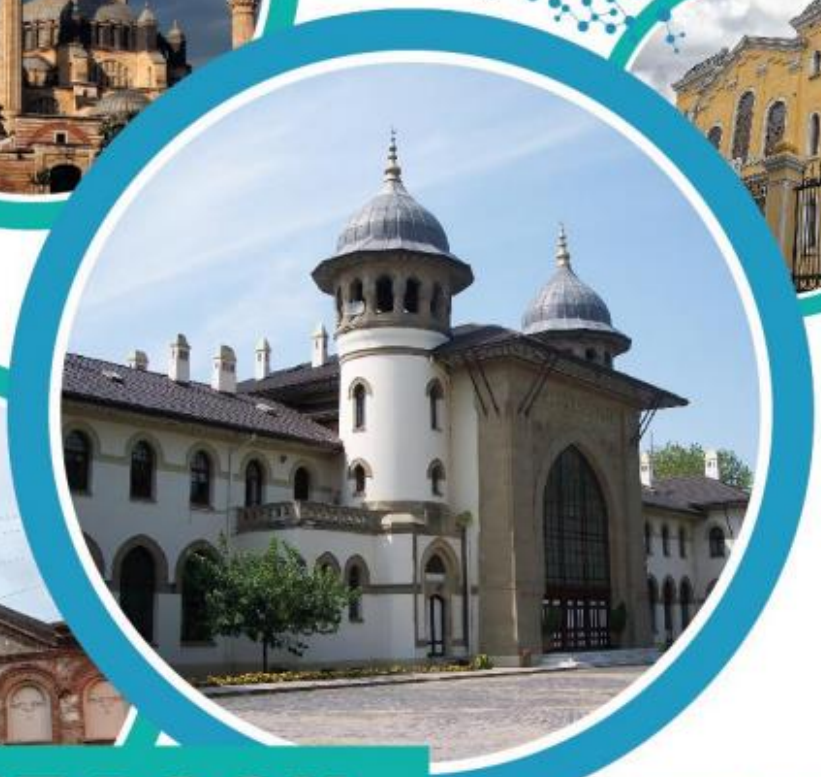
13th Balkan Congress of Human Genetics

17-20 April 2019

Trakya University, Edirne - TURKEY



ABSTRACT BOOK

Organization Secretariat

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Dear Participants,

We welcome you all for joining us in this 13th Balkan Congress of Human Genetics in Edirne between the dates of April 17-20, 2019.

We will start our congress with four different course topics specialized in the various fields of Human Genetics, where apparent associations are frequent but cause-to-effect issues are challenging.

Major subjects of the Congress will cover Prenatal Diagnosis, Preimplantation Genetic Diagnosis, Non Invasive Prenatal Screening, Pharmacogenetics, Genetics and Personalized Medicine, Orphan Diseases, Cancer Genetics, Complex Genetic Disorders, Omics Data and Bioinformatics tools.

We hope not only you will find the content of the program scientifically appealing, but also will enjoy being in Edirne, charming and lovely city of Turkey, hosted many cultures in the history.

On behalf of Board Members of Medical Genetics Association of Turkey and Balkan Congress Organizing Committee, we will be happy to see you all in Edirne and would like to thank you in advance for your scientific contributions.

Prof. Dr. Dijana Plaseska-Karanfilska

President of Macedonian Society of Human Genetics

Prof. Dr. Mehmet Ali Ergun

President of Medical Genetics Association of Turkey

SCIENTIFIC COMMITTE

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Engin Atlı

13. Balkan Congress of Human Genetics Scientific Programme

17 APRIL 2019 –WEDNESDAY	
14:00-16:30	**Pre-Congress Courses 1: Risk Assessment in Cancer and Genetic Counseling** **Chair:** ***Ajlan Tükün- Uğur Özbek***
	14.00-14.30 Breast and Ovary Cancer Risk Assesment and Management ***Dijana Plaseska-Karanfilska***
	14.30-15.00 Gastro Intestinal Cancers Risk Assesment and Management ***Timur Tuncalı***
	15.00-15.30 Familial Cancer and Risk Assessment ***Ozan Çetin***
	15.30-16.30 Case Discussion ***Kanay Yararbaş-Ayşegül Kaymak-Esra Arslan Ateş***
14:00-16:30	**Pre-Congress Courses 2: Principles of Clinical Genetic Applications in Reproductive Medicine** **Chair:** ***Rıdvan Seçkin Özen***
14:00-16:30	**Pre-Congress Courses 3: Epigenetics of Cancer** **Chair:** ***Selvihan Artan***
	Ebru Erzurumluoğlu Gökalp
14:00-16:30	**Pre-Congress Courses 4: Principles of Pharmacogenetics** **Chair:** ***İlter Güney***
	14:00-14:45 Pharmacogenetics of Drug Metabolising Enzymes and Membrane Transporters **Ingolf Cascorbi**
	14:45-15:30 Pharmacogenetic Tests **Vangelis G. Manolopoulos**
	15:30-16:30 Discussion
16:30-17:00	**COFFEE BREAK**

17:00-17:15	**Opening Ceremony** ***Mehmet Ali Ergün - Turkey*** ***Dijana Plaseska-Karanfilska - Republic o Macedonia*** **Protocol**	
	Opening Conference ***Chairs: Mehmet Ali Ergun- Mehmet Alikaşi oğlu***	
17:15-18:00	**Prenatal Diagnosis from Past to Future** ***The Hung Bui-Sweden***	
18 APRIL 2019 –THURSDAY		
	Hall A	
	Panel **Prenatal Genetics and Reproduction** ***Chairs: Seher Başaran- Derya Erçal***	
9:00-9:30	**Pitfalls of Non-invasive Prenatal Tests** ***The Hung Bui-Sweden***	
9:30-10:00	**Preimplantation Genetic Testing: Current Applications and Future Perspectives** ***Anıl Biricik- Italy***	
10:00-10:30	**Microarray Based Prenatal Diagnosis** ***Altuğ Koç-Turkey***	
10:30-11:00	**COFFEE BREAK**	
	Hall A	**Hall B**
	Panel **Precision Medicine** ***Chairs: Zehra Oya Uyguner-İlter Güney***	**Panel** **Genetics of Complex Disorders** ***Chairs: Munis Dündar- Sevilhan Artan***
11:00-11:30	**Bottlenecks and Challenges of Clinical Variant Interpretation in the Era of Precision Medicine**	**Lysosomal Enzymes in Parkinson's Disease**

	Christopher Konialis -Greece	***Tommaso Beccari-Italy***
11:30-12:00	**Translation of Experience in Genome and Personalized Medicine** ***Draga Toncheva-Bulgaria***	**GBA Associated Parkinson's Disease: From Global Resemblance to Local Differences** ***Milena Jankovic -Serbia***
12:00-12:30	**Pharmacogenetics and Precision Medicine in Medical Education** ***Ingolf Cascorbi-Germany***	
12:30-13:00	**LUNCH**	
13:00-13:50	**Satellite Meeting- GEN-ERA** ***Chairs: Ayça Aykut*** **Boutros Maroun, PhD - illumina** **Evolution of Genetic Disease Testing & the Future of WGS for Rare Disease**	
	Panel **Role of Disciplines in Precision Medicine** ***Chairs: Gökay Bozkurt - Meral Yirmibeş Karaoğuz - Hakan Gürkan***	**Panel** **Role of Disciplines in Cancer** ***Chairs: Kıvanç Ce le - Beyhan Durak Aras***
14:00-14:30	**Pharmacogenetics of Anticoagulants** ***Vangelis G. Manolopoulos-Greece***	**Multi-gene Panel Testing in Breast Cancer Management** ***Dijana Plaseska-Karanfilska -Republic o Macedonia***
14:30-15:00	**Pharmacogenomics and Pharmacotranscriptomics of Acute Leukemia in Children: A path to Personalized Medicine** ***Sonja Pavlovic-Serbia***	**Molecular Aspects of Colorectal Cancer Clinical Management** ***Aleksandar Dimovski-Republic of Macedonia***
15:00-16:00	**COFFEE BREAK**	
	Panel **Novel Therapies for Genetic Diseases**	**Panel** **Clinical Implementation of Genomics**

	Chairs: Özgür Çoğulu- Hatice Ilgın Ruhi- Ercan Mıhçı	**from Research to Bedside** ***Chairs: Ahmet Okay Çağlayan- Haluk Akın***
16:00-16:30	**Down Syndrome Treatment** ***Yasemin Alanay-Turkey***	**Highlights of Genomic NGS Applications in Prenatal and Postnatal Diagnosis of Genetic Disorders: Current State of the Art** ***Constantinos Pangalos - Greece***
16:30-17:00	**Gene Therapy in Neuromuscular Diseases** ***Haluk Topaloğlu-Turkey***	**In vitro Procedures for Genome Analysis** ***Savina Hadjidekova-Bulgaria***
17:00-17:30	**Leber's Hereditary Optic Neuropathy** ***Meltem Söylev Bajin-Turkey***	**Prospective of Genetics Testing and Genetic Councilling for Mental Disorders** ***Lejla Kapur Pojskić-Bosnia and Herzegovina***
17:30-18:30	**Oral Presentations Room 1 2 3 4 5** ***Chairs: Abdülgani Tatar- Derya Beyza Sayın Kocakap - Emine Berrin Yüksel-Eda Utine-Gözde Yeşil***	
19 APRIL 2019 –FRIDAY		
	Hall A	**Hall B**
	Panel Rare Diseases in Balkan Countries ***Chairs: Ferda Perçin-Birsen Karaman***	**Panel Cancer Genomics from Research to Bedside** ***Chairs: Naci Çine- Hilmi Tozkır***
9:00-9:30	**WES Analysis on Rare Diseases** ***Radoslava Vazharova-Bulgaria***	**Detection of BRCA1 and BRCA2 Negativeness Using Comparative Analysis of Supervised Learning Techniques and Fisher Score Feature Selection Algorithm for Prediction of Hereditary Breast Cancer**

		Betül Çelik-Turkey
9:30-10:00	**Slovenian Experience in Utilization of Exome and Genome Sequencing for Diagnosis of Rare Genetic Diseases** ***Ales Maver-Slovenia***	**RNA Profiling in Breast Cancer** ***Cengiz Yakıcıer-Turkey***
10:00-10:30	**The Art of NGS Interpretation Lessons from 3000 Patients** ***Borut Peterlin-Slovenia***	
10:30-11:00	**COFFEE BREAK**	
	Panel **Variations in Genome** ***Chairs: Burçak Vural - Öztürk Özdemir***	**Panel** **Genetics of Organ Pathologies** ***Chairs: Haydar Bağış***
11:00-11:30	**Genetic Studies in Identification of Albanian Population and Their Origin** ***Ilia Mıikerezi-Albania***	**Genetics of Hereditary Heart Diseases** ***Karin Writzl-Slovenia***
11:30-12:30	**Genome of Centenarians** ***Lyubomir Balabanski-Bulgaria***	**Genetics of Neurodegeneration with Brain Iron Accumulation: Serbian Experience** ***Ivana Novakovic-Serbia***
12:30-13:00	**LUNCH**	
13:00-13:50	**Satellite Meeting-QIAGEN** ***Chairs: Asude Durmaz*** **"Better Care with Better Knowledge"** **Rupert Yipp, PhD - Director, Hereditary Disease Solutions QIAGEN**	**Satellite Meeting** ***Chairs:Serap Sivri - Mehmet Alikaşi oğlu*** **Fabry Disease "Geneticist and clinician on the road from mutation to diagnosis and treatment"** ***Dr. Bojan Vujkovac - Slovenia***
14:00-15:30	**Panel** **Rare Diseases Policies in Balkan**	**Poster Sessions** ***Selma Demir, Emine İkbal Atlı, Sinem***

	Countries ***Chairs: Aynur Acar***	***Yalçıntepe, Engin Atlı***
	Rumen Stefanov- Bulgaria ***Uğur Özbek-Turkey*** ***Dijana Plaseska-Karanfilska - Macedonia*** ***Grigor Zoraqi-Albania*** ***Ivana Novakovic-Serbia*** ***Borut Peterlin-Slovenia***	
15:30-16:00	**COFFEE BREAK**	
	Panel **Bioinformatics** ***Chairs: Ahmet Dursun***	**Panel** **Genetics in Health Care** ***Chairs: Nur Semerci***
16:00-16:30	**Studying Rare Disease Aetiology Using Omics Data** ***Uğur Sezerman-Turkey***	**Recontacting Patients in Clinical Genetics Services** ***Hülya Kayserili-Turkey***
16:30-17:00	**From Axone to Exome** ***Sibel Uğur İşeri -Turkey***	
17:00-18:00	**Oral Presentations** **Room 1 2 3 4 5** ***Chairs: Yusuf Tunca -Ahmet Arman-Şehime Temel-Sevcan Tuğ Bozdoğan - Emin Karaca- Burak Durmaz- Kadri Karaer***	
20 APRIL 2019 –SATURDAY		
10.00-11.00	**Oral Presentations** **Room 1** ***Chair: Taha Bahsi***	
11.00-12.00	**Rational Drug Use Presentation** ***Ayça Aykut***	

Invited Speakers

Epigenetics of Cancer

Ebru Erzurumluoğlu Gökalp[1], Sevilhan Artan[1]

Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Genetics

Epigenetic modifications are defined as heritable changes in gene function, which is independent of alterations in the DNA sequence. During development, the cells gain their own identity through the epigenome integration of information encoded in the genome with all molecular and chemical signals of cellular, extracellular and environmental origins (1). One of the characteristic features of epigenetics is exhibition of alternative phenotypes by the same genome because of its different epigenetic composition. Epigenetic regulations are essential for maintaining of normal development and tissue-specific gene expression patterns and they are involved in determination of cell development, cell cycle regulation, cell state, cell fate, the ultimate responses in health and disease. The main mechanisms for epigenetic regulation are DNA methylation, histone modifications and posttranscriptional gene regulations by noncoding RNAs such as microRNAs and long noncoding RNAs that do not entail changes in the DNA sequence. Modifications of DNA and histones are dynamically established and removed by chromatin modifying enzymes. These modifications can alter chromatin structure. Aberrant epigenetic signatures are associated with abnormal development and diseases such as cancer, imprinting disorders, neurological and cardiovascular diseases. Disruption of these mechanisms may alter gene expression and confer a selective growth advantage to neoplastic cells, leading to apoptotic deficiency, uninhibited cellular proliferation, and tumorigenicity (2, 3).

DNA methylation, a well-studied epigenetic mechanism, consists of the addition of a methyl group from the cofactor S-adenosyl methionine at the fifth carbon of the pyrimidine ring of cytosine within CpG dinucleotides. (4). This modification is catalyzed by DNA methyltransferases (DNMTs) (DNMT1, DNMT3A, and DNMT3B). Sites of DNA methylation provide platforms for several proteins such as methyl-CpG binding domain (MBD) proteins (MBD1, MBD2, MBD3, MeCP2) and they leads to silencing of genes including tumor suppressor genes (TSGs) (5). The de novo hypermethylation of promoter-associated CpG islands (CGI) of TSGs and DNA repair genes, which leads to transcriptional silencing of these genes are significantly associated with tumorigenesis. Tumors with CGI hypermethylation in multiple genes are also referred to as the CpG island methylator phenotype (CIMP) but the definition varied among different tumors. Global demethylation of large intergenic and repated regions of the genome is another epigenetic alteration specific to some tumors Gene disruptions, translocations and chromosomal instability may occur due to hypomethylation of repetitive sequences. Demethylations are likely to occur in gene bodies and could be a potential source for activating oncogenes (6).

Histone modifications are post-translational modifications that include acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ADP ribosylation. Histone acetylation is an epigenetic modification characterized by the addition of an acetyl group to histone proteins, specifically to the lysine residues within the N-terminal tail. This histone modification is catalyzed by enzymes known as histone acetyltransferases (HATs). Histone acetylation allows open chromatin structure, and transcription factors can access DNA (7). Histone methylation involves the transfer of methyl groups to histone proteins via histone methyltransferases (HMTs). Histone methylation is associated with transcriptional repression or activation depending on the specific amino acid affected. Methylation of histone H3K4 and 36 is associated with activated gene expression, whereas methylation of histone H3K9 and 27 is associated with gene silencing. Researches have demonstrated a global loss of H4K16 monoacetylation and H4K20 trimethylation in cancer (8). In addition to that, the loss of histone H3K9 acetylation and K4 dimethylation or trimethylation and gain of histone H3K9 dimethylation and K27 trimethylation can contribute to tumorigenesis by silencing critical tumor suppressor genes. In human, extensive gene silencing caused by overexpression of EZH2 has been linked to the progression of multiple solid malignancies, including breast, bladder and prostate cancers *(7, 9).* Global levels

of histone modifications differ between cell types and they have been found to be associated with the clinical outcome and progression of different cancer types (10).

MicroRNAs (miRNAs) are non-coding NAs whi h bind t the 3′ ntranslated regi ns (UT s) messenger RNAs (mRNAs) to suppress protein translation or cause mRNA degradation and regulate gene expression at a post-transcriptional level (11). MiRNAs may function as either oncogenes or tumor suppressors and; therefore, dysregulated miRNAs may lead to sustaining proliferative signaling, evading growth suppressors, resisting cell death, activating invasion and metastasis, and inducing angiogenesis (12).Recent genome-wide approaches have revealed that miRNAs are globally dysregulated in cancer and its signatures could be used for tumor classification, diagnosis ,prognosis and therapeutic targets as well (11, 12).

Long non-coding RNAs (lncRNAs) are a group of non-coding RNAs composed of >200 nucleotides. Recently, it has been revealed that the functions of lncRNAs via biochemical and molecular mechanisms that include cis- and trans-regulation of gene expression, epigenetic modulation in the nucleus and post-transcriptional control in the cytoplasm have important roles in the development and progression of cancer.

In conclusion, the epigenetic dysregulation drives significant mechanisms of tumor initiation and development and the epigenomic features seems to be specific to the tumor types. Moreover, the processes targeting these epigenetic changes that are potentially reversible are also promising anticancer therapies and clinical experiments recently increased to target epigenetic regulations by small molecules.

References

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Prof. Dr. Haluk Topaloglu

Pr . Dr. Hal k T al ğl has graduated from Hacettepe University Medical School in 1978. In 1982, he became a Specialist in Pediatrics at the same institution. Between the years of 1984 and 1985, he was trained in Child Neurology in Alberta, Canada. In 1988, he started to work in Hacettepe at the Pediatric Neurology Unit. He worked as a Fellow in London (1994-1995) and at the National Institutes of Health at USA (1998-2000). He is interested in Pediatric Neuromuscular Diseases, Neurogenetics and Developmental Neurology. He was awarded with the Science Award of Hacettepe University in 2002 and TUBITAK (The Scientific and Technological Research Council) in 2003. In 2015, he became the winner of Gaetan Conte Academy Clinical Achievement Award. He is the member of Turkish Academy of Science (TUBA) and several National and Internati nal Pr essi nal Organizati ns, n tably W rld s le S iety (WS). His ”h” a t r is 50..

Yakicier Mustafa Cengiz MD. PhD

23/10/1963, Samsun Turkey , Maried (have one children), A ıbadem le lar Path l gy Lab rat ry

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Internship and specialization in Nuclear Medicine

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PROFESSIONAL EXPERIENCES & ACADEMIC DEGREES

1986- 1990	Physician, Ministry of Health and Social Welfare, Mus and Ankara, TURKEY
1990- 1991	Resident, Nuclear Medicine, Centre Leon Berard Lyon, FRANCE
1991- 1993	Resident, Nuclear Medicine, Hopital de L'Antiquaille, Lyon, FRANCE
1992- 1995	Research Fellow, Molecular Oncology Laboratory,

Centre Leon Berard, Lyon, FRANCE

1995- 1997 Research Fellow, Gastrointestinal Unit of Massachusetts

General Hospital, Harvard Medical School, Boston, USA

1997- 1999 Instructor, Department of Molecular Biology and Genetics

Bilkent University, Ankara, Turkey

1999- 2001 Research Fellow, INSERM U434 - CEPH Paris, France

2001- 2007 Deputy & Medical Director, Genetics and Biotechnology Research and Development Center (BILGEN)

(First independent testing lab authorized for molecular genetics in Turkey), Ankara

2001- 2009 Assistant Prof., Department of Molecular Biology and Genetics

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2017- De ty Dire t r (F nder with Pr . Cihan Uras), A ıbadem Instit te r Sen l gy, Istanb l

Dr Vangelis G. Manolopoulos

Dr Vangelis G. Manolopoulos is a full professor of Pharmacology, Pharmacogenomics, and Precision Medicine, and director at the department of Pharmacology of Democritus University of Thrace Medical School in Alexandroupolis, Greece and at the Clinical Pharmacology Unit of the Academic General Hospital of Alexandroupolis. He obtained a PhD from the Medical School of Patras University in 1991. Between 1992 and 1995 he did postdoctoral research at the Milwaukee Clinical Campus of the University of Wisconsin. Then he took a post as senior research scientist at the Medical School of the Katholic University in Leuven, Belgium, between 1995 and 1998. Since 1998 Dr Manolopoulos has been in a faculty member teaching basic and clinical pharmacology to medical students at his university and since 2001 he has developed and teaches a course in Pharmacogenetics, one of the first to be introduced to the Medical School undergraduate curriculum worldwide. He has authored more than 110 indexed publications that have received more than 2800 citations (H# 30), including one in New England Journal of Medicine as senior corresponding author (NEJM 369:2304, 2013). His current interests include research and clinical applications of pharmacogenomics and epigenetics in drugs used for cardiovascular diseases, diabetes, anticoagulant therapy, and psychiatric diseases. In addition he has a long-standing interest in endothelial cell physiology and atherosclerosis. He directs a masters course in Clinical

Pharmacology and Therapeutics and heads the Research Committee of his Medical School. He is the president of the Greek Society for Basic and Clinical Pharmacology. He is also President-elect of the European Society for Pharmacogenomics and Personalized Therapy (ESPT), and he is co-opted in the Executive Committee of the European Association for Clinical Pharmacology (EACPT).

Lubomir Balabanski

Lubomir Balabanski is a molecular geneticist working in the genetic laboratory of Malinov Clinic in Sofia, Bulgaria, where he is responsible for performing different genomic analyses and NGS diagnostic tests. Since 2016 he has been developing a PhD thesis on the topic of human longevity genetics under the direction of professor Draga Toncheva in the Department of Medical Genetics of the Medical University of Sofia.

Dr. Meltem Söylev Bajin

Pr ess r O hthalm l gy at D k z Eylül University, İzmir, T rkey

My special interest is in the management of patients with optic neuropathies and thyroid associated eye disease, orbital tumors and oculoplastic surgery.

I earned my medical degree from Hacettepe University School of Medicine. After completion of my residency, I w rked with Dr. Tülay Kans n Ne r -ophthalmology between 1989-1992 at Hacettepe University. In 1993 I worked with Dr. Alfredo Sadun and Dr. Steven Feldon on Neuro-ophthalmology and orbital diseases at Doheny Eye Institute, USC in California, USA.

In 1994 I established the Neuro- hthalm l gy de artment D k z Eylül University H s itals Ophthalmology Clinic.

I am a member of Turkish Ophthalmology Society and I have served as president of Neuro-ophthalmology division.

I have published about 40 articles in English, 90 in Turkish and 3 book chapters.

Christopher Konialis, M.Sc., Ph.D.

Clinical Molecular Geneticist Born in Athens, Greece, in 1953, is a high school graduate of Athens College. Studied Chemistry at the University of Thessaloniki and immediately after moved to London UK, at University College London (UCL) for seven years, where he first obtained an MSc degree in Biochemistry and subsequently a PhD degree in Molecular Genetics on human gene cloning and expression. During this period he also supervised laboratory courses for undergraduate students and was subsequently employed as a post-doctoral research fellow, working on an externally funded research project involving cloning, transfection and expression of human genes using retroviral vectors.

Overall, has more than 30 years of experience in molecular genetics and clinical molecular genetics and genomics. Is a member of various international scientific societies (ASHG, ESHG, BSGM, ESHRE and others), has published many firstauthor original papers in international journals and he actively participates as a speaker in many national and

international meetings and congresses in the field of medical genetics and genomics.

Prof. Tommaso beccarı

Professor of Biochemistry and Molecular Biology, University of Perugia, Department of Pharmaceutical Sciences, Perugia, Italy

EDUCATION/TRAINING

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University of Perugia Ph.D Biochemistry

Professor Tommaso Beccari has a l ng ex erien e n lys s mal enzymes that beg n in 1985 at the King's College of London ,UK in the laboratories of Prof. D. Robinson and Dr. JL Stirling, two pioneers in the field of lysosomes. His research has been focused on the biochemistry and molecular biology of lysosomal enzymes and to study the pathophisiology of the lysosomal storage disorders and other neurological disorders such as Parkins n's disease.

Borut Peterlin

Borut Peterlin is head of the Clinical Institute of Medical Genetics and has received training in Neurology and Medical Genetics. He is professor of Human genetics at the universities in Ljubljana, Belgrade, Rijeka and Osijek. He has been active in establishing Medical Genetics as specialisation in Slovenia and coordinated preparation of national plan for rare diseases. His main professional and research interests include translation of genomic technologies into health systems and discovering new mechanisms of monogenic and complex disorders.

Prof. Draga Toncheva

Head of Department of Medical Genetics, Medical University of Sofia, Bulgaria; Head of National Human Genome Center, National consultant of medical genetics, Bulgarian Ministry of Helath, Member of Comission for Rare Diseases, Gentic counselor at Bulgarian Presidency;; coressponding member of Bulgarian Academy of Science; President of Bulgarian Society of Human Genetics and genomics, member of directory board of Bulgarian Alliance for personalized and preccition medicine; member of European alliance for personalized medicine, member of International schizophrenia consortium; member of Scientific programme committee of European society of human genetics (four years) etc. More than 300 pubications in peer reviwe journals and mentor of 40 PhD students.

Prof. Aleksandar Dimovski MD PhD

Aleksandar Dimovski was born in Skopje on October 18, 1962. He earned his medical degree from the Faculty of Medicine in Skopje in 1987 and PhD degree in 1993 from the University of Maastricht. He is Professor of Molecular biology, Pharmacogenetics and Immunology at the Faculty of Pharmacy, member of the Macedonian Academy of Sciences and Arts and currently a Head of its Center for Geneti Engineering and Bi te hn l gy "Ge rgi D. E rem v. His rimary research interest is molecular oncology and individualized therapy. Prof. Dimovski has published more than 100 papers in peer review journals which have more than 1300 citations.

Ingolf Cascorbi

Ingolf Cascorbi is physician and biochemist. He is Professor of Pharmacology, University of Kiel and Director of the Institute of Experimental and Clinical Pharmacology, University Hospital Schleswig-Holstein.

Additionally he is Vice Dean of Education. He holds a PhD in biochemistry, an MD and is specialist in clinical pharmacology. His research interests are in pharmacogenomics and -epigenomics, mechanisms of drug resistance as well as in neuropathic pain research. He has published >250 scientific articles. He is currently President of the International Union of Basic and Clinical Pharmacology (IUPHAR) and Chairman of the German Society of Clinical Pharmacology and Therapeutics (DGKliPha).

Ales Maver-Slovenia

I have been working in the field of human genetics since 2002 with the primary focus on complex disease genetics research, bioinformatics and diagnostics of monogenic disorders. After obtaining a medical degree in 2011, I worked on the identification of rare genetic variation in familial multiple sclerosis using whole exome sequencing as a part of my PhD work. Since then, I have been directing my efforts towards translating next-generation sequencing into routine health care for patients in Slovenia and neighbouring countries. To achieve this, I participated in the establishment of the Centre for Mendelian Genomics in 2013, which now acts as a hub offering state-of-the-art technology and bioinformatics for diagnosing monogenic conditions and attempts to integrate with worldwide data exchange initiatives. In my talk, I will present our out experience in the field of deciphering rare diseases using state-of-the-art sequencing technologies.

Anıl Biricik, PhD

PGT Lab Manager, Eurofins Genoma Group Molecular Genetics Laboratories, Rome-Milan, Italy

Dr. Anıl Biri ik graduated from Istanbul University, Cerrahpasa Medical School, Biomedical Sciences in 1996. He obtained his MSc on medical biology at Marmara University in 1999. He worked at Istanbul Memorial Hospital reproductive genetics unit between 2001 - 2003 where mainly focused on preimplantation genetic testing (PGT) and genetics of male infertility. In 2003 he started to work on PGT at Genoma Molecular Genetics Laboratory. In 2011 he obtained his PhD at University of Rome Sapienza, Department of Obstetrics and Gynaecology with genome profiling of endometriosis tissues by aCGH technique. Dr. Biricik is currently managing the PGT units of Eurofins Genoma Laboratories.

Prof. Lejla Pojskic, dr.biol.sci

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Lejla P jskić w rks in the ield H man m le lar geneti s at the Instit te Genetic Engineering and Biotechnology, University of Sarajevo, Bosnia and Herzegovina.

Her research interests are into the molecular genetic basis of complex traits and novel genetic markers. Since 2005, she leads a research and diagnostics Lab for Human Genetics. Since 2013, she holds associate professorship at University of Sarajevo in the subject of Biotechnology and Genetics.

As part of job description, provides support in genetic testing and advising to patients, families, and individuals at risk of genetic-related disorders.

She is an active member of of Genetics Society in Bosnia and Herzegovina, Societty of Biochemists and Molecular Biologists in Bosnia and Herzegovina and European Society of Human Genetics.

Multi-gene panel testing in breast cancer management

Dijana Plaseska-Karanfilska , MD, PhD

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Breast cancer (BC) predisposition has been attributed to a number of high, moderate and low-penetrance susceptibility genes. Importantly, these genes are typically associated with overlapping cancer phenotypes and therefore single-gene or syndrome-specific testing may miss the underlying genetic cause. The advent of the next generation sequencing (NGS) technologies has led to an era of inexpensive, high throughput sequencing allowing the transition in the cancer predisposition genetic testing from sequential single gene analyses to multi-gene panels. Although, there are no clear recommendations on the genes that should be included in the panel for BC hereditary testing, experts agree that the minimal set should include BRCA1, BRCA2, TP53 and PALB2, all high-risk actionable genes with evidence of clinical impact. Other genes often included in the panels are PTEN, STK-11, ATM, CHEK2, CDH-1, MLH1, MSH2, MSH6, BRIP1 and RAD51D/C. In addition, studies using comprehensive cancer gene panels or whole exome sequencing (WES) are suggesting that other known and novel genes are involved in BC predisposition.

Although multi-gene panel testing provides a more comprehensive and efficient approach to testing an individual for a hereditary BC susceptibility, there are some risks and consequences. Multi-gene testing strategies result in a higher likelihood of detecting moderate and low penetrance variants for which no clear evidence-based management guidelines are available. Additionally, as more genes are tested, the likelihood of identifying variants of uncertain significance (VUS) increases, which represents a considerable challenge due to potential psychological consequences in the carriers and their families. Another concern with the multigene panel testing is the increased need for genetic counseling and cancer support decisions.

Although the use of multigene panel testing for hereditary BC is challenging in the diagnostic setting, it represents an important tool for understanding cancer risk that can impact the care of the BC patients and their families.

Dijana Plaseska-Karanfilska, MD, PhD

Dijana Plaseska-Karanfilska is employed at the Research Centre for Genetic Engineering and Biotechnology "Georgi D Efremov", Macedonian Academy of Sciences and Arts, Skopje, Macedonia where she holds a position of Full Professor and Head of laboratories for Genomics and Molecular diagnostics. She is also inv lved in ndergrad ate, master and PhD st dies at the University “St. Cyril and eth di s” in Sk je. She has s ess lly ment red 6 PhD and 10 S st dents.

She has been engaged in the molecular diagnostics of inherited, malignant and infectious diseases and has contributed to the molecular characterization of different monogenic diseases in the Republic of Macedonia and translation of a number of molecular genetic tests to clinical practice. She has coordinated an infrastructural project that has strengthened the national research capacities in the fields of genomics and proteomics.

She has published more than 100 papers in peer-reviewed journals, several book chapters and has participated with more than 160 presentations on different scientific events. Her recent research interest focuses in reproductive genetics, breast cancer and rare diseases.

She is editor of the Balkan Journal of Medical Genetics, president of the Macedonian Society of Medical Genetics, member of the Board of the European Society of Human Genetics, member of the COST Scientific Committee and a coordinator for Macedonia in the European Biotechnology Thematic Network Association.

Microarray Based Prenatal Diagnosis

Altuğ Koç

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Prenatal diagnosis and postmortem investigation of a pregnancy product frequently include conventional karyotyping by Giemsa (G)-banding. The usual approach is labor intensive, unable to identify submicroscopic gene mi de e ts namely " y n mber variati ns (CNVs)" and req ires l ng term lt re s it has l ng turnaround time. Fluorescence *in situ* hybridization (FISH) and quantitative fluorescence polymerase chain reaction (QF-PCR) assays are also commonly used for specific chromosomal regions to decrease turnaround time and increase the detection rate. In addition, chromosomal microarray (CMA), which is a molecular cytogenetic technique, is developed to overcome the restrictions of karyotyping. It has the ability to detect gains and losses on every chromosomes with a shorter turnaround time. The resolution is greatly increased in contrast to conventional G-banding. Depending on the number of spots belonging to chip, the minimum resolution ranges from 50 to 200 kilo base pairs (kbp), that is 3-5 mega base pairs (Mbp) for G-banding.

Current CMA have copy number probes (oligonucleotides for comparative genomic hybridization) to detect copy gains and losses, and also single nucleotide polymorphism (SNP) probes to detect similarity in single nucleotide sequences (homozygosity). SNP probes give the opportunity to detect uniparental disomy (UPD) of chromosomes. Fetal microarray studies demonstrate that 3.1 to 7.9 percent of the fetuses with an ultrasound abnomality and normal karyotype indeed have pathogenic CNVs. Diagnostic yield with CMA is also greater for stillborn fetuses in contrast to traditional karyotype.

Although the obvious su eri rity t kary ty ing, the dete ti n "variants n ertain signi i an e" is the main limitation for CMA in prenatal diagnosis cases. It is challenging to interpret. But VUS would cause less trouble as the databases evolve.

As mentioned by the recent obstetric guidelines, G-banding or CMA is appropriate for patients who have a structurally normal, viable fetus, but the CMA is preferred for fetuses with structural abnormalities.

In this report, we would like to share recent progress in the use of prenatal microarray and the experience in our region.

The utility of preimplantation genetic test in couples with history of infertility and pregnancy loss

S. Hadjidekova[1,2] and S. Yaneva Staykova[1], R. Staneva[1,2], M. Pancheva[2], M. Serafimova[2], K. Nikolova[2], D. Toncheva[1], G. Stamenov[2]

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Abstract

Preimplantation genetic test (PGT) is cutting-edge technology for early detection of genetic abnormalities in embryos prior to their implantation in the uterus. It allows during IVF procedures to avoid transfer of an affected embryo and termination of pregnancy in case of pathological outcome. In our study we report the results of 185 couples with history of infertility and pregnancy loss that underwent IVF procedure with PGT. Trophectoderm biopsy was carried out on 497 blastocyst stage embryos originating from 231 oocyte retrieval cycles. Array-based comparative genomic hybridization (aCGH) and next-generation sequencing (NGS) were performed. 196 embryos had balanced profile (40.16%) and 292 embryos showed unbalanced profile (59.84%). Embryo transfer was performed in 109 cases (58.92%) and biochemical pregnancy was reported in 33.03%. Live birth rate was 29.36% and pregnancy loss occurred in 3.67% of cases. Our results show that PGT reduces the number of meaningless transfers and eliminates the trauma of termination of desired pregnancy and possible medical complications. In couples with reproductive failure PGT increases the chance of conceiving with a chromosomally balanced embryo and live birth of a healthy offspring per transfer and decreases the risk for pregnancy loss.

Savina Hadjidekova

From 2014 to the present associated professor at the Department of Medical Genetics, Medical University of Sofia.

From January 2013 to the present Head of the Genetic Laboratory at Nadezhda Women's Health Hospital, Sofia – responsible for medical and genetic counseling of patients with reproductive problems, pregnant women with genetic risk, families with hereditary diseases, children with intellectual disability and congenital anomalies. Performing a large set of studies mainly related to the diagnosis of reproductive problems - karyotyping; prenatal genetic diagnosis, non-invasive prenatal test; pre-implantational genetic tests for chromosomal and monogenic diseases.

Optogenetics in the Clinic: THE PIONEER STUDY: a Phase 1/2 Gene Therapy Program for Retinitis Pigmentosa

Katz B, Esposti SD, Boulanger-Scemama E, Martel J, Galluppi F, Vernadal E, Gray D, Taiel M, Sahel JA

INTRODUCTION:

Retinitis pigmentosa is a family of inherited retinal diseases involving progressive degeneration of rod and cone photoreceptors. Vision loss commonly begins in the retinal mid-periphery and progresses centrally, with marked constriction of visual fields. GS030 is an investigational treatment combining both a novel gene therapy and a medical device currently in active clinical development to address this unmet medical need.

METHODOLOGY:

The drug product of GS030 is an optogenetic gene therapy targeting retinal ganglion cells (RGCs) and encoding an optimized form of channel rhodopsin ChrimsonR, *ChrimsonR-tdTomato (ChR-tdT).* Visual interface stimulating goggles. ChR-tdT is delivered by a modified AAV2 vector administered via a single intravitreal injection (IVT). PIONEER is a Phase 1/2a, open-label, non-randomized, dose-escalation study to evaluate the safety and tolerability of GS030 in subjects with end-stage non-syndromic RP and vision of light perception or no light perception.

RESULTS:

The first human subject was injected with 5E10 vg/eye of ChR-tdT in the fall of 2018. First use of the medical device post gene therapy was initiated two months following IVT without untoward effects or safety signals.

CONCLUSIONS:

PIONEER is the first clinical trial combining the simultaneous action of a gene therapy and a medical device. A retinal optogenetic therapeutic approach independent of underlying genetic defects is of major import in RP. As RP advances, both rod and cone photoreceptors are lost, though RGCs are preserved. Under such conditions, a therapeutic intervention that converts RGCs into photo-responsive cells via an optogenetic protein offers great promise for this family of disease.

Genetic diseases and their prevention in Albania

Grigor Zoraqi

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In the last 15 years, from 2004, the aim of our Center of Molecular Diagnostic and Genetic Research, have been the characterization of the most common genetic diseases in Albania, identification of the corresponding mutations, and the identification of carriers using various protocols, in order to perform prenatal diagnosis.

Cystic Fibrosis and the complete pattern of CFTR mutations in Albania.

A pattern of CFTR mutations was found analyzing 152 CF Albanin patients from 2004 to 2019 (1, 2). The new pattern of CFTR gene include 16 different CFTR mutations, which accounted for 90 % (274/304) of CF Albanian alleles. Eight CF mutations presented at frequency more than 1%: p.Phe508del (70.06%), c.489+1G>T (4.27%), p.Gly542X (3.61%), p.Glu822X (2,15%), p.Gly85Glu (1.97%), R1066C (1,43%), p.Arg1158X (1,42%) and c.579+1G>T (1.31%) accounted for 86.2%. Other 8 mutations at frequency lower tha 1% were found: p.Arg1070Gln (0,72%), and c.54-5490_273+10250del21kb)(0,72%), G1349D (0,36%), W401X (0,36%), 1811 +1 G>C (0,36%), p.Asn1303Lys (0,36%), p.Ser466X (0,36%), p.Ser549Arg (0,36%), accounted for 3,6% of all CF mutations in Albania. Three complex alleles: S466X-R1070Q (0,72%), S466X-E822X (0,36%) and G822X-F1052V (0,36%) are identified in CF Albanian patients. The freqyency of CF carriers in Albania is about 1/20.

Prenatal diagnosis was performed in pregnant women based in familial history. A small number of prenatal diagnosis was based in CFTR mutations found in the pregnant women. About 20% of expected newborns affected by CF were prevented by our lab.

Thalassemia in Albania, the pattern of mutations and prevention

The pattern of mutations and their frequency is well known in Albanian population. Previous studies on Albanian patients (3,4,5) including our laboratory data identified a small number of mutations that covering 85% of the patients and 9 mutations covering the rest of the patients.

Our data presented the following pattern: IVS-I-110 (0,418); Cod 39 (0,238); IVS-I-6 (0,050); IVS-I-5 (0,025); COD (-44) (0,037); IVS-I-I (0,011); COD5 (-CT) (0,011); COD82/83 (-C)(0,011); HbS-COD6 (GTG) (0,194); HbC (0,011); Hb Lepore, Boston (0,011), HbE (0,011%), HbD-Punjab (0,011).
We used RDB protocols and direct sequencing of globine gene.
It was suggested that about 6% of Albanian population are carriers of beta-thalassemia, but we have not clear data about the carriers. Every year we would expected about 30 newborns affected by Thalassemia in about 35.00 newborns per year.

Our laboratory can prevent about 20% of expected newborns affected by thalassemia. Other prenatal diagnosis are performed by private hospitals and clinics, but we have not exact information about the number of prenatal diagnosis.

This year our laboratory proposed a National Prevention Project for beta-thalassemia in Albania, based in the identification of carriers in the pregnant women, using blood analysis, Hb electrophoresis and DNA tests.

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Prof. Asc. Grigor Zoraqi

Grigor Zoraqi is a genetist, Head of the Center of Molecular Diagnosis and Genetic Research, University Hospital of Obstetrics and Gyneacology, Tirana, Albania. From 2004, when the Center was setup, is involved in molecular diagnosis of genetic diseases in Albanian population.

The main research field is the identification and prevention of most common genetic diseases in Albania.

Last year Zoraqi foundet the Albanian Society of Human Genetics and was elected the President of the society.

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Different Genetic Analysis Reveals Interesting Data on Genetic Structure and Relationships of Albanian Human Population.

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The study of population genetic structure is of great interest because it serves as a main source to understand its genetic history. In this context, it is important to understand genetic relationships between different internal local subpopulations and, on the other side, genetic relationships with other foreign populations. A number of historical processes and events have contributed to the composition of the present genetic structure of Albanian human population. In order to better understand the role of migrations, isolation and other micro evolutionary processes that have produced actual genetic variability of Albanian population, different approaches and methodologies have been used.

By isonymic method, as defined by Crow and Mange (Crow J F, Mange A 1965), it was analyzed the present structure of Albanian population in three administrative levels: prefectures, districts and communes. Different parameters that define genetic population structure were calculated based on the information on 3.068.447 persons for a total of 37.184 surnames. The data were the surnames of electors of 2009 general election database. Interestingly, two main clusters were identified by MDS analysis that corresponded to two main ling isti areas the ntry: Gegë in N rth Albania and T skë in S th. A t ally, m st internal migrati ns seemed to take place mainly towards the capital and other main cities (Mikerezi I, et al. 2013)

On the other side, it may be concluded that the actual population structure has been composed as consequence of the joint effect of directional short-range migration and drift. The results obtained by multivariate analysis pointed out that migration processes in the North-South direction and from eastern regions towards West have been important processes.

In the context of genetic structure of Mediterranean Basin area populations the genome variation patterns of Albanians, Albanian s eaking (Arbëreshë) S th Italy and Si ily were investigated al ng with ther related populations of Sicily, South Italy, part of Greece, Cyprus and Crete, as well.

One of the main questions posed in this investigation was: Is there any evidence of genetic links between the Arbëreshë and Greek speaking ethno-linguistic minorities of Southern Italy and their putative populations of origin? Could our data provide additional insights into their dem gra hi hist ry as re ent “ lt ral islands”? (Sarno S et al 2017). Di erent geneti analysis revealed geneti ntin ity Albanian s eaking (Arbëreshë) with Albanian source of Balcan. In addition, various genetic exchanges within Balcan Peninsula could explain genetic similarities between Albanian and mainland Greek populations. Like in other populations of Southern Balkans, Greece and Southern Italy, Albanian populations share a Neolithic-like genetic component. On the other side, incr easing frequencies of the European-like component are observed in Albanians and mainland Greeks as well as in the rest of the Balkan Peninsula (Sarno S et al 2017, Sarno S, et al 2014).

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Ilia Mikerezi

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His research is focused on Genetics of human populations with a special focus on Genetic relationships among Albanian populations and relationships with European ones. Prof Mikerezi has participated in different national and international research projects in Genetics of human populations and is author and co-author of different scientific papers. He currently resides in Tirana with his family and can be contacted at imikerezi@yahoo.com

Genetics of Neurodegeneration with Brain Iron Accumulation: Serbian Experience

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INTRODUCTION: Neurodegeneration with brain iron accumulation (NBIA) is an autosomal recessive disorder characterized by dystonia, Parkinsonism, cognitive and visual impairment, and iron accumulation in brain. Majority cases of NBIA result from mutations in the *PANK2* gene that encodes pantothenate kinase 2, a key regulatory enzyme in the biosynthesis of coenzyme A.

MATERIAL AND METHODS: Over the last 10 years we have analyzed 16 Serbian patients with clinically suggestive NBIA, using direct sequencing of the *PANK2* gene. In 6 carriers of common PANK2 mutation we performed the analysis of linkage disequilibrium (LD) and organization in haplotypes of 23 single nucleotide polymorphisms (SNPs) adjacent to *PANK2* gene in patients and their parents, as well as in 30 healthy child-parents trios originating from the same geographical region.

RESULTS: Pathogenic changes were detected in 12 patients all of whom had c.1583C>T mutation (p.T528M) either in homozygous or in compound heterozygous state. In majority of compound heterozygous cases the remaining mutation was deletion c.1418del7, while two additional PNK2 mutations have been detected in single cases. Clinical findings in our patients were markedly similar, characterized by early onset and fast progression of symptoms with particular speech affection. Different LD structure between patients with *PANK2* 1583 C>T mutation and controls is revealed, and 1583T allele was significantly associated with particular haplotype. Key words: NBIA, pANK2 mutations, Serbia

Ivana Novakovic, CV

Ivana Novakovic is full professor in Human Genetics at Faculty of Medicine, University of Belgrade, Belgrade, Serbia. She works in the field of Human and Medical genetics for over three decades covering education, laboratory practice and research. Currently she is head of Medical Genetic section of the Serbian Genetic Society. Her major scientific interest is focused to neurogenetics. The first topic was genetics of neuromuscular disorders, particularly dystrophiopathies. Recently, work has been forced in genotype-phenotype correlation in neurodegenerative disorders as well as in the role of DNA polymorphisms in susceptibility for multifactorial diseases. She is author or co-author of more than 50 papers published in journals from JCR list, with more than 880 citations and h-index 14.

GBA Associated Parkinson's Disease: From Global Resemblance to Local Differences

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Parkins n's disease (PD) is the se nd m st mm n ne r degenerative dis rder with m lti a t rial etiology [1]. The genetic basis of PD is very complex and more than 28 chromosomal regions (PARK loci), associated with the disease, are described so far [2]. Homozygous and compound heterozygous mutations in gene encoding for lysosomal enzyme glucocerebrosidase (*GBA* gene) are cause of autosomal recessive Ga her's disease (GD), but both homozygous and heterozygous mutations in this gene are also associated with PD [3,4]. Although, majority of mutation carriers will never develop PD, *GBA* mutations are the most common known mutations in PD patients and represent a strong risk factor for the disease [5]. *GBA* mutation frequency differs among populations, so it is important to establish relative frequency in different ethnic groups, in order to create national guidelines for genetic testing strategy for PD [6].

In this study, *GBA* exons 8-11, harbouring the most common mutations [6], were amplified and directly sequenced by Sanger method in 481 Serbian PD patients and 348 ethnically matched controls. Subjects identified with the D409H mutation were also sequenced for H255Q (exon 7).

Ten different variants were detected in selected exons of the *GBA* gene: R329H (c.1103G>A), T369M (c.1223C>T), N370S (c.1226A>G), D380V (c.1256A>T), P391L (c.1289C>T), N392S (c.1292A>G), D409H (c.1342G>C), L444P (c.1448T>C), R463C (c.1504C>T) and R463H (c.1505G>A). Also, three complex, re mbinant alleles were nd: e Δ5 (.1263–1317del55), [D409H;H255Q] (c.1342G>C, c.882T>G) and RecNcil (c.1448T>C, c.1483G>C, c.1497G>C). In total, 58 heterozygous mutations were detected in PD atients, three m nd heter zyg s and ne h m zyg s in atients with Parkins n's and Ga her's disease, 12 heter zyg s in relatives atients with Ga her's disease, and 17 heter zyg s in healthy controls. Very frequent variant, T369M, already described as polymorphism, was analysed separately, and excluded from further statistical analysis. Mutation frequency was significantly higher in patients with PD (37/481; 7,69%) compared to controls 1,5% (4/348; 1,5%) (OR= 7,17; CI 2.53–20.3), confirming that *GBA* mutations represent the most robust genetic susceptibility factor for PD in Serbian population. The most common mutation in our study, N370S, with frequency of 2,08% in patients and not detected in controls, represents a significant independent risk factor for PD in Serbian population. In contrary, L444P mutation alone was underrepresented compared to other studies, with frequency of 0,4% in patients and 0,3% in controls [5]. Higher frequency of L444P was detected in recombinant allele RecNcil (0,83% of patients and none of controls). Also, the second most common mutation in our study, D409H, with frequency of 1,87% in patients and 0,6% in controls, was found only as part of [D409H;H255Q] allele, which is in concordance with other studies that found the high frequency of the that complex allele in Balkan patients [7]. Also, we detected two heterozygous variants, D380V and N392S, in single patient each that has been described in previous study as novel variants, only in Serbian patients [8].

Clinically, PD patients with *GBA* mutations have an earlier age of onset, more likely have a positive family history for PD and more prevalent non-motor symptoms compared to PD patients without *GBA* mutations [9]. In our study, clinical presentations of the disease in *GBA* mutation carriers were not different compared to non-carriers in most parameters studied. The only presenting symptom that was significantly more frequent in *GBA* carriers (10.3%) than in patients without mutations (3%) was pain (more often on the upper limbs). Three patients with pain as initial symptom were heterozygous carriers of [D409H; H255Q] complex, mutated allele, which belongs to severe mutations, while one patient was a heterozygous carrier of R463H mutation.

Establishing mutation frequency and type is the important step to *GBA* genetic testing implementation in routine diagnostic procedures for PD. Considering the high frequency of *GBA* mutations detected in our group of patients, as well as differences in clinical presentation among *GBA* mutation carriers and non-carriers, its recommendable to include *GBA* selective exon screening as one of the first steps in algorithm for PD genetic testing.

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Highlights of Genomic NGS Applications in Prenatal and Postnatal Diagnosis of Genetic Disorders: Current State of the Art

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Although genetic diseases are considered to be generally rare, they are estimated to occur at a frequency of ~60 per 1000 births. Epidemiological studies show that if we also take into account all congenital anomalies, then about 8% of people will develop a genetic disease before they reach adulthood. Until recently, the 'classic' a r a h t the diagn sis geneti diseases n erned the targeted analysis s e i i genes, s h as β-thalassemia, cystic fibrosis, etc. However, in daily clinical practice, we are often faced with diagnostic puzzles involving a large number of complex and heterogeneous genetic diseases, for which conventional targeted genetic tests, based on the observed clinical phenotype, do not yield substantial results. These classical approaches are accompanied by severe limitations, as many patients with apparently genetic diseases do not receive a specific diagnosis, with serious consequences for themselves and their families. Similarly, in the course of routine ultrasound examination of all pregnancies, 3-5% of these present with ultrasound findings, which may be related to the presence of fetal congenital abnormalities (1, 2). Approximately 10-15% of these cases are due to the presence of chromosomal abnormalities, while in ~85% of cases the genetic cause remains undiagnosed, leading to an inability to provide a precise diagnosis and accurate reproductive and fetal risk assessment (3, 4, 5). The ability we now have at our disposal to massively analyze our genome, through Whole Exome Sequencing (WES) and Next Generation Sequencing (NGS) technologies, provided us with a new genetic 'super-weapon' and we are now theoretically able to uncover the underlying cause of any genetic disease in an affected individual, who has not been diagnosed through other conventional diagnostic options.

Regarding diagnostic prenatal WES applications and starting in early 2015, we designed and implemented an expanded exome sequencing-based test, coupled to a bioinformatics-driven variant prioritization algorithm, targeting gene disorders presenting with abnormal prenatal ultrasound findings. Further to the original publication in 2016 (6), we present recent developments and discuss the latest data from the overall application of this approach (the *Fetalis*® test) in 66 pregnancies with ultrasound findings, which led to the diagnosis of many complex and unsuspected genetic diseases in the embryos. Exome sequencing results were typically available within 10±3 days. Overall, ath geni m tati ns ass iated with a kn wn geneti dis rder were detected in 24 out of 66 cases (36%, 3 abortuses, 21 on-going pregnancies). No pathogenic mutations were detected in the remaining 42 cases (64%) and as far as we know in at least 18 of these cases an apparently healthy child was born. The genetic disorders diagnosed in the affected fetuses included Noonan syndrome, Nemaline myopathy, X-linked myopathy with excessive autophagy, Bartter syndrome, Congenital myasthenic syndrome, etc.

In the prenatal setting, our expanded targeted exome sequencing-based approach provides strong evidence suggesting a diagnostic yield of ~36% in fetuses with troubling sonographic abnormalities and a normal chromosomal constitution. Data from a recently published study (7), involving primarily WES-trio testing of 610 fetuses, with a broad range of fetal structural anomalies, demonstrated an overall diagnostic yield of 12.5% and this is somewhat lower than that suggested through our experience and other published studies (8, 9), most likely due to differences in inclusion and ascertainment criteria. It is important to note, however, that our testing strategy overcomes many of the problems and limitations associated with clinical wide-scale WES testing in a prenatal setting, by reporting only highly confident clinically actionable results and avoiding the problems associated with the interpretation and communication of uncertain findings in the course of pregnancy (10, 11). Regarding postnatal WES applications, since late 2011 our team developed and applied genomic analyses, mostly through WES, in a total of ~400 postnatal patient cases involving complex and genetically heterogeneous phenotypes, such as retinopathies, hearing loss, neuromuscular diseases, epilepsy, neuropathies,

etc.). Especially with regard to neonatal and pediatric cases (<16 yrs old), we have performed WES testing for a variety of clinical phenotypes, such as epileptic encephalopathy, multiple congenital anomalies, developmental and/or psychomotor retardation, neurogenetic diseases, etc. WES analysis, either through single proband WES or WES-trio (proband plus parents), led to the discovery of the underlying genetic cause and the successful diagnosis of the genetic disease in ~71% of cases in this patient group and we highlight clinically interesting cases. Similarly, WES applications in affected adults primarily with late/adult-onset disorders, led to a diagnosis in ~65% of cases and we highlight selected cases where the results led to the diagnosis of an unsuspected and/or complex genetic disease. We did not observe a significant difference in diagnostic yield between neonatal/pediatric cases and adult cases (71% vs 65%), with an average overall diagnostic yield of ~66%.

In conclusion, genomic testing through WES appears to provide a highly beneficial molecular diagnosis for a significant number of patients with diverse clinical indications, albeit with certain limitations, and is nowadays an indispensable diagnostic tool in the emerging era of Genomic Medicine and Precision Medicine, by providing medically actionable information leading to patient management and guidance, and in some cases, to disease-specific treatment options that may result in a significant improvement in quality of life.

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Pharmacogenomics and pharmacotranscriptomics of acute leukemia in children: a path to personalized medicine

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Personalized medicine, also known as precision medicine, aims to individualize the treatment of every patient, so that each patient gets the most efficient treatment. It is essential to fulfill the directive of pr viding “the right dr g t the right atient at the right d se, at the right time”. D e t this dire tive, the medi ine the XXI century is focused on disciplines which contribute to the individualization of therapy, like, pharmacogenomics and pharmacotranscriptomics. Pharmacogenomics and pharmacotranscriptomics aim to elucidate the ass iati n between atients’ interindivid al gen mi and trans ri t mi variability and e i a y/t xi ity a drug. Aside from discovering specific genes and transcripts which might influence the response of a patient to a drug, pharmacogenomics and pharmacotranscriptomics also try to identify markers associated with a disease, which can be targets for new therapeutics. The goal of pharmacogenomics and pharmacotranscriptomics is to create an effective therapy strategy based on the genomic and transcriptomic profile of a patient.
Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. It is one of the pediatric malignancies with the highest cure rate. Almost all patients achieve remission, and about 85% of the patients are expected to be cured with modern treatment protocols. However, efficient therapy causes side effects in 75% of childhood ALL patients. It is estimated that 1-3% of pediatric ALL patients have a lethal outcome due to the consequences of treatment side effects. Considering that more efficient treatment of pediatric ALL has not been achieved by introduction of novel drugs into the treatment protocols, but by trying to diminish the adverse effects of the drugs that are already included in the protocols, it is understandable why pharmacogenomics and pharmacotranscriptomics became very important in this field.
Standard treatment protocols for childhood ALL include several commonly used drugs, i.e., glucocorticoids, vincristine, asparaginase, anthracyclines, thiopurines and methotrexate. Numerous pharmacogenomic and pharmacotranscriptomic markers of drug response or toxicity in pediatric ALL have been discovered. However,

only few of them have been validated and reached as high level of evidence as to be beneficial in clinical practice [1,2].

Some of the most promising markers for glucocorticoids are found in pharmacogenes *NR3C1*, *ABCB1* and *GSTs* [3]. Additionally, the expression of long noncoding RNA GAS5 has been shown to be associated with a poor GC response in childhood ALL during the remission induction phase of therapy [4].

A number of studies brought encouraging results about pharmacogenes and pharmacogenomic variants involved in vincristine-related sensory and motor peripheral neuropathies and anthracycline-related cardiotoxicity. Also, several pharmacogenomic markers were associated with adverse drug reactions in children with ALL that received asparaginase during standard treatment ALL protocol.

One of the first clinically recognized pharmacogenomic markers, now mandatory for testing prior to administering mercaptopurine therapy, are variants in *TPMT* gene [5,6]. Mercaptopurine drugs dosage is routinely adjusted according to patients *TPMT* genotype in childhood ALL, [7]. Furthermore, variable number of tandem repeats (VNTR) in promoter of *TPMT* gene has been proposed to be a novel pharmacogenomic marker [8]. Testing the number and type of the repeats, VNTR architecture, can be potentially used as a pharmacogenomic marker to predict toxicity due to mercaptopurine treatment in childhood ALL patients [9,10]

Methotrexate is one of the key drugs of ALL treatment, which is given in all phases of ALL therapy protocols. Response to methotrexate therapy is associated with activity of key enzymes and transporters involved in methotrexate and folate metabolic pathway, such as MTHFR, DHFR, TYMS, SLCO1B1. It was shown that these are the most promising pharmacogenes for methotrexate therapy response [11,12].

A very small number of studies on pharmacotranscriptomic markers in childhood ALL are performed so far. Therefore, the related data are deficient.

Even smaller number of studies of somatic mutations relevant for pharmacogenomics in ALL have been conducted. A patient with a malignancy has two genomes: the constitutional genome and the tumor genome, which is characteristic for malignant clone that contains acquired genetic variants and which changes during the evolution of tumor clone. Variants in the constitutional genome, germinative variants, influence the transport and the metabolism of drugs, making them responsible for the efficacy of the drugs and the side effects, while somatic mutations are responsible for the resistance of the tumor to drugs. Next generation sequencing (NGS) technology has enabled genomic profiling of each patient. Especially, targeted NGS has facilitated analysis of somatic mutations in leukemia patients. Using targeted NGS, new variants were detected in the study of pharmacogenomic markers in childhood ALL patients. All of them were in the genes involved in Ras/RTK signaling pathway which is frequently mutated in childhood ALL patients [13]. Pharmacogenomic and pharmacotranscriptomic profiling of each patient will be indispensable for novel therapy approaches. Detection and initial analysis of novel variants will become a standard procedure for the design and development of individualized therapies for children with ALL, leading to improved patient outcomes.

Population pharmacogenomics research has shown that the study of pharmacogenomic markers in various populations is of great importance. The population-specific genotyping panels could be used pre-emptively, prior to or at the point of taking the required medication [14]. This would lead to the reduction of healthcare expenditure and to a better treatment of patients.

Big data in pharmacogenomics ad pharmacotranscriptomics was produced so far, but their implementation in clinical practice is poor. Research efforts ought to be directed to data analysis and design of prediction models using machine learning algorithms. Bioinformatics tools and implementation of artificial intelligence are expected to open the door wide for personalized treatment of childhood ALL.

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Whole exome sequencing - deciphering rare disease diagnosis

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Background: Clarifying the genetic basis of rare Mendelian diseases is challenging and many patients remain undiagnosed despite extensive clinical, laboratory and imaging studies. The conventional diagnostic process used by most clinical / medical genetics specialists includes the recognition of a specific phenotypic pattern which guides further a step by step series of laboratory studies of candidate-genes. The majority of the discovered so far disease-related gene variants are located in the exons, suggesting that whole exome sequencing (WES) is an attractive approach to reveal pathological mutations in rare monogenic diseases.

Materials and methods: The pilot study includes a series of 15 individuals referred for genetic testing because of a suspected diagnosis of monogenic disease with locus heter geneity and 8 “healthy” ad lts. To ensure the high quality of sequencing data WES was outsourced to a commercial company (BGI). The targeted region includes 180000 exons of 22000 human genes. Average sequencing depth on target was >50x and the fraction of targets covered ≥20x was >98%. All clean data of each sample were mapped to the human reference genome (GRCh37) using Burrows-Wheeler Aligner (BWA) software and Genome Analysis Toolkit was used for variant calling. The search for the disease-causing m tati ns sed n variants with a q ality s re ≥20 and verage ≥20×, l ated tside segmental d li ati ns and sim le re eats.

Results: A specific genetic alteration associated with the leading clinical manifestations was found in 6 patients with suspected monogenic disorder and variants of unknown significance have been observed in all individuals.

Detailed phenotyping of studied individuals is a prerequisite for results interpretation and may be critical in a clinical setting.

Conclusion: Some questions related to WES still remain to be answered when we try to apply this approach in medical praxis: sensitivity of the test, data storage and protection, reporting and clinical utility of results and many more.

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Oral Presentations

S-01 - A case report of X-Linked Hypophosphatemic Rickets (XLHR) with a novel mutation in the PHEX gene

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Introduction and Aim X-linked hypophosphatemic rickets, inherited in a dominant manner, is the most common form of familial hypophosphatemic rickets. Clinical manifestations of XLHR can vary but most patients will present with limb deformity, primarily affecting the legs and short stature. A 2-year-old boy presented to us with a complaint of curvature of the legs. Physical examination revealed pectus carinatum and genu varum deformity. His mother had short stature and hypochondroplasic-disproportional body view. Biochemical blood measures were as follows: ALP:827 U/L, iP:2.6 mg/dL, PTH:107.1 pg/mL, calcium:10.37 mg/dL. We aimed to contribute to the literature by sharing the novel mutation of PHEX gene we found in our case. Material and Method With peripheral blood sample, the FGFR3 and PHEX genes were analyzed by sequence analysis and next generation sequencing (NGS) method respectively. Results FGFR3 gene sequence analysis revealed a heterozygous c.1082-13C>T alterati n in the intr n 8, near the ‘’s li e site’’. His m ther had the same alteration; his brother without symptoms also had the mutation. Later, PHEX gene analysis revealed a hemizygous c.436+1G>T splice donor novel mutation in the intron 4. Discussion The phenotypic spectrum of XLHR ranges from isolated hypophosphatemia to severe lower-extremity bowing. The clinic of our case was compatible with this disease. Initially, the alteration in the FGRF3 gene suggested that it could not cause phenotype in our case because it was detected in the healthy brother. By showing a novel mutation in the PHEX gene, we highlighted the diagnosis of XLHR.

KEYWORDS: PHEX, hypophosphatemic rickets , NOVEL, NGS

S-02 - A New Case Of Chromosome 3q13.31 Deletion Syndrome

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Introduction and Aim; Microdeletion and microduplication syndromes are well-known causes of congenital malformations and developmental delay. Chromosome 3q13.31 deletions have rarely been reported and their features are developmental delay and dysmorphic features. We aim to report a case that exhibits the genotype-phenotype correlation of a very rare syndrome. Material and Method; A complete physical examination was performed to a patient with developmental delay and dysmorphic features. Molecular karyotyping (CytoScan Optima Array Kit from Affymetrix) was performed to evaluate differential diagnosis of submicroscopic deletion and duplication syndromes. Results; A female patient was presented with postnatal overgrowth, severe developmental delay, dysmorphic facial features (prominent forehead, epicanthal folds, depressed nasal bridges and anteverte nares) and agenesis of corpus callosum. After molecular karyotyping a 3 Mb microdeletion of the 3q13.2q13.31 region was found. Discussion; The deleted region of the current patient contains four morbid OMIM gene and two of them (DRD3 and ZBTB20) are suggested to be responsible for the developmental delay.

KEYWORDS: microarray, microdeletion, developmental delay, 3q13.31

S-03 - Application of NGS technology in rare diseases diagnostics: a Serbian experience

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Introduction and Aim. Majority of rare diseases (RDs) are genetic diseases (80%) and identification of specific gene defect in each patient is important. High-throughput methodology, such as next generation sequencing (NGS), has enabled diagnosis of many RDs, especially genetically heterogeneous diseases. Material and Method. IMGGE is the first institution is Serbia that applied NGS methodology in research and diagnostics of RDs. Over 200 RDs patients were analyzed using Clinical-Exome Sequencing TruSight One Gene Panel which includes 4813 recognized disease-associated genes. Results. Diagnosis of more than 50 RDs (hematological, metabolic, endocrinological, pulmonary, immunological, orthopedic, dermatological, ophthalmological) was established. F r m n geni diseases, iltrati n and ri ritizati n variants were er rmed a rding t "in-h se" i eline, sing virt al gene anels. F rtherm re, diseases with verla ing lini al manifestations, such as glycogen storage diseases, branched-chain organic acidurias, primary ciliary dyskinesia, MODY or mitochondriopathies, were accurately diagnosed. Novel variants detected in DNAI1, MUT, PAH, PCCB, SLC37A4, SPAG16 and SPAG17 genes were functionally characterized in adequate in vitro systems, resulting in their unambiguous diagnostic interpretation. Also, we used TruSeq-Amplicon Cancer Panel to analyze childhood and adult rare hematological malignancies. We performed association studies of diagnostic, prognostic and pharmacogenomic markers and the course and outcome of rare hematological malignancies, resulting in recommendations for therapeutic modalities in accordance with genomic profile of the patient. Discussion. Our approach leads to timely and accurate genetic testing, sets definite diagnosis and enables rapid implementation of optimal therapy for patients with RDs in Serbia. This work has been funded by MESTD, Republic of Serbia (III41004).

KEYWORDS: rare disease, next generation sequencing, genetic diagnosis, hematological malignancies

S-04 - A de novo 6q21q22.33 deletion in a boy with microcephaly, developmental delay and dysmorphic features

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Introduction and Aim: Microcephaly is described as a head circumference more than two standard deviations below the mean for age and gender. Microcephaly may be due to genetic or environmental reasons. It may be associated with syndromic microcephaly, multiple congenital anomalies, neurological signs, or dysmorphic features. It may be due to single gene defects, numerical or structural chromosomal abnormalities. In this study, we aimed to discuss the phenotype-genotype relation in a case of microcephaly and dysmorphic features with microdeletion detected by microarray. Material and Method: At twelve months of age, the male patient was referred to us with atypical facial appearance and had a head circumference of 42 cm (<3p), a height of 72 cm (10p), a weight of 8 kg (<3p). Physical examination revealed epicanthus, hypertelorism, depressed nasal bridge and micrognathia. He had neuromotor developmental delay. Cytogenetic analysis was reported as 46, XY. Also his aunt's daughter has microcephaly. Results: Microarray detected de novo deletion of chromosome 6q21q22.33. This region is pathogenic according to the DECIPHER and ISCA databases and contains 78 genes. Discussion: Phenotypic features such as mental disability, autism, delayed speech and language development, hypertelorism, microcephaly, strabismus, and wide nose bridge were noted in cases with similar deletions in previously defined regions. In this study, we aimed to contribute to the literature by presenting a case of 6q21q22.33 deletion with similar phenotypic features.

KEYWORDS: microcephaly, developmental delay, 6q21q22.33 deletion, microarray

S-05 - Interpretation of m.3243A>G in mtDNA in Clinical Expressivity Versus Tissue Heteroplasmy Ratios with Text Mining Analysis

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Introduction: MELAS (mitochondrial-encephalomyopathy, lactic-acidosis, and stroke-like episodes) is multisystem disorder, typically presented between the ages of two to 40 years, associated with pathogenic mtDNA variants. Approximately 80% of the patients present with m.3243A>G of MT-TL1 encoding mitochondrial tRNA-leucine1 (UUA/G). Clinical variability basically attributed to the mutation load in tissues. Material and method: 319 articles published on m.3243 A>G, between the years of 1995-2018, are investigated for the number of cases attributed with age of definitive diagnosis, gender, inheritance, clinical and biochemical spectrum and tissue distribution of the heteroplasmic ratios. Data recorded on spread-sheets, extracted to charts by using Vim text editor, statistical analysis performed with Python. Results: 468 out of 730 total reported atients' data with heter lasmy revealed. 42,9% had my athies (201/468), 30.8% had ne r l gi al symptoms (144/468), 16.7% had cardiovascular (78/468), 11% had ear/eye problems (53/468), and 4.1% had gastrointestinal complications. Methods of heteroplasmy measurements differed in reports. Clinical groups under additional findings of either with hearing loss, ocular abnormalities and endocrinological problems, 48 with 73.6±13.6%, 19 with 63.2±19.6% and 18 with 61.7±20.8% m tati n l ads were al lated. s le and bl d meas rements in 79 atients were 63.6±19.3% and 25.7±19.3%, res e tively. Similarly, 17 atients' rati s were re rted r rine and bl d, 55.9±21% and 20.7±10.4%, res e tively. Discussion: Leukocytes are the major tissue used in diagnosis, nevertheless has lower accuracy. Urine was as valuable as muscle for obtaining threshold values, moreover convenient since non-invasive. Majority of the m.3243A>G variant of mtDNA was associated with myopathic findings and least with episodic vomiting.

KEYWORDS: mitochondria, MELAS, mtDNA, m.3243A>G, heteroplasmy

S-06 - A six - year retrospective study of amniocentesis: one centre experience

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Objective: To retrospectively investigate the 6-year experience of prenatal diagnosis of fetal chromosome anomalies by second-trimester genetic amniocentesis. Material and Method: Data were collected at Trakya University Faculty of Medicine, Department of Gynecology and Obstetrics, Division of Perinatology between January 2013 and February 2019 from cytogenetic analyses of cultured amniocytes from second-trimester amniocentesis. The main indications for amniocentesis included abnormal first and second trimester maternal serum screening results, and abnormal ultrasound findings. After performance of ultrasound, amniocentesis was done by free hand technique between 15-24 weeks pregnancy, 20-22 G needle was used. 20 cc of amniotic fluid collected exluding 1 cc for maternal contamination. The cases are evaluated in respect to amniocentesis indication and genetic results. Results: A total of 749 amniocentesis were performed and analyzed for chromosome anomalies. Among these, 434 (%57,9) were for abnormal maternal serum screening results, 253 (%33,7) for abnormal ultrasound findings, and 62 (%8,4) for other reasons. Chromosomal anomalies were detected in 55 (%7,3) cases, including fetuses of 34 mothers with abnormal serum screening results, 21 mothers with abnormal ultrasound findings. Abnormal karyotypes were; 32 (%4,2) Trisomy 21, 7(%0,9) Trisomy 13 , 6(%0,8) Turner 45X0, 5 (%0,6) Trisomy 18, 2 (%0,2) Triploidy , 2 (%0,2) DiGeorge Syndrome (22q11.2), 1 (%0,1) Tetraploidy. Conclusions: Amniocentesis is still a widely used technique in prenatal diagnosis due to low fetal loss rate and high diagnostic ability. For daily practice, our data could offer a database for proper genetic counseling, such as termination issues and future pregnancies.

KEYWORDS: Amniocentesis, chromosomal anomalies, prenatal diagnosis

S-07 - The second reported family as Santos syndrome with a novel mutation in WNT7A

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Intr d ti n and Aim: "WNT7A-related syndr mes with ng eal and ib lar de e ts" s e tr m nsist Fuhrmann (FS), Al-Awadi/ Raas-Rothschild (AARS) and Santos syndrome (SS), which could be differentiated by clinical findings. SS (MIM #613005) was characterized by fibular agenesis or hypoplasia, clubfeet with oligodactyly, motion limitations of the forearms and/or hands, and severe nail hypoplasia or anonychia. It is the first time six patents from a Brazilian family have been described as SS with a different and milder phenotype comparing FS and AARS. Here we report a 7 year-old female with short stature, bilateral fibular agenesis, bilateral second finger nail hypoplasia, oligodactyly in left feet, bilateral clinodactyly and hypoplasia of right hand 5th metacarpal bone, movement limitations of right knee, elbow and other minor skeletal changes. His parents was first degree cousins. We aimed to elucidate molecular basis of this clinical picture. Materials and Methods: We performed sequencing of all exons and exon-intron boundaries of WNT7A in proband and dete ted variants' stat s were investigated ther amily members. es lts: A n vel h m zyg s missense mutation c.560C>T, in 3rd exon of WNT7A was detected in proband. Both of the parents and one of sibling were heterozygous carrier. This mutation was evaluated with ACMG 2015 criteria and classified as likely pathogenic. Discussion: The proband had the mildest phenotype comparing all patient with WNT7A mutations. Our family is the second report as SS in the literature. Evaluation of much more patients with WNT7A mutation will provides to better understand clinical spectrum of WNT7A disorders and involvement degree

KEYWORDS: WNT7A, fibular agenesis, nail hypoplasia, Santos syndrome, novel mutation

S-08 - Identification Of a Novel Mutation and Regression of Macular Edema with Topical Treatment in Gyrate Atrophy

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Gyrate atrophy (GA) is a rare autosomal recessive inherited metabolic disorder with an ornithine aminotransferase (OAT) enzyme deficiency, characterized by progressive and degenerative chorioretinal findings. The main complaints of GA patients during ophthalmologic examinations are a low vision, night blindness, and peripheral vision loss. Posterior subcapsular cataract, myopia, choroidal neovascularization, epiretinal membrane, and intraretinal cysts are the possible accompanying vision loss reasons. We report a patient with GA who had applied to our clinic with vision loss (20/100 for Snellen best-corrected visual acuity) secondary to posterior subcapsular cataract and intraretinal cysts in the retina. He was followed with an only topical treatment of brinzolamide (b.i.d) and nepafenac (t.i.d) eye drops without any diet modification or supplementation. One month after this treatment, we observed a significant resolution in his macular edema with 2 and 1 Snellen lines of visual gain in his right and left eye, respectively. Also, we detected a novel homozygous mutation in the Genetic assessment of the OAT gene: c.1253T>C (p.Leu418Pro). Recently, GA doesn't have unique and well-known therapy. Diet, vitamin supplements, systemic or topical carbonic anhydrase inhibitors (CAI), and non-steroidal anti-inflammatory drugs (NSAIDs) are the most used treatments for macular edema or retinal cysts. The benefit of these treatments is variable. Carbonic anhydrase inhibitors and/or NSAIDs may be useful to control macular edema and the genetic variants may be also a determinant in the responsiveness of the type of treatment.

KEYWORDS: macular edema, mutation, OAT

S-09 - A Very Rare Double Marker Chromosome Case:Phenotypic Variation of 8p Tetrasomy

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Marker chromosomes are reported in a frequency of1/2500 and 8p tetrasomy cases are seen extremely rarely. In this study,a case defining two different marker chromosomes arise from p arm of 8thchromosome was examined. A-16 year-old female patient referred to our clinic due to short stature and irregular menstruation cycles.In clinical examination, dysmorphic features were detected including buffalo hump at neck, facial hirsutism, stria at abdomen, partial syndactyly between 2nd-3rd toes. Her body height was 140cm(<3p) and she had menstruation twice per year. She also had mild intellectual deficiency and secundumtype atrialseptaldefect. Peripheral blood sample were cultured for72 hours and GTL banding was used for chromosome analysis.50 metaphases of 45 showed a marker chromosome,and also of 11 showed a second marker and karyotype was reported 47,XX,+mar1[34]/48,XX,+mar1,+mar2[11]/46,XX[5].Second marker expressed a centromere with C-banding.Both markers had no satellite at NOR-banding. Parent's karyotype were normal. XX signal pattern were detected and there was no signal for SRY region. Subtelomeric FISH analysis identified two additional signal patterns related to 8pter region on an extra chromosomal structure that suggest us 8p tetrasomy. For molecular karyotyping, Affymetrix Cytosan Optima(315K)microarray system was used and the results were analyzed in CHAS3.2.0/GRCh37/hg19programme. A tetrasomy of 11788 kbp was observed including the 8p23.3p23.1 region and a trisomy of 5887 kbp was observed including the 8p11.21q11.1 region in the microarray analysis of the patient,and reported as arr[hg19]8p23.3p23.1(158048_11945856)x4,8p11.21q11.1(41666354_47553557)x3. Patient's findings support that marker hr m s mes has a variety lini al indings and it’s aimed t dis ss the ase in the ntext phenotypic expression.

KEYWORDS: Marker chromosome, 8p tetrasomy, mosaic karyotype, dysmorphology

S-10 - Diagnosis of a rare disease with variable phenotype in two patients via "genotype to phenotype" approach: Desbuquois dysplasia 1

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Introduction and Aim: Desbuquois dysplasia 1(DBQD1), is an autosomal recessive inherited chondrodysplasia that has highly variable phenotype including short stature, dysmorphic findings, joint laxity, advanced carpal ossification, intellectual disability, developmental delay and hypotonia. The patients with this rare disease caused by mutations in the CANT1 gene could have severe findings result with death in utero or survive to adulthood with normal intelligence. Here, two patients have been reported with homozygous CANT1 mutations diagnosed via exome sequencing. Material and Method: Patient one was a 13-year-old male whose parents were consanguine, was evaluated for short stature, skeletal dysplasia, mild intellectual disability, joint laxity and osteoporosis. He had also a sister who died at the age of 4 due to suspicion of mitochondrial myopathy. The second patient was a two-months-old male with multiple anomalies such as intrauterine onset growth retardation, prematurity, congenital glaucoma, joint laxity, hepatomegaly and hydronephrosis and died after a month. There was also consanguinity between his parents. Two of them were evaluated with whole exome sequencing. Results: Two of the patients were diagnosed with DBQD1 with the presence of homozygous CANT1(NM_001159773.1):c.898C>T mutation in the first patient and homozygous CANT1(NM_001159773.1):c.375G>C mutation in the second one res e tively. Dis ssi n: “Phen ty e t gen ty e” a r a h has been m stly sed r the diagn sis DBQD1 t date. I y d n t have m h time for clinical diagnosis and there is an individual with additional findings in the family, WES is useful for diagn sis with sing “gen ty e t hen ty e" a r a h.

KEYWORDS: Desbuquois Dysplasia 1, CANT1, Whole Exome sequencing

S-11 - LAMM SYNDROME; TWO NEW PATIENTS, ONE NOVEL MUTATION AND ONE NEW MECHANISM

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İntr d ti n: LA syndr me is a rare a t s mal re essive syndr me hara terized by mi r tia, mi r d ntia and inner ear abnormalities like Michel aplasia (labyrinth aplasia). Mutations in the FGF3 gene cause LAMM syndrome. FGF3 gene is localized on 11p13.2-p13.3 and has 3 exons. Up to date, 20 mutations are identified in the FGF3 gene. Cases: Our first patient is a 6 years old girl whose parents are consanguineous and who has congenital deafness because of Michel aplasia and microtia. We thought it could be LAMM Syndrome so designed primers for FGF3 gene. DNA Sequencing analysis of FGF3 gene revealed a novel homozygous missense mutation c.8C>T (p.Leu3Arg) in FGF3 gene. Segregation analysis of probands' parents revealed that they are both heterozygous for this novel mutation. The second patient is a 6 years old boy. He also had microtia, microdontia, and Michel aplasia. His parents are the first cousins. After FGF3 sequencing we found homozygous c.324+2T>C mutation in exon 2. Until now no pathogenic mutations have identified in databases such as HGMD, ClinVar that affect splicing. In silico analysis predicted this mutation as pathogenic. After segregation analysis of his parents, they were found to be heterozygous carriers. Conclusion: We have planned to do a functional analysis for this new mechanism to prove that this mutation has damaging effects on protein function. If we show that c.324+2T>C mutation affects protein function it will be the first splice site mutation reported for this gene. Our study will expand the mutation mechanisms for this rare disease.

KEYWORDS: FGF3, Splicing mutation, Deafness, Inner ear abnormalities, Microdontia

S-12 - Molecular diagnosis of connective tissue disorders using targeted gene panel screening

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Introduction and Aim: Disorders effecting human connective tissues including Marfan Syndrome are observed in people with a wide range of symptoms effecting multisystems in human body. Molecular diagnosis of these diseases is highly important in order to detect the specific gene variations causing abnormal proteins of connective tissue. Materials and Methods: DNA was isolated from peripheral blood of 19 patients showing symptoms for connective tissue disorders. All exons and exon-intron boundaries of 19 Connective Tissue Disorders related genes were sequenced in MiSeq (Illumina) System. Virtual panel was created using 19 Connective Tissue Disorders related genes. Additionally, FBN1 gene screening was performed in 23 patients with Marfan Syndrome using Marfan MasterDX Assay(Multiplicom) and MiSeq (Illumina) instrument. Sophia DD lat rm and S hia Geneti s' OKA s tware was sed r variant analysis and ann tations. Pathogenicity of variants were analyzed using online tools (HGMD, ClinVAR, MutationTaster, SIFT, Polyphen) and ACMG criteria. Results and discussion: Creating virtual panel for connective tissue disorders becomes more important since this group of diseases have a broad phenotypical spectrum.We identified 120 variants totally (1 Likely pathogenic, 22 Variant of uncertain significance) and 7 of them were novel variations in; FBN1, MYLK, SMAD6 and FLNA genes. Two patients with Marfan symptoms tested FBN1 gene and found no mutation then they were also screened in connective tissue gene panel. No mutation was detected in one of them while other case had VUS variants in genes associated with his connective tissue phenotype.

KEYWORDS: connective tissue disorders,marfan.nextgen

S-13 - Reverse phenotyping revealing rare ADAM22 gene mutation detected by whole exome sequencing in 2 early infantile epileptic encephalopathy siblings.

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Early infantile epileptic encephalopathy 61 is a very rare disorder which caused by mutations of the ADAM22 gene. ADAM22 gene is a member of the ADAM (a disintegrin and metalloprotease domain) family and members of this family are membrane-anchored proteins structurally related to snake venom disintegrins, and have been implicated in a variety of biological processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis. Unlike other members of the ADAM protein family, the protein encoded by this gene lacks metalloprotease activity since it has no zinc-binding motif and this gene is highly expressed in the brain and may function as an integrin ligand in the brain. We present 2 siblings with homozygous mutations in ADAM22 gene detected by whole exome sequencing. First case was 8 years old boy. When he was one month old he had contractions of the whole body and seizures. His sister, 6 years old she had similiar clinical findings at the same age. Parents were first degree cousins. Both cases have homozygous c.818 C>A (p.Ala273Glu) mutations in the ADAM22 gene. Herein, we describe 2 patients with ADAM22 gene mutations which were reported very rarely. We emphasize the importance of WES analysis leading to reverse phenotyping in diagnosis of rare autosomal resessive disorders.

KEYWORDS: ADAM22, encephalopathy, infantile, epilepsy

S-14 - The Usefulness Of Whole-Exome Sequencıng In A Patient Wıth A Broad Clinical Spectrum

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Introduction and Aim: Mitochondrial diseases are notoriously difficult to diagnose due to extreme locus and allelic heterogeneity, with both nuclear and mitochondrial genomes potentially liable. Also, in cases in which patients have a broad clinic spectrum, more than one mutation may lead the clinical findings. Using whole-exome sequencing we demonstrate the ability to rapidly and cost-effectively evaluate the nuclear genome to obtain a molecular diagnosis of mitochondrial disorders. Moreover, detection of coinciding mutations in a patient may explain additional clinical findings. Material and Method: Chromosomal abnormalities were excluded by conventional karyotyping and microarray. DNA was isolated from peripheral blood samples. First, mtDNA sequence analysis was performed and the result was normal. Subsequently, whole exome sequencing was performed. All variants were confirmed by Sanger sequencing method. Results: Patient was referred to our clinic with suspicion of mitochondrial or metabolic disease based on these findings: hypotonia, blindness, cortical and frontal atrophy on MRI and unexplained anemia. Sequence analysis of the patient revealed a novel homozygous c.151C>G mutation on UQCRQ gene (Mitochondrial complex III deficiency, nuclear type 4, AR). Additional mutations we detected are; a heterozygous c.2011dupA on RP1 gene (retinitis pigmentosa type1, AD), a heterozygous c.223dupC on NRL gene (retinitis pigmentosa type27, AD), a heterozygous c.10859T>C on USH2A gene (retinitis pigmentosa type 39, AR) and a heterozygous c.7189delG on PIEZO1 gene (hemolytic anemia). Discussion: Using whole exome sequencing in a patient with a broad clinic spectrum may be useful because of cost-effectiveness and also can provide rapid diagnosis.

KEYWORDS: Mitochondrial disease, Whole-exome sequencing

S-15 - Diagnosing process in a newly described extremely rare disease by whole exome sequencing re-analysis

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Whole exome sequencing (WES) is a genetic diagnosis method that is widely used in routine practice in the diagnosis process of rare diseases. However, in some cases, if a mutation cannot be detected in known genes, it becomes difficult to diagnose. Therefore, re-analysis of such patients is recommended at regular intervals. Here, we report a patient with an extremely rare new disease diagnosed via WES re-analysis in whom first WES analyasis revealed no known variants in 2016. A 3-year-old male patient, who was the first child of the consanguinios couple, presented with muscle weakness, gait disturbance and speech disorder. As a result of the investigations, cerebellar atrophy was detected in cranial MRI. The patient did not have significant dysmorphism, and a specific genetic diagnosis could not be considered at the initial examination. Chromosome analysis and arrayCGH analysis were performed and the results were normal. After that Trio-WES analysis was planned and the WES result was reported as normal in 2016. Two years later, the re-analysis at the end of 2018 revealed a de novo variant of NM_001328: exon8: c.1024C> T (p.R342W) in the CTBP1 gene. We saw that this mutation of CTBP1 gene was defined as the cause of "HYPOTONIA, ATAXIA, DEVELOPMENTAL DELAY, AND TOOTH ENAMEL DEFECT SYNDROME; HADDTS (OMIM # 617915)" in 2018, and only 4 cases was reported so far in the literature. Periodic re-analysis of WES data would increase the diagnostic rate of WES in negative cases.

KEYWORDS: whole exome sequencing re-analysis rare disease

S-16 - A case with multiple dislocations associated Larsen Syndrome; a novel variant of FLNB gene

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Introduction The FLNB gene encodes Filamin B protein which helps building the network of protein filaments (cytoskeleton) that gives structure to cells and allows them to change shape and move. Filamin B is involved in the development of the skeleton before birth and expressed in many cells included chondrocytes. The FLNB related disorders, which are Boomerang dysplasia, Atelosteogenesis type I and III, Spondylocarpotarsal synostosis syndrome and Larsen syndrome (LS), present highly variable clinical features. LS is a rare skeletal dysplasia characterized by congenital dislocation of large joints, foot deformities, scoliosis and distinctive craniofacial abnormalities. The diagnosis is based on clinical and radiographic findings confirmed with FLNB molecular genetic testing. Case report A premature newborn with multiple congenital joint dislocations has been sent for consultation. He had bilateral knee dislocations, congenital hip dislocation, equinovarus, camptodactily. In his follow-up he could manage to seat with support after several operations and physical rehabilitations at two years old. He has mild intellectual disability. Although he has minor facial dysmorphism, we performed clinical exome sequencing test because of multiple dislocations. We determined c.236dupA p.(Asn79Lysfs*12) variant at exon 1. Discussion and Conclusion According to Uniprot and Clinvar data, 289 variants of the FLNB gene have been reported to date. From 36 pathogenic and likely pathogenic variants 31 were missense, 3 nonsense and 2 frameshift mutations. We described frameshift mutation but still need to verify it with Sanger sequencing. This is a novel variant associated with LS. References 1. Stephen Robertson, FLNB-Related Disorders, 2013 GeneReviews

KEYWORDS: FLNB gene, multiple dislocation, Larsen Syndrome

S-17 - Contribution of microtubule-regulatory proteins to SMA pathomechanisms

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Introduction and Aim: Spinal muscular atrophy (SMA) is a neurodegenerative disease with an incidence of 1 in 6000-10.000 live births. Survival of motor neuron 1 (SMN1) mutations are responsible from the loss of SMN protein, leads to impairments in various cellular functions including snRNP biogenesis and endocytosis. Defects in SMN-deficient models indicated an involvement of SMN to the regulation of cytoskeleton, especially in neurons. In an in-vitro SMA model, we previously detected an upregulation in microtubule-associated protein 1B (MAP1B), regulatory protein for microtubule dynamics. MAP1B regulates microtubule structure with its interaction partners, tubulin tyrosine ligase (TTL) and end-binding 3 (EB3). TTL functions in alpha tubulin tyrosination, while EB3 plays role in microtubule growth, therefore in this study we investigated whether these proteins are also dysregulated in SMN-deficient cells. Material and Method: TTL, EB3 and tubulin detyrosination levels were analyzed by Western blot in SMN knock-down NSC34, motor neuron-like cell line. Alterations in microtubule re-polymerization were investigated by immunoflourescence microscopy. Results: Western blot results showed an upregulation in TTL and downregulation in alpha tubulin detyrosination in SMN knock-down cells. A significant downregulation in EB3 protein level was also found in SMN-depleted cells compared to controls. Quantitative immunoflourescence analysis showed an alteration in microtubule re-polymerization in SMN deficient cells. Discussion: Our results suggest that dysregulated MAP1B together with TTL and EB3 may affect structural properties of microtubules. Further studies are ongoing to investigate functional consequences of EB3 reduction.This study was supported by Hacettepe University S ienti i esear h Pr je ts C rdinati n Unit (TYL201817434,THD201712939), TÜBİTAK (216S770).

KEYWORDS: Spinal muscular atrophy, microtubule, MAP1B, EB3, TTL

S-18 - A Case With Rare Compound Heterozygous FBN1 Gene Mutation

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In this report, we aimed to discuss the uncommon FBN1 gene compound heterozygosity in a family.An 11 weeks pregnant case was directed to our clinic due to a history of unknown neonatal death at 3rd day. The baby's l w-hairline, beaked nose and arachnodactyly were remarkable.No consanguinity between parents was reported. It was learned that they had cardiac valve disease which was not followed up. In the surveillance of the pregnancy amniocentesis was performed and consistent with normal karyotype. However intraventricular hemorrhage, cardiac failure and non-immune hydrops fetalis were detected in 32th weeks fetal USG. In the physical examination of the parents, father was detected to have pectus excavatum and chest asymmetry, wrist and thumb sign and pes planus.Mother was remarkable for dolicocephalia, downslanting palpebral fissure, prominent nose, dental abnormality and arachnodactyly. Parents were decided to be searched related to marfanoid habitus. In father, scoliosis, lens subluxation and myopia, mitral valve propalsus (MVP) and dilated ascending aorta anomalies were found. Mother had MVP and glaucoma. Karyotype analysis and FBN1 gene analysis were planned to the parents. A novel, frameshift, heterozygous, pathogenic c.7603_7604delTG mutation was detected in mother, and father was found to carry a missense heterozygous c.4192G>A (D1398N) variation in FBN1 gene. And we confirmed that fetus had carried both mutations.Compound heterozygosity in the FBN1 gene is a rare condition. There are limited contradictory publications in the literature about the degree of clinical findings. Mutations related to the FBN1 gene and their reflections in our case were compiled

KEYWORDS: FBN1, compound heterozygous, intrauterine death

S-19 - Heterogeneous Etıology Of Hearing Loss-Molecular Analysis

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Introduction and Aim: Hearing loss is the most common sensory defect around the world. Hearing loss may be syndromic or non-syndromic and nearly 50 % of it is due to genetic causes. Variety of protein coding genes such as gap junctions, motor proteins, cytoskeletal, ion channels, structural proteins, transcription factors and additionally microRNA genes are involved in hearing loss etiology. Material and Method: 35 cases (23 females, 12 males, mean age 21.31) were referred to Trakya University Medical Faculty Medical Genetics Department with hearing loss. In all cases 82 genes were sequenced with QIAseq Targeted DNA Panel kit (CDHS-14623Z-3968) in Illumina MiSeQ system. Results: Pathogenic variations in 18 cases (51.42 %), variants of unknown clinical significance (VUS) in 13 cases (37.14 %) were detected. Pathogenic variations were detected on GJB2, SMPX, MYO7A, GATA3, USH2A, TECTA, MYO15A, MYH9, MARVELD2, PCDH15, WFS1, SLC26A4, TMIE, CDH23, OTOGL, TRIOBP genes. Variants of unknown clinical significance were detected on GJB2, TECTA, USH2A, OTOGL, MYO15A, OTOG, MYH9, PTPRQ, CDH23, CLDN14, SMPX, ADGRV1, POU3F4, SLC26A4 genes. Discussion: The main problem in the deafness etiology is its heterogenicity. Analysing various genes for deafness etiology will be cost-effective and time-saving in diagnosis. Early diagnosis is important in speech progression and social skills of the children which would lead to better life of these individuals. The benefits of this understanding and knowledge, not only help the families of at risk but also may help in treatment, control and genetic counselling of hearing loss.

KEYWORDS: Hearing loss, Next Generation Sequencing, Sensory Defect

S-20 - Ellis Van Creveld Syndrome: Report of Four New Cases

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Aim: Ellis van Creveld (EVC) Syndrome with the other name chondroectodermal dysplasia is a rare autosomal recessive disorder. It affects mainly skeletal system, oral cavity and heart. Short limbs, short stature, narrow thoracic cage, axial or postaxial polydactyly, hypoplastic nails, multipl oral frenulas, hypodontia are typical findings of the disease. Nearly 60 % of the patients have congenital heart defects. The typical heart defect is a wide atrial septal defect (ASD) creating single atrium appearance. The causative genes are EVC and EVC2 genes. This dis rder is art a gr dis rders alled " ili athies", in di erential diagn sis we sh ld consider short rib thoracic dysplasias as short rib polydactyly and Jeune syndromes in this group. Here we report four new cases of EVC Syndrome. Cases: Two of our patients (3 boys, one girl) were diagnosed in the newborn period, the others were diagnosed in the first year of life. The follow up period was changing from10 months to 7 years. All had polydactyly, short stature, short limbs, narrow thoracic cage, hypoplastic nails, hypodontia, multipl frenulas. One had bifid tip of the tongue. Two patients got single atrium type ASD. One patient got a mutation in EVC gene (homozygous p.Leu620_Leu626del (c.1858_1878del21)), one patient got mutation in EVC2 gene (homozygous p.Leu263Profs*10 (c.788_794delTGGAACC)). The others probably got intronic or large deletion-duplication kind mutations preventing PCR of some parts of EVC gene. Conclusion: We resented new ases EVC Syndr me and we shared r ex erien e this dis rder's diagn sis and follow up.

KEYWORDS: Ellis van Creveld Syndrome, EVC, EVC2, Short Rib Thoracic Dysplasia, Chondroectodermal Dysplasia

S-21 - ATN1 gene mutation in patients with Huntington disease-like phenotype

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Introduction and Aim Huntington disease (HD) is a neurodegenerative disorder characterised by chorea, cognitive decline and behavioural disturbances. Approximately 99% of patients have CAG repeat expansion in HTT gene. Patients lacking HD mutation are said to be HD phenocopies and there are several genetic conditions called HD-like syndromes leading to HD phenotype. Dentatorubral-pallidoluysian atrophy (DRPLA) is one of the most frequent disorders among them therefore we aimed to investigate ATN1 gene mutation, responsible for DRPLA, in these patients. Material and Method Eighty-four patients with HD phenotype, negative for HTT and TBP mutations, were included in the study. ATN1 CAG repeat region was amplified by polymerase chain reaction (PCR) with labeled primers and PCR products were analysed by fragment analysis on ABI3130 Genetic Analyzer. Results Two patients (2.4 %) were found to have ATN1 gene CAG repeat ex ansi n in ll enetran e range (≥48 CAG re eats). In ne these atients, there was a str ng amily history of epilepsy, a suggestive finding of DRPLA, both in juvenile and adult cases. The other patient was of Azerbaijani origin. Discussion DRPLA is predominantly seen in Japanese population and is extremely rare in other ethnic groups. It is also reported that HD-like syndromes are responsible for only 1-7 % of patients with HD phenotypes. Despite the low frequency of these syndromes in this group of patients and their variable prevalance among different populations, the identification of genetic basis is important for genetic counseling and prediction of the clinical course of the disorder.

KEYWORDS: Huntington disease, Huntington disease-like syndromes, Dentatorubral-pallidoluysian atrophy, Huntington phenocopy

S-22 - A Rare Case with Warkany Syndrome (Trisomy 8 Mosaicism)

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Trisomy 8 mosaicism syndrome (T8mS) also known as Warkany syndrome is a rare genetic condition characterized by extreme phenotypic variability ranging from severe congenital malformations to minor dysmorphic changes. The most common clinical features of this condition are mental retardation and vertebral anomalies. Here, we present a case with a diagnosis of T8mS who was followed up due to syndromic appearance and mental retardation. A 12-year-old boy admitted to our outpatient clinic with hearing loss and mental retardation. On his physical examination dysmorphic appearance with flattened nose root, wide nose wings and scoliosis was detected. He has speech disorder, severe constipation, frequent re rrent ral a t. İt was learned that; he was treated r e ile ti seiz re and hy erbilir binemia r 21 days in the newb rn ıntensive care unit. Liver hemangiomas, single kidney, ASD, myopia and hearing loss was detected in laboratory and clinical examinations. Karyotype analysis by GTG banding result was 47,XY,+8[7]/46,XY[23] and in FISH analysis three signals were observed in 40% of cell confirming three copies of chromosome 8. Karyotyping of both the parents was normal. Molecular karyotyping analysis (microarray) was performed to exclude additional genetic variations. There was no other structural changes than T8mS. We think that in each case of mental retardation with or without other dysmorphic finding, it is necessary to make a cytogenetic analysis. Postponement of Genetic investigation in too many cases with dysmorphic features is still a problem.

KEYWORDS: Warkany Syndr me, T İSO Y 8, are Disease, T8mS, m sai ism

S-23 - TWO NOVEL VARIANTS OF AGL AND GBE1 GENES IN GLYCOGEN STORAGE DISEASE PATIENTS

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Glycogen storage disease (GSD) results from deficiencies of various enzymes or transport proteins in glycogen metabolism pathways. In this case, we aimed to present two cases with novel variants in *AGL* and *GBE1* genes respectively that may be associated with the pathogenesis of glycogen storage disease.

First case was a 9-year-old male presented to our clinic with hepatomegaly and muscle weakness. Pathology report for liver biopsy was consistent with glycogen storage disease. Echocardiography showed mild left ventricular wall hypertrophy. Family history gave no additional clues and parents were not consanguineous.

Second case was a 21-months-old girl referred to clinic with hepatosplenomegaly and elevated liver enzymes. On physical examination microcephaly was notable. Abdominal ultrasonography revealed grade 2 hepatosteatosis. Patient also had thrombocytopenia and anemia on complete blood counts. Bone marrow aspiration revealed Niemann-Pick foamy histiocytes. Family history was not remarkable.

Next generation sequencing (NGS) for GSD was ordered for both cases.

For first case sequencing revealed likely pathogenic c.4295_4296insA variant in exon 32 and probable pathogenic, nonsense c.1999 C>T novel variant in exon 15 in trans position of *AGL* (ENST00000294724) gene. GSD type III diagnosis was made.

Sequence analysis of second case revealed homozygous, novel, likely pathogenic c.1561 A>G (p.K521E) variant in *GBE1* gene which is compatible with GSD type IV.

It may be good practice to consider GSD in broader spectrum because of ever growing patients with atypical presentations of the disease. With massive parallel sequencing techniques GSD diagnosis is becoming more effortless and less invasive.

KEYWORDS: GLYCOGEN STORAGE DISEASE, AGL, GBE1, NOVEL MUTATION

S-24 - Clinical Exome Sequencing Analysis for Diagnosis of Retinitis Pigmentosa and Vision Loss

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INTRODUCTION: Retinitis pigmentosa (RP) includes a group of clinically and genetically heterogeneous inherited retinal dystrophies with the primary degeneration of rod and cone photoreceptors. Patients with RP have autosomal dominant, autosomal recessive, X-linked or digenic inheritance. More than 80 genes have been related with RP. This complex heterogenity could be a confusing when finding underlying mutated gene. RP is a most known cause of visual disability and it's revalen e is variably re rted in ne ase r ea h 2500-7000 persons. METHOD: For forty three patients with initial clinical diagnosis is RP or vision loss, we made clinical exome sequencing that contain 4493 gene using Illumina NextSeq-500 sequencer with Sophia Genetics Clinical Exome Solution kit verion-2. All single nucleotide variations (SNV) and also copy number variations (CNV) have analyzed by S hia DD ® S tware with iltering retinal disease related 650 genes. ESULTS: F r fortythree patients we found mostly novel mutations on different 60 genes. There is no recurrent mutations or copy number variation mutations. CONCLUSION: RP/ vision loss genetics is very heterogenous. There is no hotspot genes or mutations. Half of patients have multiple variant of uncertain significance mutation (VUS) then require segregation analysis. Not a single gene or oligogenic sequence panels could be successfull method for diagnosis of RP. We will have better understanding of the Turkish RP patients mutation spectrum with our findings.

KEYWORDS: Clinical Exome Sequencing, Retinitis Pigmentosa, Genome Editing

S-25 - A New Approach (EDIZ) for Big Data Variant Prioritization

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Whole exome sequencing (WES), workflow consists of the following steps: raw data quality assessment, pre-processing, alignment, post-processing, variant calling, annotation, and prioritization. WES of human samples was reported to detect approximately 20,000–30,000 SNV and indel calls on average. So, it is very important to choose the best tool that suits the related study.In this study, we aimed to upgrade our previous in-house variant prioritization method (SELIM) in order to analyse WES data without using in-silico methods. By this method, the annotated data have been decreased by means of 52.3 times. So, we both established a successful WES workflow for increasing the diagnostic rate of patients with reducing the raw data. Recently, we are also building a web based workflow in order to help the users from all over the world.

KEYWORDS: Whole exome sequencing, variant prioritization, dataset

S-26 - A novel mutation of a rare genetic condition: Primary hypertrophic osteoarthropathy

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Introduction and Aim Primary hypertrophic osteoarthropathy (PHO), also named pachydermoperiostosis, is characterized by clubbed nails, periostosis, pachydermia(1). There are two subtypes; primary hypertrophic osteoarthropathy, autosomal recessive 1 (PHOAR1) and 2 (PHOAR2) caused by HPGD and SLCO2A1 gene deficiency, respectively(1). Material and Method An 18 years old boy was referred to us with coarse face. Clinical features were thi kened a ial skin, rr wed rehead, ain knees at d rsi lexi n. O r atient's m laints started with re bertal eri d and had anemia a ew years ag b t existn't n w. adi gra hi features were supporting PHO. Echocardiogram revealed a mild tricuspid regurgitation. There was a HPGD gene analysis report revealed no mutations. We planned SLCO2A1 gene analysis. Results SLCO2A1 gene analysis revealed c.86delG(p.G29Afs* 48) mutation which classiefied as likely pathogenic in silico analysis. This mutation was a novel homozygote, frameshift mutation in exon1 of SLCO2A1. We diagnosed the patient as PHOA 2 with th se indings. Dis ssi n O r atient's maj r m laint was his a ial a earen e. Botulinum injections and plastic surgery may improve the appearance of the face and scalp(2). Founded mutation is a novel homozygote, frameshift mutation not reported before and can contributed to the literature. References 1.Hou Y, Lin Y, Qi X, Yuan L, Liao R, Pang Q, et al. Identification of mutations in the prostaglandin transporter gene SLCO2A1 and phenotypic comparison between two subtypes of primary hypertrophic osteoarthropathy (PHO): A single-center study. Bone. 2018 Jan;106:96-102. 2.Schwartz RA, Goyal S, Richards GM. Pachydermoperiostosis Treatment & Management.2018. https://emedicine.medscape.com/article/333735-overview

KEYWORDS: Primary hypertrophic osteoarthropathy, pachydermoperiostosis, SLCO2A1 gene

S-27 - A rare case of severe microcephaly caused by pathogenic variant of NDE1

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Introduction and Aim: NudE Neurodevelopment Protein 1 (NDE1) gene encodes a protein required for microtubule organization, mitosis and neuronal migration. Homozygous pathogenic variants of NDE1 is associated with severe microcephaly, neuronal migration defect and profound developmental delay. Here we report a 20 year old male patient referred to our clinics due to microcephaly and intellectual disability. Material and Method: Conventional cytogenetic and clinical exome sequencing analyses were performed on peripheral blood sample of the patient and his parents. Results: Head circumference of the patient was 40 cm (-10SD) and he had severe global developmental delay as he has never lifted his head, never sat or never talked. His psychical examination was consistent with mild dysmorphic features. He had joint contractures and scoliosis because of being bedridden for years. Cranial CT revealed that the brain structure was not normal and there was excess of cerebrospinal fluid on supratentorial region. The parents were nonconsanguineous but they were from the same village. The other two pregnancies of the family were terminated because of microcephaly during prenatal period and another one was spontaneously aborted. Chromosomal examination showed normal karyotype and homozygous c.680_681delAC (p.P229W*85) change in NDE1 gene was found by clinical exome analysis. Both parents were heterozygous carrier of the same variant. Discussion: The variant was reported before and deleterious effect of it was shown by functional studies. There are only few papers about NDE1-related disorders, therefore clinical findings of our patient is important to clarify phenotypic spectrum the disease.

KEYWORDS: microcephaly, NDE1, NGS

S-28 - Novel LEPR and MC4R gene mutations in two early onset obesity patients

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Introduction and aim: Leptin is mainly secreted from the adipose tissue, acts on the leptin receptors in the hypothalamus and activates MC4R pathway to control eating behavior and energy metabolism of body. Inactivating mutations of MC4R pathway genes such as LEPR and MC4R cause early onset obesity. We aim to present the characteristics of two morbid obese cases with a novel LEPR and MC4R gene mutations. Material and Method: We studied monogenic obesity gene panel by next generation sequencing analysis (NGS). Results: Our first case was 23 months old male patient. His weight gain started in the first few months with hyperphagia. His BMI was 27.74 kg/m2 (5.05SDS). FSH result was 0.38 mIU/ml (1.27-19.26). His parents were first degree cousins. In NGS analysis, we detected novel, homozygous c.1603+2T>C variaton on the LEPR gene (ENST00000349533.6). Our second patient was 15 years old male who was suffered from obesity since he was 5 years old. We detected novel, heterozygous c.655G>A variation on the MC4R gene (ENST00000299766). Discussion: Monogenic obesity syndromes may cause endocrine problems such as hypogonadotropic hypogonadism and hyperinsulinemia. After detection of pathogenic variation both of our cases were started to follow up by pediatric endocrine clinic. Also after genetic diagnosis patients may benefit from potential treatments with MC4R agonists such as setmelanotide. In conclusion, the importance of MC4R pathway genes in early onset obesity patients has been demonstrated and two novel pathogenic variants in LEPR and MC4R genes have been presented.

KEYWORDS: early onset obesity, LEPR gene, MC4R gene, novel mutation

S-29 - Spectrum of Skeletal Abnormalities and Pathogenic RUNX2 Variants in 50 Cleidocranial Patients from Turkey

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Introduction: Cleidocranial dysplasia (CCD, MIM #119600), is a rare autosomal dominant disorder, caused by pathogenic variants of RUNX2, encoding a member of RUNX family transcription factor that is known to regulate amelogenesis, osteogenesis, and involved in osteoblast differentiation. Short stature, facial dysmorphisms, cranial, skeletal and dental abnormalities are the characteristic findings. Genotype-phenotype correlation of CCD cases in the context of clinical and radiological findings is investigated and pathogenic variant frequencies are reported. Material and Methods: 50 CCD patients (29 index, 21 their afflicted family members) investigated for clinical, radiological and genetic findings. Algorithmic genetic approach is followed by Sanger sequencing of RUNX2 gene as the initial test, followed by MLPA (P-080), only for the cases with incompatible sequence result. Results: Graphies of 36 patients from 28 families were analyzed for morphological features. The most frequent radiological findings are persistent metopic suture, supernumerary teeth, hypoplasia/aplasia of the lateral clavicle, hypoplasic iliac wing. Brachycephaly frequency was between 80-98%. 28 of the families disclosed with 18 different pathogenic variants, 9 being novel. Missense in 10, frame shift in eight, nonsense in four, splice site in three and gross deletion in a single patient were revealed. Discussion: Mutation detection rate (93%; 27/29), was higher than the reports in the literature. This may be due to the strict clinical criteria applied to families for the enrollment to the investigation. Broad femoral head with short femoral neck was frequent while hypoplasia of femoral head was infrequent radiological marker for our CCD cases.

KEYWORDS: Cleidocranial dysplasia, skeletal findings, RUNX2, clavicular aplasia-hypoplasia

S-30 - Investigation of Genetic Causes in Oculoauriculovertebral Spectrum

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Oculo-Auriculo-Vertebral Spectrum(OAVS) is a genetically and phenotypically heterogeneous disorder and considered as a neurocristopathy due to developmental defects of first and second branchial arches. Main clinical findings consist of microtia, skin tag, hemifacial microsomia, epibulbar dermoid and vertebral anomalies. The underlying etiology is complex since genetic, epigenetic and environmental factors are involved. We report on 23 OAVS patients with diverse clinical and molecular findings. Patients were screened for copy number variations (CNVs) using the Affymetrix CytoScan Optima platform and also screened for MYT1 mutations. Furthermore, two patients underwent WES analysis. Using these approaches, three CNVs were found and considered potentially pathogenic. An additional derivative chromosome that consists of de novo unbalanced translocation between the chromosomes X and 4 was also shown and thought to be pathogenic. In this context, in order to determine the X inactivation pattern and the spreading of X inactivation throughout the 4th chromosome, fluorescent immunostaining was planned using BRDU antibodies. Lastly, WES analysis revealed novel heterozygous mutations in RNF213 and EFTUD2 that were previously suspected as candidate genes for OAVS. Duplication of 16p13.11 region, aneuploidies of X chromosome and single point mutations were previously implicated in OAVS molecular etiology. In this study we further strengthen the genetic heterogeneity of OAVS by identifying several CNVs and single gene defects in the patients and confirm the importance of microarray-based studies and WES analysis in a complex phenotypic disorder such as OAVS. This study was supported by H.U. Faculty of Medicine Scientific Research Projects Coordination Unit (TTU-2018-16935).

KEYWORDS: OAVS, neurocristopathy, microarray, 16p13.11, EFTUD2

S-31 - MICROCEPHALIC OSTEODYSPLASTIC PRIMORDIAL DWARFISM TYPE II CASES WITH NOVEL MUTATIONS HAVING CENTRAL NERVOUS SYSTEM EVIDENCE WITH EARLY AND LATE-ONSET

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Microcephalic osteodysplastic primordial dwarfism type II (MOPD II) is a rare, autosomal recessive genetic disorder characterized by prenatal and postnatal growth retardation, microcephaly, distinct facial features (prominent beaked nose, receding forehead), characteristic skeletal dysplasia, abnormal dentination, an increased risk for cerebrovascular disease, and insulin resistance. It is associated with defects in the pericentrin (PCNT) gene, which encodes a centrosomal protein functioning in the organization of mitotic spindles. Here we report two MOPD II cases with early and late-onset of central nervous system findings They were affected by severe intrauterine and postnatal growth retardation, microcephaly and facial dysmorphisms. Both of them were born to consanguineous parents at term. The patients were diagnosed as MOPD II on the basis of clinical and radi l gi al eat res skeletal dys lasia. The atients' DNA seq en ing the PCNT gene revealed tw n vel homozygous pathogenic variations in exon 25 (c.4652_4653delAG, homoallelic) leads to a premature stop codon (p.E1554Vfs*4) of the boy and in exon 5 (c.844dupG, homoallelic) leads to a premature stop codon (p.E282GVfs*46) of the girl. When the boy was 2 years 5 months old right sided hemiparesis was developed. Then infarct areas and findings concerning with moyamoya disease were detected in brain imaging. Psychotic symptoms such as persecution and reference delusions, agitation, visual and auditory hallucinations became apparent after a reduction mammoplasty operation of the girl at 21 years old. Brain imaging revealed no evidence to explain this condition.

KEYWORDS: microcephaly, dwarfism,central nervous system, novel mutation

S-32 - A de novo novel frameshift variant in thepenultimate exon of FBN1 gene cause of rare Marfan lipodystrophy syndrome

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Introduction: Marfan lipodystrophy syndrome (MFLS) or Progeroid Marfan syndrome is a rare, FBN1 gene-related disorder which is characterized by congenital lipodystrophy, marfanoid facial features, tall stature, arachnodactyly, hyperextensibility of the finger joints, myopia and normal psychomotor development. Case: We report a 10-year-old boy who presented neonatal progeroid features, congenital lipodystrophy, and marfanoid features. He also was diagnosed with bilateral lens subluxations. For these reasons, we carried out the FBN1 gene analysis. We found a heterozygous, de novo, novel frameshift variant in the penultimate exon (NM_000138.4/Exon 65; c.8188delC, p.Arg2730Glyfs*22) of FBN1 gene. This variant was not observed in the arents the atient. The variant nsidered as " ath geni " a rding t AC G g ideline. Dis ssi n: The genotype-phenotype relationship in the FBN1 gene has not been fully demonstrated, but this relationship has been clearly identified in some fibrilinopathies. For instance, all FBN1 mutations related to acromicric dysplasia and geleophysic dysplasia are located in exons 41 and 42. Up to now, only 7 cases of MFLS have been reported in 6 publications. Interestingly, all mutations are located in exon 65 (in old transcripts known as exon 64) or canonical splice sites near this exon. Why exon 65 mutations led to such a phenotype has not yet been elucidated. Further functional studies are needed to understand the pathogenesis. Reference: Graul-Neumann LM, Kienitz T, Robinson PN et al. 2010. Marfan syndrome with neonatal progeroid syndrome-like lipodystrophy associated with a novel frameshift mutation at the 3' terminus of the FBN1-gene. Am J Med Genet Part A 152A:2749–2755.

KEYWORDS: Marfan lipodystrophy syndrome, Progeroid Marfan, FBN1 gene, fibrilinopathy

S-33 - Evaluation of BRCA1 p.Tyr179Cys, p.Phe486Leu and p.Asn550His mutations in Turkish Breast Cancer Patients

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Introduction: Inherited mutations of BRCA1 and BRCA2 genes are the most common cause of hereditary breast and ovarian cancer (HBOC). BRCA1 p.Tyr179Cys, p.Phe486Leu and p.Asn550His mutations are rare variations with aproximately 0.0003 allele frequency according to Exome Aggregation Consortium and reported as benign variants by ENIGMA Consortium when evaluated one by one. However it is reported in cis position in many studies. The aim of this study is to discuss the clinical and molecular datas of four families diagnosed as HBOC, having these three mutations in cis (CLH-allele). Methods: Five families having CLH-allele were evaluated via clinical history and pedigree analyses. BRCA1-2 genes were sequenced via next generation sequencing and duplication-deletion anlyses were also performed via MLPA from peripheral blood lym h ytes' DNA. es lts: All r bands were arrying the CLH-allele. Two of them had postmenapousal and three premenapousal unilateral breast cancer. In two family we detected a second known mutation in BRCA2 (c.5073dupA, c.3318C>G). BRCA2 c.3318C>G mutation was detected in proband which was inherited from her 66 year-old healty mother with CLH-allele. BRCA2 c.5073dupA mutation was detected in a 57year-old healty sister with CLH-allele and other 55year-old healty sister alone but not in proband. Conclusion: Incomplete penetrance and multifactorial habitus of hereditary cancers make genetic testing difficult. In our laboratory this allele was found in 6 of 330 HBOC patients. In three patients CLH-allele was the only variation might be ass iated with breast an er in B CA1 and B CA2. H wever we didn't ex l de the m tations in other breast cancer susceptibility genes yet.

KEYWORDS: BRCA1; BRCA2; hereditary breast and ovarian cancer

S-34 - Evaluation of the pathogenic variants of BRCA1 / BRCA2 genes in breast cancer patients admitted to Ankara Abdurrahman Yurtaslan Oncology Training and Research Hospital Medical Genetics Department

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Breast cancer is the most common cancer type and leading cause of cancer-induced mortality in females. Although many genes are associated with the condition, pathogenic variants of BRCA1/2 are revealed in large proportion in hereditary forms, since revealed in 5-10% of all cases. Pathogenic variants of BRCA1/2 in 321 breast cancer patients, consulted to Ankara Abdurrrahman Yurtaslan Oncology Training and Research Hospital Medical Genetics Clinic, were evaluated. Histopathological type, surgical and clinical staging were recorded and only the variants were evaluated. Samples were analyzed on Illumina-Miseq next generation sequencing platform, variants were evaluated by the Clinical Insight Variant Analysis program, Varsome, Clinvar, HGMD, MutationTaster and literature review was conducted. As a result, 25 patients revealed with mutations, 15 in BRCA1 and 10 in BRCA2. One gross deletion in exon 11 of BRCA1 was confirmed by MLPA. c.2800C> T (p.Gln934Ter) in three, c.181T> G (p.Cys61Gly) in two patients identified in BRCA1 respectively and c.631+4A>G in BRCA2 in two patients were the most frequent pathogenic alterations revealed in this study. Rest of each was with distinct mutations. The incidence of mutations in BRCA1/2 was found to be 7.8% that was in consistent with the literature. Seven of the pathogenic changes in the BRCA1 gene were in exon 10, two in exon 4, two in exon 19, one in each of exons 3, 7, 13 and 22. Three of the pathogenic changes detected in the BRCA2 were found in intron-exon junction, two were in exon 11, 10, 25 and 20.

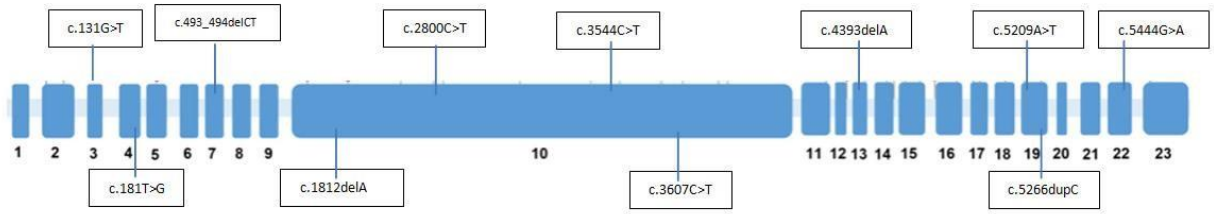

Figure 1. Distribution of *BRCA1* mutations according to exons in patients

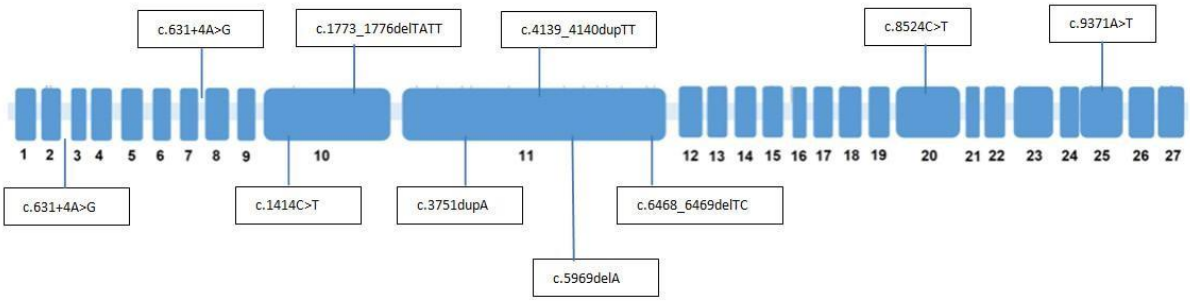

Figure 2. Distribution of *BRCA2* mutations according to exons in patients

KEYWORDS: Breast Cancer, BRCA1, BRCA2, Mutation

S-35 - Analysis of pre-chemotherapy WBC, PLT, monocyte, hemoglobin and MPV levels in acute myeloid leukemia patients with WT1, FLT3 or NPM gene mutations

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Introduction: NPM gene mutations, along with FLT3-ITD mutation, play a role in determining the treatment approach to acute myeloid leukemia (AML). The aim of this study was to analyze the levels of WBC (White blood cell), platelet, monocyte, hemoglobin, and mean platelet volume (MPV) in AML patients with WT1, FLT3 or NPM gene mutations, attempting to detect and compare possible differences in these values. Methods: The study included 71 patients with AML known to have WT1, FLT3 or NPM gene mutations from the patient files in the archives of the Hematology Polyclinic at the University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital. The patients with complete blood count (CBC) results obtained before chemotherapy were divided into three groups: (1) patients with WT1 mutations, (2) patients with NPM mutations and no accompanying mutations other than WT1 at the time of diagnosis, and (3) patients with FLT3 mutations and no accompanying mutations other than WT1 at the time of diagnosis. Statistical analyses were performed with IBM SPSS Statistics 24.0 software package. Known mutation statuses in the patient files were retrospectively evaluated for the study. Results: There was a statistically significant di eren e between the gr s in terms WBC arameters ($\chi 2$=13.685; =0.001). WT1 gr had significantly lower levels of WBC than those of FLT3 and NPM groups. No difference was found between the groups in terms of hemoglobin, platelet, MPV and monocyte levels. Conclusion: High WBC levels could be seen in patients with FLT3-mutated AML.

KEYWORDS: Hemogram, mutation, FLT3, WT1, NPM

S-36 - IMPORTANCE OF CYTOGENETIC ANALYSIS IN HEMATOLOGICAL MALIGNANCIES: WITH TWO RARE CASES REPORTS

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Introduction and Aim: Cytogenetic is a useful method to detect aberations that do not analyses by RT-PCR and FISH techniquies in rutine. We reported cytogenetically insteresting two cases with acute leukemia. We aimed to share our experience in the cytogenetically analysis of samples of these rare patients. Material and Method: Bone marrow samples from two cases (AML, B-ALL) were analysed by conventional cytogenetics, FISH, RT-PCR, NGS. Results: Case no.1 was positive for t(8;21) revelead by RT-PCR and FISH (nuc ish (RUNX1T1x3,RUNX1x3),(RUNX1 con RUNX1T1x1)). Thus, karyotype was as follow:45,X,-Y,der(8)t(8;21)(q21;q22)t(8;5;21;4)(q21;q13,q22,q31),der(21)t(8;21)t(8;5;21,4),der(5)t(8;21)t(8;5;21,4),der(4)t(8;21)t(8;5;21,4)[12]/46,XY[2]. In addition to D820G and N822K mutations were reported on C-KIT gene by NGS. Case no.2: t(12;21), t(9;22) and MLL rearrangement were negative by FISH. Karyotype was as follow: 47,XX,t(4;12)(4q21;12p13),del(6)(q?),+8[4]/48,XX,idem,+del(6)(q?)[2] . After this result, ETV6 rearrangement was positive by FISH study with ETV6 BA probe. Discussion: Approximately 3-4% of AML with t(8;21) have variant translocations. Clinical significance of variant translocations of t(8;21) is controversial. Four way variant translocations is very rarely reported. t(8;5;21,4) have not been previously reported in literature. The patient reported by us has been allogeneic transplanted. t(4;12) has been reported in only 24 AML and 5 ALL cases. In AML patients, t(4;12) is associated premature phenotype and poor prognosis, but effect on prognosis in ALL patients is not clear because them karyotypes are complex. The case, we reported, was relapse and died one year after diagnosed. Considering the results of analysis of both patients, it is observed cytogenetics is still gold standard method.

KEYWORDS: Cytogenetic, Hematological malignancies, FISH

S-37 - Trisomy 21 as a posttransplantational aberration in patients with AML. Is it a sign of relapse?

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Here we report a case of trisomy 21 detected as a chromosomal abnormality in a patient with acute myeloid leukemia (AML) who has subsequently relapsed 5 years after allogeneic bone marrow transplantation (BMT). A 66 years old male who has been followed up in our BMT outpatient clinic was evaluated for loss of chimerism in peripheral blood and pancytopenia requiring transfusions. The patient had been diagnosed with standard-risk AML in 2011 November and was treated with Standard induction chemotherapy consisting of 3 days of anthracycline and 7 days of cytarabine. After that he received four cycles of HIDAC as consolidation. The patient relapsed in 2012 and received subsequent chemotherapy and was considered refractory at this time. The patient received salvage chemotherapy and has undergone allogeneic BMT from a HLA full-match family donor in 2013. His condition was stable until august 2017, at that time loss of donor chimerism was detected, however, the bone marrow aspiration and biopsy revealed remission. The patient was given 3 cycles of donor lym h yte in si n (DLI) r l ss himerism. Des ite DLI, himerism rate did n t in rease the atient's condition began to deteriorate and he became increasingly transfusion dependent. Initial Bone marrow aspiration in December 2018 was negative for relapse but cytogenetic study showed tisomy 21. Repeat bone marrow biopsy showed high blast count (20 %) and the patient considered as relapsed. This case demonstrates trisomy 21 as a relatively early cytogenetic abnormality in bone marrow cells prior to relapse in AML

KEYWORDS: Trisomy 21, Acute myeloid leukemia,

S-38 - Experience of a single center in southern Turkey with CALR mutation screening

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Introduction and Aim: Myeloproliferative neoplasms(MPNs) are clonal disorders which are driven by one of three driver mutations that cause activation of JAK/STAT signaling. MPNs have classically been divided into three main conditions; essential thrombocythemia(ET), polycythemia vera(PV) and primary myelofibrosis(PMF). CALR mutations act as a driver mutation early in the pathogenesis of these disorders and the mutations in exon 9 of CALR gene occur in approximately 30% of patients with MPNs. The commonest two mutations(type-1 and type-2) are a nting r ≈80% m tated ases: ty e-1 (c.1179_1230del) resulted from a 52-bp deletion, more frequent in PMF, and type-2 (c.1234_1235insTTGTC) resulted from a 5-bp TTGTC insertion. The aim of this study is to describe the prevalence and mutation disturbance of CALR mutations in MPNs in Adana region of Turkey Material and Method: Genomic DNA was isolated from peripheral blood samples. A real time PCR test was used to detect type-1, type-2 and other 34 minor variants. Results: CALR mutations were detected 19/72 of the patients. Among the 19 patients with CALR mutations, 10 of 19 patients had at least one mutation. Three of 10 patients displayed type-2 and 7 of 10 patients displayed the other 34 rare mutations. Five of 19 patients had both type-1 and one of other 34 mutations, 4 of 19 patients had both type-2 and one of 34 other mutations. Discussion: Identifying the type of driver mutation is important for the diagnosis and the progress. Though, our study shows the disturbance of the mutations in our region of Turkey.

KEYWORDS: Myeloproliferative neoplasms, CALR, driver mutations

S-39 - A CASE OF A VARIANT PHILADELPHIA TRANSLOCATION INVOLVING CHROMOSOMES (7;9;22)(q22;q34;q11) IN CHRONIC MYELOID LEUKEMIA

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Introduction: Chronic Myeloid Leukemia (CML) is a clonal hematological disorder of hematopoietic stem cells and is characterized by the Philadelphia chromosome (Ph). Less than 10% of patients present with a variant Ph chromosome including one or more additional chromosomes, other than chromosomes 9 and 22. The clinical profile and the prognostic significance of those translocations have not been well understood. Material and Method: A 57-year-old woman presented incidentally with leukocytosis. Cytogenetic studies were performed with unstimulated 24 and 48 hour cultures using bone marrow aspirates. BCR-ABL fusion was analysed by FISH. RT-QPCR for BCR-ABL fusion transcripts (p210 and p190) were performed with commercial kits based on Taqman technology. Results: Conventional G banding analysis showed 46,XX,t(7;9;22)(q22;q34;q11). The p210 fusion transcript was found as 26,14% and the 190 wasn't dete ted. Using the d al l r d al si n BCR-ABL FISH probe, the BCR-ABL fusion was found to have an atypical pattern (2G2R1F). Discussion: We reported a case of the variant Ph complex translocation including an additional chromosome 7 in a CML patient. Abnormalities of chromosome 7 are frequent findings in myeloid malignancies. Various structural changes involving chromosome 7 often lead to poor prognosis. Treatment with imatinib mesylate was started to our patient. A case representing the same karyotype with our patient was reported in the literature. But that patient did not receive TKI therapy, and died during hydroxyurea therapy after 4 months from diagnosis. Therefore it is difficult to predict the response of our patient to TKI therapy due to this chromosomal rearrangement.

KEYWORDS: CML, variant translocation, TKI

S-40 - Investigation of the Effect of EGFR on PD-L1 and Related Pathways in Non-Small Cell Lung Cancer Cells

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Introduction: Lung cancer is the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. EGFR mutations are frequently encountered in NSCLC. Programmed cell death ligand 1 (PD-L1), one of the important targets in immunotherapy. PD-L1 expression is modulated in cancer cells by the tumor microenvironment and constitutive oncogenic signaling pathways. Material and Method: The aim of the present study was to investigate the relationship between EGFR and PD-L1 in NSCLC and the potential pathways that may be responsible for PD-L1 regulation. For this purpose, EGFR-siRNA was transfected into HCC-827 non-small cell lung cancer cells. Phosphokinase antibody array analysis was performed to obtain clues about the possible pathways that regulate this relationship. Results: EGFR gene expression was suppressed in HCC-827 cells. It was determined that PD-L1 gene expression was significantly reduced in EGFR suppressed cells. Array analysis in EGFR suppressed cells showed that the levels of phosphorylated JNK 1/2/3, EGFR, GSK-3α/β, CREB, FAK, PRAS40, c-J n and HSP60 r teins de reased and the levels h s h rylated 53 and β-Catenin proteins increased. Discussion: This study showed a significant relationship between EGFR gene and PD-L1 expression in HCC-827 cells. As a result of array analysis, it can be concluded that this relationship can be ntr lled by PI3K/AKT/mTO , APK and Wnt/β-Catenin pathways and proteosomal degradation. When these pathways are considered together, it is thought that this relationship between these genes could be regulated via the MYC oncogene, where all of them interacted together.

KEYWORDS: EGFR; siRNA; Non Small Cell Lung Cancer; PD-L1

S-41 - Targeted gene panel sequencing for hereditary Cancers: Diagnostic Efficiency

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Genetic heterogeneity of inherited cancers is always a burden effect on genetic diagnosis. Hereditary cancer gene panels facilitate diagnosis in many cancer syndromes by Next-generation sequencing (NGS) as they become affordable and reliable. In this study, 193 (23M-170 F) patients who admitted to our clinic between 2017 December and 2018 December with BRCA1/2 negative Hereditary Breast/Ovarian Cancer (HBOC) or different hereditary cancer syndromes were screened for 27 genes related with Hereditary Cancers. 60 of these cases are previously reported as BRCA1/2 negative by our facility. All exons and exon-intron boundaries of 27 genes were amplified using Hereditary Cancer Solution (Sophia) (156 cases) and BRCA Hereditary Cancer Mstr plus (Multiplicon) (37 cases) kits and sequenced with MiSeq (Illumina) system. Sophia DDM platform and S hia Geneti s' OKA s tware was sed r variant analysis and ann tati ns. Pathogenicity of variants was analyzed using online tools (HGMD Professional, ClinVAR, MutationTaster, SIFT, Polyphen) and ACMG criteria. We identified the total of 146 variant; of these variants pathogenic (11), likely pathogenic (8), variant of uncertain significance (VUS)(112) and conflicting interpretation of pathogenicity (15) seen in HC patients. Additionally in 60 BRCA1/2 negative HBOC patient, we found 3 pathogenic, 3 likely pathogenic, 34 VUS and 5 conflicting variants. Targeted gene panels for hereditary cancers can be used for BRCA1/2 negative HBOC patients and as well as other familial cancer syndromes.

KEYWORDS: Hereditary cancers, Next Generation Sequencing

S-42 - Identification of BRCA1/2 Variants via Next Generation Sequencing for Therapeutic Approach

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Introduction: BRCA1/2 which are tumor suppressor genes, play crucial role in the progress of hereditary breast and ovarian cancer (HBOC) syndrome. Analyzing BRCA1/2 mutations is important because obtained knowledge may help clinicians to assess novel options for diagnostic, prognostic and therapeutic strategies. Aim:To identify of BRCA1/2 variants for classification and improve therapeutic approaches. Material and Method:In this study, 359 patients who admitted to our clinic between 2018 February and 2019 January with breast/ovarian cancer were screened for BRCA1/2. Exon and the exon-intron boundaries were amplified using "B CA ASTE Pl s Dx Assay Kit"(lti li n) and seq en e analysis was er rmed via Ill mina iSeq™System. S hia DD lat rm and S hia Geneti s' OKA s tware was sed r variant analysis and annotations. Pathogenicity of variants were analyzed using online tools (HGMD, ClinVAR, MutationTaster, SIFT, Polyphen) and ACMG criteria. Results and Discussion: As a result of this study, in 359 patient (347 female, 12 male) , 141 variants and 24 CNV (copy number variation) were annotated via Sophia-DDM platform. 39/141 heterozygous variants are evaluated as pathogenic, likely pathogenic or VUS and 25 distinctive variations (33 female, 3 male) are reported as pathogenic in all databases and prediction tools. In addition to these, we found 11 novel variants (4 pathogenic, 7 VUS) by ACMG criteria. Variants were confirmed by Sanger sequencing in probands and the family members. Briefly, NGS is high-throughput method for identifying and investigating BRCA1/2 mutations and therefore contribute effectively to the treatment process.

KEYWORDS: BRCA1/2, Next-Generation Sequencing, Breast Cancer, Ovarian Cancer, Variation

S-43 - Gain of 1q21 locus in a multiple myeloma patient

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Multiple myeloma (MM) is a malignant disease characterized by monoclonal expansion of plasma cells in bone marrow. It accounts 1% of all types of malignancies and approximately 12% of hematologic malignancies. It shows clinical heterogeneity due to organ damage caused by increased plasma cell and immunoglobulins. Genetic anomalies cause malignant transformation of B lymphocytes in MM. These anomalies make up the cytogenetic risk profile which may help clinicians to determine the prognosis and to choose the appropriate treatment. 1q21 gain is one of the chromosomal aberrations seen in MM. Although the genes within 1q21 locus remain unclear, overexpression of the CKS1B gene has been associated with poor prognosis and resistance to bortezomibe. In this study, we present a patient who was diagnosed with multiple myeloma with the findings of anemia, lytic lesions in the bones, elevation of Ig G levels and gain of 1q21 locus. A 62 year old female patient was admitted to the hospital with generalized pain in the bones. Hematological investigations revealed mild anemia and X-ray scans of the thorax showed multiple lytic lesions. Serum biochemical examinations revealed increased total protein, globulin, Ig G, urine beta-2 microglobulin. Bone marrow aspiration revealed a hypercellular marrow with plasmacytosis. Karyotype obtained from bone marrow was normal whereas gain of 1q21 locus (41%) was detected in our FISH panel. These findings together with genetic analysis confirmed the diagnosis of multiple myeloma. The patient was started bortezomibe, cyclophosphamide and dexamethasone. The response to therapy has not been evaluated yet.

KEYWORDS: multiple myeloma, 1q21 gain, FISH, CKS1B gene

S-44 - Microarray Analysis of Recurrent Clivus Chordoma Samples: Potential Targets for Chordoma Treatment

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Chordoma is a kind of rare bone tumor thought to be arisen from the remnants of embryonic notochord. Surgery with wide margins followed by radiotherapy is the standard treatment for clivus chordoma. Although chordoma has a slow-growing characteristic, it is locally destructive and patients with chordoma undergo multiple surgeries or die due to recurrence. Consequently, recurrence-related genes are potential target for chordoma treatment. In this study, microarray analysis showed the differentially expressed genes between recurrent and primary clivus chordoma samples. Hereafter, prognostic significance of selected genes was evaluated in chordoma patient cohort. Finally, the first recurrent clivus chordoma cell line, YU-Chor1, which was established by our group, compared with UM-Chor1, a primary clivus chordoma cell line, according to their characteristic. Our results revealed that 81 genes are differentially expressed in recurrent chordoma samples compared with primary chordoma samples. IGFBP6 and LGR5 are associated with decreased Overal Survival (OS), recurrence and metastasis in our patient cohort. Moreover, YU-Chor1 cell line had several loss and gains in their genome, increased expression of chordoma markers and resistance to chemotherapy. In conclusion, we firstly established and characterized recurrent clivus chordoma cell line named YU-Chor1 and genes differentially expressed in recurrent samples could have been contributed chordoma pathogenesis. Further studies are needed to explore role of genes in recurrence of chordoma.

KEYWORDS: Chordoma, Recurrence, IGFBP6, LGR5, Chemoresistance

S-45 - DETERMINATION OF ZINC FINGER PROTEIN 384 (ZNF384) GENE FUSIONS IN CHILDHOOD ACUTE LEUKEMIA PATIENTS

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Acute leukemias are a rapidly progressive group of diseases that produce a large number of abnormal cells in the bone marrow and spread these cells to blood and other tissues. ZNF384 gene rearrangements are one of the new oncogenic subtypes of B cell precursor acute lymphoblastic leukaemia (ALL). ZNF384 gene rearrangements were reported 1-6% in childhood B cell precursor ALL (BCP-ALL), and 5-15% of adult BCP-ALL cases. ZNF384-rearrangements were also reported in mixed phenotype and young adolescence ALL patients.The aim of this study was to determine the frequency of the most common ZNF384 fusions in patients with B-ALL and mixed phenotype acute leukemia. One hundred twenty nine pediatric ALL patients (54 emales, 75 males) were in l ded in this st dy. T tal NA was is lated r m atients' b ne marr w at diagnosis and cDNA synthesis was performed by using random hexameres and MMLV reverse transcriptase. The most common fusions (ZNF384-TCF3, ZNF384-EP300 and ZNF384-TAF15) containing five different breakpoints were examined by using RT-PCR. ZNF384 gene rearrangement was found 7,7% in paediatric ALL patients. We identified ZNF384 fusions 7,8% in mixed phenotypic leukemia and 7,6% in BCP-ALL groups. A novel breakpoint was also identified in ZNF384-TCF3 fusion. There is limited number of data about the clinical impact of ZNF384 gene rearrangement. Patients carrying ZNF384 fusions are classified into medium risk group need more attention and novel molecular genetic markers are very important for risk adopted treatment strategies. Examinations of different phenotypic ALL subgroups will be help us to understand the clinical impacts of novel markers.

KEYWORDS: FUSİON GENE,ZNF384, İXED PHENOTYPE ACUTE LEUKE İA, BCP-ALL

S-46 - Phenotypic Variability of Pyridoxine-Dependent Epilepsy

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Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder characterized by seizures in neonates or infants, which is unresponsive to antiepileptic drugs but controlled by pyridoxine. The phenotypic spectrum of ALDH7A1 mutations are very heterogeneous ranging from not only refractory epilepsy but also neurodevelopmental delay to multisystem neonatal disorder. We presented two cases of different age groups with ALDH7A1 mutations. First case is a 14-year-old girl with history of epilepsy,ataxia and developmental delay who was admitted to the hospital for recurrent seizures not responding to conventional antiepileptic drugs. Second case is a 15-month-old girl who has neonatal seizures beginning in the first hour of life that was resistant to antiepileptic drugs. Molecular analysis was revealed a homozygous mutation of ALDH7A1 both of the patients. Also these cases's seiz res were ntr lled lini ally and ele tr gra hi ally a ter the treatment pyridoxine, successfully. These cases highlights that PDE is a rare but a treatable cause of unexplained severe epilepsy. Neonatal seizures are a great threat for neurocognitive impairment, especially if they occur in early life. As in our case, physicians may overlook this diagnosis, considering treatable causes has great importance to prevent complications and avoid developmental disabilities in patients who has intractable epilepsy. Because of this life treatening issues it is important to keep in mind PDE as other treatable conditions and request genetic counselling.

KEYWORDS: Pyridoxine-dependent epilepsy, neonatal seizures

S-47 - Next-generation sequencing-based comprehensive molecular analysis of Turkish patients with retinitis pigmentosa

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Retinitis pigmentosa (RP) is a group of hereditary, degenerative retinal disorders characterized by progressive retinal dysfunction, outer retina cell loss, and retinal tissue atrophy. The aim of this study was to learn about disease prevalence and to identify the responsible genes in Turkish patients with nonsyndromic retinitis pigmentosa (RP). Targeted next-generation sequencing (NGS) is an efficient diagnostic tool for identifying mutations in patient with RP. NGS was performed in 34 unrelated patients. Disease-causing mutations were identified in 95% of 31 RP patients. Mutations in ABCA4 accounted for 23% of disease cases. Further mutations were identified in BBS4, C2ORF71, CERKL, CNGA1, CRB1, EYS, FAM161A, MERTK, PDE6B, PDE6C, PDE6H, PROM1, RBP3, RDH12, RGR, RHO, RP1, RPE65, USH2A and TULP1. In addition, nine patients carried variants of uncertain significance. This study presents a brief overview on mutation spectrum of the 58 genes in a Turkish cohort with RP Identification of mutations enriched our understanding of variations in these genes and their associated phenotypes.

KEYWORDS: NGS, ABCA4, retinitis pigmentosa

S-49 - An interstitial 6q25.1 microdeletion syndrome in a patient with dysmorphic features, intellectual dysability and stereotypical movements

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6q25 microdeletion syndrome is a rare contiguous gene deletion syndrome. It is mainly characterized by congenital heart defects, developmental delay, intellectual disability, microcephaly and dysmorphic features. The phenotypic variability depends on the size of the deletion and genes involved . Here we report a 7-year-old male patient who was referred to our outpatient clinics from Pediatrics department for dysmorphic features. He was born to a nonconsanguineous healthy parents at 28 weeks of gestation with 1800 gr of birth weight due to ectopia cordis anomaly detected at his twin who has died in hours after the delivery. He had operation for bilateral undescended testis and inguinal hernia. In his echocardiography biscuspid aortic valve, mitral valve prolapsing and regurgitation was detected. He had mild intellectual disability and stereotypical movements. In physical examination; his weight was 25kg (-0.12SD), his head circumference was 51cm (-0,99SD) and height was 114 cm (-2,24SD). He had disproportionately short stature with limbs shortening. Also he had hypertelorism, upslanted palpebral fissures, anteverted nostrils, prominent and low set ears. G-banded karyotype analysis of the patient revealed a normal karyotype, so SNParray analysis was performed and 2,1 Mb loss encompassing 34 genes (18 OMIM genes) on the 6q25.1 region was detected. Our patient shared the similar features as the patients reported in the literature with interstitial 6q deletions. Further analysis in additional patients is required to define the critical interval and elucidate the phenotype-genotype correlation.

KEYWORDS: 6q25.1, rare, microdeletion, syndrome, interstitial

S-50 - A COHORT OF PATIENTS WITH HYPERTROPHIC AND DILATED CARDIOMYOPATHY

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PURPOSE: Hypertrophic cardiomyopathy (HCMP) is an unexplained left ventricular hypertrophy and dilated cardiomyopathy (DCMP) is characterized by left ventricular dilatation and dysfunction. Familial HCMP is an autosomal dominant disease caused by mutations in genes encoding sarcomeric proteins in heart muscle. The aim of this study was to explain genotype-phenotype correlations in patients with DCMP or HCMP. METHODS: 17 patients with HCMP and 1 DCMP were evaluated with physical examination, family tree analysis and cardiac examination. Five genes associated with HCMP and DCMP were sequenced with the Illuminated Miseq device using the Agilent HCM Master next generation sequencing kit. RESULTS: Seventeen patients with HCMP and one patient with DCMP were referred to our clinic between 2016 – 2018. MYBPC3, MYH7, TNNI3, TNNT2, MYL2 genes for the patients were sequenced and mutations were detected in five patients guided by HCMP. Four heterozygous mutations were detected in the MYH7 gene and one heterozygous mutation was found in the TNNT2 gene. Although c.2155C> T (p.Arg719Trp) and c.1987C> T (p.Arg663Cys) mutations in MYH7 gene were previously reported in the literature, c.2224G> C (p.Ala742Pro) and c.3508G> A (p.Glu1170Lys) mutations in the MYH7 gene are novel. c.311G> A (p.Arg104His) mutation in TNNT2 gene was also previously reported. The c.258delC (p.Leu88Trpfs * 27) mutation in TNNI3 gene is homozygous in the patient with diagnosis of DKMP whose parents are first degree cousins. CONCLUSION: Six atients' geneti eti l gy related t ardia ath l gy were determined. Seq en e analysis ther clinically relevant genes and MLPA analysis were planned for other patients.

KEYWORDS: Hypertrophic cardiomyopathy (HCM) ,dilated cardiomyopathy (DCM), TNNT2, MYH7, TNNI3

S-51 - Is MTHFR C677T polymorphism risk factor for Turkish Alzheimer Disease's patients?

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Introduction and Aim:Alzheimer's Disease is a geneti ally m lex dis rder that a ses r gressive mem ry lost. Elevated levels of homocysteine (Hcy) have been linked to AD. Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme involved in the folate-dependent metabolism of Hcy. A functional polymorphism (rs1801133, namely C677T) in the MTHFR gene results in increased Hcy levels and has been associated with the risk of AD. We aimed to investigate the association between MTHFR C677T polymorphism and AD in a cohort of Turkish patients. Material and Method:The study group consisted of 257 AD atients (mean age: 75.9 years ± 10.4) and 414 ntr ls (mean age: 62.2 years ± 13.1). Gen ty ing was performed by quantitative real-time polymerase chain reaction using hydrolysis probes. Results and Discussion:The distribution of MTHFR C677T genotypes in the AD group were 36.3%, 51.6% and 12.1% for the CC, CT, TT gen ty es, res e tively. The THF min r 'T' allele req en y was 30% in AD atients while the frequency for the controls was 33%. However, no significant differences were found in the allele and genotype distributions between AD and control groups, as well as in the sub-groups of APOE e4 carriers and non-carriers. Also, no significant AD risk was found in carriers o THF 'T' allele (CT+TT vers s CC). We can conclude that the MTHFR C677T polymorphism might not be a risk factor for our Turkish cohort of AD patients. However, the effect of other polymorphisms in that gene cannot be ruled out and further studies in larger cohorts are necessary to confirm the

KEYWORDS: Alzheimer's Disease, MTHFR gene, polymorphism, risk, genotyping

S-52 - Evaluation of 22q11.2 anomalies via two pediatric patients

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Introduction and aim: Deletions and duplications in the proximal long arm of chromosome 22 can cause various genetic disorders. Deletion in chromosome 22q11.2 is associated with diagnosis of DiGeorge, velocardiofacial and conotruncal anomaly face syndrome, whereas the duplication of the same region results in a distinct phenotype named as 22q11.2 duplication syndrome. Here we present two cases of whom one carries a deletion, other carries a duplication in 22q11.2. Case 1: A 6-month-girl was referred to our clinic for genetic counseling because of truncus arteriosus and ventricular septal defect. She was clinically diagnosed as DiGeorge syndrome. Her karyotype was 46, XX. FISH analysis showed a deletion in the 22q11.2 region confirming DiGeorge syndrome. Segregation analysis revealed that the mother also had the same deletion. On clinical examination, the mother had only nasal speech and otherwise she was normal. Case 2: A 9-year-boy born to non-consanguineous family was referred to our clinic due to growth retardation, intellectual disability, ear anomalies and bilateral hearing loss. On physical examination, hemifacial microsomia was observed. In order to investigate chromosomal abnormalities, karyotyping and microarray were performed. On chromosomal microarray, 22q11.2 duplication was detected. Conclusion: Copy number variations (CNVs) involving 22q11.2 region are respectively common. Deletions cause phenotypic abnormalities more often, while duplications are rarely associated with clinical features. Here we wanted to emphasize the importance of microarray analysis to detect CNVs, presenting two cases having different abnormalities in the same chromosomal region.

KEYWORDS: DiGeorge Syndrome, 22q11.2, deletions, duplication, microarray

S-53 - Alterations in Promoter Methylation Pattern of IL-16 and MMP-3 Genes in Rheumatoid Arthritis

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Introduction and Aim: Rheumatoid arthritis (RA) is a chronic inflammatory disease influenced by both genetic and environmental factors. To investigate possible effect of DNA methylation to the etiology of rheumatoid arthritis, we investigated promoter methylation pattern of IL-16 (Interleukine 16) gene which is a pro-inflammatory cytokine and MMP-3 (Matrix metalloproteinase 3) gene which is involved in the breakdown of extracellular matrix. Material and Methods: Promoter methylation profiles of IL-16 and MMP-3 genes were assessed in 87 cases (49 RA patients and 38 healthy controls). Alterations in DNA methylation pattern were detected through methylation specific PCR with specific primers. Genomic DNA specimens were isolated from whole blood samples and subjected to bisulfite treatment before methylation specific PCR. The PCR products were then examined by using agarose gel electrophoresis and visualized under UV illumination. Results: Based on the data obtained, in RA group, unmethylation in MMP-3 gene promotor was higher than control group ($p=0.004$). There was no significant difference for methylation pattern of IL-16 gene promoter between RA patients and controls ($p=0.5$). Discussion: Our results suggest that, the unmethylated MMP-3 promoter was correlated with chronic inflammation in RA patients who had not yet started any drug therapy. However, there was no correlation with methylation status of IL-16 promoter and disease activity. References 1. Klein K, Gay S. Epigenetics in rheumatoid arthtritis. Curr Opin Rheumatol. 2015;27:76-82. 2. https://www.ncbi.nlm.nih.gov/gene/4314 3. https://www.ncbi.nlm.nih.gov/gene/3603

KEYWORDS: Methylation, Rheumatoid arthritis, IL-16, MMP-3

S-54 - High-throughput DNA sequencing-based genomic profiling analysis reveals novel homozygote mutations-phenotype association for severe dilated cardiomyopathy in a Turkish heritage patient.

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A high-throughput sequencing technology has dramatically changed the nature of molecular diagnosis. Past two decades, exome sequencing has emerged as a comprehensive and cost-effective approach to identify pathogenic variants in the protein-coding regions of the genome. Generally, suggestive clinical features can be used to distinguish one condition from another; however, in some cases these clinical features overlap with several other genetic conditions. Dilated cardiomyopathy, a disorder characterized by cardiac dilation and reduced systolic function, represents an outcome of a heterogeneous group of inherited and acquired disorders. The functional consequences of dilated cardiomyopathy-causing mutations have been limited to a few cases where patients with known mutations had heart transplants. Here we report a case of 16-year-old male from a consanguineous parent with severe dilated cardiomyopathy. The patient was admitted to pediatric cardiology policlinic with the complaints serenoprotein deficiency, overgrowth symptoms and intellectual disability. Sequence analysis revealed two novel homozygous variants (c.5202A>C and c.5565G>C) within the OBSCN gene. Also, pseudoxanthoma elasticum causing pathogenic heterozygote mutation (c.2359G>A; p.Val787Ile) in ABCC6 gene, hyperglycinuria causing homozygote pathogenic mutation (c.260G>T) in SLC36A2 gene and intellectual disability causing pathogenic homozygote mutation (c.63_64delAG; p.(Asp23Argfs?10)) in ACBD6 gene were determined. The reported patient is the extreme case with known genotype causing a different, unusual and severe phenotypic feature for dilated cardiomyopathy with intellectual disability. Therefore, this study widens the complex phenotype-genotype spectrum of dilated cardiomyopathy and contributing disease to be more severe during gene-gene interaction as well as increasing our knowledge on this complicated and severe genetic disorder.

KEYWORDS: dilated cardiomyopathy, Turkish, OBSCN, novel variant, NGS

S-55 - Mutations on human Growth Hormone-Releasing Hormone Receptor gene affect GHRH-GHRHR signaling Pathway

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Background: Isolated Growth hormone deficiency (IGHD) is defined as a medical condition associated with growth failure due to insufficient production of growth hormone (GH) or lack of growth hormone action. Mutations in the gene encoding for growth hormone releasing hormone receptor (GHRHR) have been detected in patients with IGHD type IB. We identified novel 5 missense, one frameshift and one nonsense mutations in GHRHR gene but the function of mutations on GHRHR signaling was not shown. Objective: Purpose of our research was to identify the function of mutations on GHRHR gene causing IGHD in GHRHR signaling in cell culture system. Methods: Mutations found in our IGHD patients were prepared by using wt GHRHR gene as template provided by Prof. Dr Kelly E. ay 'dan (N rthwestern University, Evanst n, IL, USA). Als , we prepared CRE-luc reporter vector for determining of the function of GHRHR mutations. Mutant PCR products for GHRHR gene were transformed into XL1 competent cells and positive clones were obtained and the mutations on GHRHR were determined by DNA sequencing. The mutant GHRHR plasmids and CRE-luc reporter vector were transfected into CHO cells and the cells expressing wt and mutant GHRHR analogs were treated with GHRHR and their luciferase activities were measured. Results: In this studies, CHO cells was used by negative control but CHO cells expressing wt GHRHR was used as positive control. Although the cells carrying G369V and T257A reduced reporter acitivity small amount but the cells expressing K264E, S317T ve S330L mutations reduced reporter activity a lot. Also no reporter activity was not seen on cells expressing 72X mutation and no hGHRHR. Conclusions: Our mutations blocked GHRHR signaling pathway different levels.

KEYWORDS: GHRHR, IGHD, Mutation

S-56 - The 15q11.2 BP1–BP2 Microdeletion Syndrome with Variable Expressivity

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Introduction and Aim: Chromosome 15q11.2 BP1–BP2 deletion (Burnside-Butler) syndrome is a relatively rare autosomal dominant disorder with incomplete penetrance. TUBGCP5, CFYIP1, NIPA1 and NIPA2 genes are non-imprinted, highly conserved genes and located in chromosome 15q11.2 region. Clinical features are characterized as developmental delay, language deficit, intrauterine growth restriction, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), obsessive-compulsive disorder, seizures and dysmorphic features. Here we report microarray analysis results and clinical findings of two additional cases. Material and Method: Conventional cytogenetic and CGH+SNP Microarray (Agilent,180K) analyses were performed. Results: First case was a 13-year-old girl who had hearing loss, intellectual disability, developmental delay and impaired speech skills. Dysmorphic findings of the patient were hypertelorism, downslanting palpebral fissures, high palate and happy face expression. Second case was a 3-year-old boy who had hypothyroidism, pulmonary stenosis, hypotonia, developmental delay and growth retardation. His dysmorphic findings included microcephaly, depressed nasal bridge, anteverted nares, chin dimple and cup-shaped ears. Their parents were both healthy and non-consanguineous. Cytogenetic analysis (550 GTG-banding) revealed normal karyotype in both cases. CGH+SNP Microarray analysis of first patient demonstrated a 317 kb loss of 15q11.2 region inherited from phenotypically normal father. The second patient had a 257 kb loss of the respective region. Segregation analysis of the second patient was not performed yet. Discussion: This microdeletion has high frequency in the general population and clinical features may range between mild to severe due to variable expressivity and incomplete penetrance. Therefore individuals with 15q11.2 deletion should be evaluated elaborately.

KEYWORDS: Burnside-Butler, Microarray, 15q11.2 deletion

S-57 - Alternative Perspective İn Clınıcal Varıatıon Of Fmf

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In this study we aimed to investigate the presence of clinical symptoms of familial Mediterranean fever which is an inflammatory disease and different mechanisms that may cause this situation. We have been focusing on MCP-1 that these is effective chemokines on monocytes / macrophages undertaking a critical role in Familial Mediterranean Fever Disease and its receptor CCR2. We aimed to investigate the MCP-1 (A-2518G), which is the most effective of these functions, and CCR2 (G190A) polymorphisms as well as the MCP-1 (A-2518G) expression levels because it is in the promoter region. For this purpose, a total of 125 male and 104 female 229 individuals were included in the study. Of these, 75 were homozygous for the mutant gene MEFV, 77 of them did not carry mutations in the MEFV gene while 77 of them were the heterozygous mutant individuals. 120 people have FMF clinic while 107 people did not have the FMF clinic when they are also clinically evaluated according to the criteria in Tel Hashomer. Genotyping analysis was performed by PCR-RFLP technique. Expression analysis method also worked with real-time PCR method. The results were statistically analyzed. MCP-1 (A-2518G) and CCR2 (G190A) genotypes and allele frequencies of them with FMF disease / genetics were no significant relationship in the evaluation of what we do. Also This increase was higher in the MEFV homozygous groups while The group with heterozygous mutant MEFV MEFV gene mutation increased the expression of MCP-1 a rding t the gr d n't have EFV gene m tati n. In additi n, CP-1 expression in homozygous and heterozygous mutant groups were found to be increased that is being higher in the group homozygous mutant. It was concluded that the expression of MCP-1 with these findings that is important FMF disease, may explain the clinical differences between FMF patients and may be an indication of suspicious circumstances. We also thought that the expression of MCP-1 mutations associated with MEFV mutations and MEFV mutations may exacerbate inflammation by increasing the transcription of MCP-1. Furthermore interpreted that MCP-1 (A-2518G) mutations to increase expression of MCP-1 also contribute to disease in the FMF.

KEYWORDS: MEFV, MCP-1, CCR2, ekspresyon

S-58 - The effects of human chorionic gonadotropin-based hormonal therapy on the expression levels of proliferating cell nuclear antigen

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

KEYWORDS: azoospermia, infertility, HCG, PCNA, spermatogenesis

S-59 - Copy number variation analysis from targeted next generation sequencing panel data

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Introduction and Aim: Copy number variation (CNV) is form of critical genetic variation that leads to abnormal number of copies of genomic regions that plays an important role in molecular etiology of genetic disorders. Microarray and MLPA tests have been standard technologies to detect large and small CNVs in genomes, respectively. During the last several years, next generation sequencing(NGS)-based analysis has been widely applied to identify both germline and somatic CNVs. However, CNV analysis from targeted NGS data is challenging because of smaller size of the target regions compared to WES or WGS. In this study, we aimed to detect gen mi CNVs r m targeted NGS anel data sing GATK's latest CNV dete ti n t ls with m di ied arameters. aterial and eth d: First, 22 Ill mina Tr sight Can er Panel's raw data re-processed using GATK's best ra tises i eline. And then, read nts were collected as hdf5 file format from all samples. These count files were processed using GATK germline CNV detection tools and parameters were optimized for targeted panel data. Finally, presence of CNVs in all samples were investigated. Results: Evaluation of the analysis showed BRCA1 deletions in 2 samples. BRCA deletion genomic locations were different in two samples. Exact locations of these deletions confirmed using MLPA analysis. Discussion: In this study, we n irmed that GATK's latest t ls is e ective and useful for CNV analysis from targeted NGS by optimizing the parameters. It was also shown that, both point mutations and CNVs could be detected by using bioinformatics tools effectively with a single genetic test.

KEYWORDS: next generation sequencing, NGS, copy number variation, CNV, targeted panel

S-60 - Interpreting CFTR Gene Variants Using Machine Learning Algorithms

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Cystic fibrosis (CF) is a genetic condition that causes persistent lung infections and multiple tissue problems because of faulty chloride secretion. CF transmembrane conductance regulator (CFTR) gene is responsible for CF which encodes apical membrane protein of exocrine epithelial cells. CFTR functions as cAMP-induced chloride channel. In addition to clinical variability of the patients, almost 2000 CFTR gene mutations have been reported and those mutations are grouped into six classes according to protein defects. Despite well known mutations there are rare mutations which are difficult to interpret clinical effects. Machine learning or artificial intelligence algorithms are gaining wider usage as a result of computational improvements and data processing feasibilities. In this study we performed supervised learning model for CFTR mutations. Predefined 1514 CFTR mutations are provided from public ClinVar database. Dataset are spited into two random groups 0.7 and 0.3 respectively where first group is used for logistic regression model to predict clinical effects using Microsoft Azure Machine Learning Studio and rest of the data is used for scoring the model. Despite suspicious and limited clinical data, the model was able to identify almost 70% pathogenic variants and also 97% of the variants were truly recognized that are tagged as uncertain significant in advance. Major deficit of the model was the limited amount of benign tagged variants. But the overall accuracy of the model was 0.70 and average accuracy was 0,96.

KEYWORDS: CFTR, Cystic Fibrosis, Machine Learning, Bioinformatics

S-61 - IN SILICO APPROACH FOR ANALYSIS OF SNPs IN THE ABAD/HSD17B10 GENE

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Introduction and Aim: Hydroxysteroid (17beta) dehydrogenase 10 (HSD10) is a mitochondrial multifunctional enzyme encoded by the HSD17B10 gene which is known ABAD gene, as well. The mutations in the HSD10 gene a se the r tein related devel ment Alzheimer's disease. The aim this st dy was t determine deleterious/damaging SNPs (single nucleotide polymorphisms) on the protein structure encoded by HSD17B10 gene by using computer based software tools. Material and Method: Missense SNPs in the HSD17B10 gene were obtained from the NCBI dbSNP database in January, 2019. The possible deleterious/damaging effects of the SNPs on the protein structure were predicted using SIFT and PolyPhen-2 software tools. By using the I-Mutant 2.0 and Project HOPE software tools, the alteration, stabilization, and the three-dimensional structured modeling of the protein were determined. Results and Discussion: The results showed that 784 SNPs were found in HSD17B10 gene and 62 SNPs among them were found to be as missense mutations. 7 SNPs were determined to be deleterious/damaging types of mutation by both SIFT and PolyPhen-2 software tools. The amino acid properties such as size, charge, hydrophobicity of mutant and wild type amino acid residues and the three-dimensional structured modeling of protein were obtained from Project HOPE software. The I-Mutant 2.0 results showed that all deleterious/damaging SNPs decrease the protein stabilization. We thought that the results obtained in our study will give an idea and provide data to the future experimental studies.

KEYWORDS: ABAD, HSD17B10, Alzheimer disease, single nucleotide polymorphism (SNP), in silico

S-62 - Evaluation of the novel variants found incidentally during diagnostic process in terms of N6-methyladenosine (m6A) modification

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Introduction N6-methyladenosine (m6A) is the most abundant RNA modification which is found in mRNAs and known to effect splicing, stability and translational efficiency of mRNAs. Methylation and demethylation of adenine is catalyzed by specific type of enzymes. When methylated, adenine (m6A) can be recognized by a specific group of proteins with YT521-B homology (YTH) domain. Binding of YTH-domain protein leads to downstream events which result in differential expression of the gene. N6-methylation targets the adenine residues which are located in a consensus sequence characterized by DRACH motif, and some SNPs (m6A-SNP) may cause loss or gain of this motif. In our department, we use Sanger sequencing for the diagnosis of more than 400 single-gene diseases. In addition to disease causing mutation, we identify numerous novel variants, which may play modifier role in disease phenotype. To investigate whether these novel variants may cause loss or gain of DRACH motif, we have retrospectively evaluated variants found in our patients. Material and methods For known m6A-SNPs, we used databases. Scoring loss or gain of DRACH motif in the presence of each variant found in our patients was performed with Python3.6. Results From databases, we exported more than 280.000 m6A-SNPs. In approximately 2.000 of our patients analyzed to date, we have found 1290 known SNPs. None of these SNPs was included in m6A-SNP dataset. Investigation of novel variations which is still in progress will be presented. Discussion This ongoing study is expected to help explaining the clinical heterogeneity of some set of our patients.

KEYWORDS: RNA methylation, epitranscriptomics, variation

S-63 - Genetic evaluation of the CFTR gene and comprehensive analysis of the sequence variants using bioinformatic tools.

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Introduction and aim: CFTR gene sequence variants may affect the function of the CFTR protein and modulates the phenotypic characteristics of the CFTR-related disorders. Thus, we aimed to identify and comprehensively evaluate the CFTR sequence variants for appropriate diagnosis of the patients with these disorders. Materials and Methods: All exons and exon-intron boundaries of the CFTR gene were amplified and sequenced in 218 patients who were admitted to our clinic between 2016 December and 2018 July by using CFTR MASTR Dx Assay (lti li m) kit ll wing man a t rer's re mmendati n. The seq en ing was performed in Miseq (llumina) instrument. Variant analyses and annotations were carried out by using Sophia DDM data analysis platform and Sophia Genetics' MOKA software. Online bioinformatics tools (HGMD, ClinVAR, MutationTaster, SIFT, Polyphen) and ACMG variant classification were used for evaluating pathogenicity of variants. Results: In total, 139 variants (82 exonic, 57 intronic) were detected in the CFTR gene including PolyT and PolyTG repeats. Of 82 exonic variants, 16 were likely pathogenic (LP), 20 were pathogenic (P) and 36 were variant of uncertain significance (VUS). We identified common polymorphisms, known disease associated variants as well as five novel VUS missense variants. Two novel variant carriers had no other P/LP/VUS variants. Other three carriers for novel missense variants were also heterozygote for pathogenic p.Phe508del variant. Discussion: Molecular screening of the CFTR gene revealed novel variants that may be associated with CFTR-related disorders. All novel variants are being validated for confirmation and their functional importance yet to be investigated by future studies.

KEYWORDS: CFTR, Next-generation sequencing, cystic fibrosis, genetic screening, variant classification

S-64 - Diagnostic Efficiency of Multiple Gene Panel in Cardiomyopathy and Hereditary Arrhythmias

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OBJECTIVES: Efficiency of targeted- next generation sequencing (NGS) gene panels are evaluated to detect candidate pathogenic variant in Turkish cardiomyopathy (CM) and Hereditary Arrhythmia (HA) patients. BACKGROUND: Cardiomyopathies and Hereditary Arrhythmias are heterogeneous disorders and genetic testing is crucial is for diagnosis, prognosis, treatment, family screening, and reproductive planning. NGS is considered to be best practice for diagnosis. Large gene panels also have the capacity to evaluate non-prevelant genes and andidate variants s e i i r lati ns. ETHODS: Patient's DNA was is lated r m eri heral blood. All exons and exon-intron boundaries were sequenced with the MiSeq (Illumina) system and confirm with sanger. We used two different panels which include 103 and 73 known CM-HA associated genes 50 of which is common in both. These multiple gene panels are used to detect genetic variants in 61(38M/23F) (41 HA and 20 CM) Turkish patients. Annotated variants are classified according to ACMG criteria with in-silico tools and also investigated thoroughly by online databases such as HGMD professional 2018-4 edition and Clinvar. RESULTS: We identified, CNV in one patient, 38 pathogenic, likely pathogenic, and uncertain significance variants in 24 of 41 HA patients (58 %) in 22 different genes. Similarly, 31 variants are determined in 17 of 20 CM patients (85 %) in 16 distinct genes. Besides these variations, we found 71 variations which are not reported before in literature or databases. CONCLUSIONS: As multiple genes contribute to the CM and HA conditions, multiple gene panels should be evaluated as a solution in routine genetic diagnostic practice.

KEYWORDS: Cardiomyopathy, Hereditary Arrhythmia, targeted next-generation sequencing, multi-gene panel

S-65 - Emerging concept in liquid biopsy: analyses of different biological samples via next generation sequencing

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Introduction and Aim: The use of plasma cell-free tumor DNA -liquid biopsy- has shown promise in characterizing tumors via next generation sequencing (NGS) and monitoring them over time, but its use in other biological samples has been limited. Thus, using circulating tumor DNA (ctDNA) of metastatic cancer patients from cerebrospinal fluid (CSF) and pleural effusion (PE) may be a feasible approach in the near future, according to our recent presented study. Material and Method: Cell-free ctDNAs were isolated from peripheral blood plasma samples and those matched with CSF and PE. Then, the most relevant biomarkers in terms of choice of therapy, were next-generation-sequenced via targeted multi-gene panel (AKT1, ALK, BRAF, DDR2, EGFR, ERBB2, ESR1, FGFR1, MET, KIT, KRAS, MAP2K1, NRAS, NTRK1, PDGFRA, PIK3CA, PTEN, ROS1 and RICTOR genes with EGFR, ERBB2, FGFR1, MET and RICTOR gene amplifications). Quality assessments and NGS efficiencies were evaluated in complete NGS workflow for each samples and compared to those in plasma. Results: We observed diversity in the DNA concentrations among different types of matching samples even though the procedure was well optimized. Besides, the total yields of next-generation-sequencing were rrelated. We dete ted a thera y sensitivity related variant in a atient's CSF while mat hing plasma ctDNA resulted in no clinically significant genetic change that showed the higher sensitivity in CSF and PE than in plasma. Discussion: Our study demonstrated the power of next generation sequencing of pleural effusion and cerebrospinal fluid when coupled with the right bioinformatics pipeline and the right patient.

KEYWORDS: Liquid biopsy, next generation sequencing, novel diagnostics, precision medicine

S-66 - Identification of driver gene mutations and microsatellite instability in liquid biopsy samples of colorectal cancer

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Introduction and Aim: The success rate of check point inhibitors in the treatment of patients with colorectal cancers displaying microsatellite instability (MSI) underscores the need for novel techniques, because of the fact that serial tumor specimens are usually not available. We hypothesized that liquid biopsies could provide an important source of cancer-derived DNA readily obtainable by minimally invasive means. Material and Methods: Formalin-fixed paraffin-embedded (FFPE) tumor tissue and liquid biopsy samples were collected from 23 colorectal cancer patients. Genomic DNA and circulating cell-free DNA (ccfDNA) were isolated, then concentrations and qualities were compared. Microsatellite alterations were scored by comparing the electrophoretic profiles of each biomarker (targeted gene regions of BAT-25, BAT-26, NR-21, NR-24, MONO-27, Penta-C and Penta-D) in genomic DNA versus ccfDNA. Driver mutations were screened using the customized 12 gene panel related to CRC in NGS. Results: The electrophoretic profiles of microsatellite biomarkers tested in ccfDNA matched those in the respective primary tumors in all cases with the higher quality in liquid biopsy samples relatively. In 7 of 23 cases where a driver mutation was identified in the primary tumor, concordance of those mutations in matched ccfDNA samples was examined by NGS. Discussion: The relative sensitivity of detecting ccfDNA MSI appears to be at least as sensitive as detecting diriver mutations by next-generation sequencing (NGS) approaches.

KEYWORDS: colorectal cancer, liquid biopsy, microsatellite instability, driver mutations, next-generation sequencing

S-67 - Role Of MIR-18a And MIR-584 On Ampk Pathway In Endothelial Cells

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Introduction and Aim AMPK plays role in maintaining cellular energy homeostasis. Previous studies showed that dysregulation of autophagy and decreased AMPK activity lead to atherosclerosis. MicroRNAs are found to be regulators of important metabolic processes. In a previous study, it was shown that miR-18a is a regulator of autophagy. In addition, studies showed that miR-584 downregulated in patients with CAD. The aim of this study was to determine the expression of atherosclerosis-related miRNAs and to test the dependence of their expression on AMPK activity in HUVEC. Methods In order to investigate the differential expression of miR-18a and miR-584, and A PKα gene, HUVEC were treated with A PK a tivat r (AICA) and inhibit r (Compound C). Quantitative RT-PCR and western blot were performed for the determination of the expression levels. Results Activation of AMPK by AICAR was found to increase the ex ressi n A PKα while decreasing the expression of miR-18a and miR-584 in HUVECs. Protein expression studies showed that the h s h rylati n A PKα in reased in the lt re nditi ns with AICA . An in rease in the ex ressi n levels of miR-18a and miR-584 was observed in conditions that contain Compound C when compared to condition includes AICAR. Discussion In this study, it was found that the expression of miR-18a and miR-584 is affected by the activation and inhibition of AMPK. These results suggest that miR-18a and miR-584 could be important in the development of CAD and could be therapeutic targets for the disease. The Research Support Unit of Istanbul University supported this study with the project no:51865.

KEYWORDS: ATHEROSCLEROSIS, AMPK, MIRNA, HUVEC

S-68 - The investigation of epigenetic changes in NFATC1 and FOS genes in post-menopausal cases

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Decreased level of estrogen during menopause directly related with postmenopausal osteoporosis and RANK/RANKL pathway has an important role for stimulating osteoclast differentiation. NFATC1 and FOS are two genes which are the down targets of RANK/RANKL pathway and also, NFATC1 is the key transcription factor in osteoclastogenesis. In this study, we analyzed NFATC1 and FOS gene methylation in blood samples of 35 post-menopausal and 30 pre-menopausal cases. NFATC1 promotor were methylated in 11 (31.4%) and unmethyalted in 24 (68.8%) of the post-menopausal women. In the control group; 19(63.3%) of the samples were methylated and 11 (36.7%) of the samples were unmethylated. Here is a statistically significant association between post-menopause and unmethylation of NFATC1 promotor ($p = 0{,}010$). FOS promotor were methylated in 6 (17.1%) post-menopausal women and unmethylated in 29(82.9%) of women ($p > 0.005$). In vitro studies showed the inhibition of the NFATC1 causes suppression of osteoclast formation so it is a master transcriptional regulator of osteoclasts. Here, we can speculate that the unmethylation of NFATC1 gene can increased osteoclast activity but we cannot prove this hypothesis because of we used blood samples. These results will help to design further epigenetic studies on osteoclast cells in postmenopausal cases. This study is the first epigenetic study that investigated the NFATC1 and FOS methylation in post-menopausal cases. Although the limited number of sample size in our study and lack of epigenetic studies in this field proves our results crucial and therefore, our results showed magnitude of epigenetic profile of Turkish Cypriot post-menopausal women.

KEYWORDS: MS-HRM, FOS, NFATC1, post-menopause, methylation

S-69 - Management of chromosome 10q22.3q23.2 deletion syndrome

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Introduction and Aim: Chromosome 10q22.3q23.2 deletion syndrome (MIM#612242) is a rare microdeletion syndrome, characterized with mild dysmorphic features, several multiple congenital anomalies, developmental and speech delay. Also, juvenile polyposis syndrome (JPS) is known to accompany in some cases(1). We report a 18 year-old patient with intellectual disability,mild dysmorphic features,slender body and pectus excavatum. He was operated from bilateral external acoustic meatus atresia and cleft palate. A 7,43 Mb loss on chromosome 10q22.3q23.2 was the genetic etiology. The aim of this report is to highlight the importance of management and counseling of this syndrome and discuss unexpected findings of comprehensive genetic testing as well. Material and Method: Chromosomal microarray analysis was performed Affymetrix, CytoScanOptima 315K SNP microarray platform. Results: A loss, sized 7,43 Mb, was detected on chromosome 10q22.3q23.2 of the patient. Deleted region harbors NRG3, GRID1 and SNCG genes that are related with neurodevelopmental processes. Besides, BMPR1A gene was in the region. Discussion: Despite being a useful technology for multiple congenital anomaly patients, microarray may be resulted with unexpected findings. Heterozygous mutations and deletions of BMPR1A are detected in approximately 21% of patient with JPS(2). Baseline JPS screening was recommended including complete blood count, colonoscopy and upper gastrointestinal endoscopy to our case,although not showing any JPS symptoms. Analysis of further patients with 10q22.3q23.2 deletion will improve managing patients and counseling. References: Singh et al.,Interstitial deletion of 10q23.1 and confirmation of three 10qdel syndromes.Singapore Med J.2011,52(7):143-146 Dahdaleh et al.,Juvenile polyposis and other intestinal polyposis syndromes with microdeletions of chromosome 10q22-23.Clin Genet.2012;81(2):110-6.

KEYWORDS: microarray, unexpected findings, counseling, 10q22.3q23.2 deletion, juvenile polyposis syndrome

S-70 - Isotretinoin exposure during pregnancy and teratogenic effects in fetus

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Isotretinoin is a very effective drug for treating severe acne. Besides this beneficial effect on acne treatment, it has been accepted as one of the most teratogenic agent after thalidomide. Isotretinoin exposure in the postconception was associated with an increased risk of spontaneous abortions and serious birth defects. In this study, the teratologic effect in fetus of isotretinoin was investigated. The study prospectively identified 109 women who had been treated for acne with isotretinoin during the periconception and referred to the Teratology and Genetic Center in Department of Medical Geneti s, Cerrah aşa edi al S h l, Istanb l University-Cerrah aşa between 2012 and 2018. 54 ases t 109 were treated rally with is tretin in d ring postconception. These 54 cases had 7 (13%) congenital abnormalities, 6 (11%) intrauterin ex, 6 (11%) abortion and 17 (31%) curetage with voluntarily. Overall 73 pregnant women delivered healthy babies. Our study reports that rate of babies born with anomalies or healty exposure occurred during the teratogenic risk period. And further states the importance of teratological counseling to the families.

KEYWORDS: Isotretinoin, teratology, fetus.

S-71 - Three Patients with Joubert Syndrome and KIF7 gene mutations: Genotype phenotype correlation

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Joubert Syndrome(JS) is a group of diseases characterized by psychomotor retardation, ataxia,abnormal eye movements,cerebellar agenesis and respiratory dysregulation.It is autosomal recessively inherited.JS shows clinical and genetic heterogeneity.Retinal degeneration,renal cysts,liver fibrosis and skeletal involvement can be observed.Molar Tooth Sign(MTS) detected in the Axial-BrainMRI imaging is a pathognomonic marker in JS. KIF7 encodes a siliary protein.Mutations detected in KIF7 gene have been associated with hydrolethalus and acrocallosal syndromes, and recently there have been a number of publications on the relationship between KIF7 gene mutations and JS.In this report, we present 3 new, independent patients with JS syndrome carrying KIF7 mutations. Case Report:Case-1:3 year old female patient had dysmorphism, motor mental retardation, relative macrocephaly, frontal bossing, breathing problems, laryngomalasia, bifid hallux of right foot, polysyndactyly and secundum ASD.Case-2:3 month old female patient had dysmorphism,hypotonicity,relative macrocephaly,frontal bossing,breathing problems,broad right hallux,bilateral partial syndatyly of 2-3th toes.Case-3:15 years old female patient had dysmorphism,macrocephaly,frontal bossing, breathing problems,broad right hallux,bilateral partial syndatyly of 2-3th t es. All 3 atients had ‘m lar t th sign’ and agenesis of cerebellar vermis in MRI. Genetic analysis of 3 patients revealed homozygous missense mutations in KIF7 gene.Case-1 had Arg154Ter (NM_198525.2:c.460C>T) mutation,case-2 and case-3 had Arg973Ter (NM_198525.2:c.2917C>T) in KIF7 gene. Conclusion:We presented three patients with JS with mutations.Common features of our patients were developmental retardation,dysmorphism,toe finger involvement,syndactyly,MTS and cerebellar vermis agenesis.Cranial,facial and digital involvement were remarkable.Retinal dystrophy and renal or hepatic involvement were not observed.And more to this, we believe that there seems to be a founder effect in northern Turkey for KIF7 mutation.

KEYWORDS: Joubert, KIF7, Molar tooth sign

S-72 - Importance Of Clınıcal Genetıcıst In Patıent's Data Analysıs Wıth Samples

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The development of technology and the reduction of costs increased the use of disease panels which contain many genes, whole exome or whole genome tests for clinical diagnosis. However, as is the case in many countries, the question of who will carry out these tests in our country is still not clear. Genetic diseases are diseases that concern all systems and should be considered as a whole. It is a whole that cannot be reduced to simplicity, which should be evaluated by people who have the capacity to handle both analysis and clinic. The importance of the role of clinical geneticists in test prompts and evaluations will be emphasized with examples of patients diagnosed in our clinic.

KEYWORDS: CLINICAL GENETICIST, DATA ANALYSIS

S-73 - DIFFERENT PRESENTATIONS OF LONG QT SYNDROME

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Long QT syndrome is a rare disorder of myocardial repolarization characterized by a prolonged QT interval. It can lead to syncopes, ventricular arrhythmias and sudden cardiac death, especially after increased sympathetic activity and caused by defects in the ion channel genes. A 49 year old male diagnosed with hypertrophic cardiomyopathy (HCM) and had a family history of sudden death and HCM had long QT in ECG. Next generation sequence (NGS) analysis was revealed a pathogenic heterozygous mutation in the KCNQ1 gene. Family screening also revealed similar mutation in his daughter. The other case was a 16 year old boy who had a family history of sudden death. The QT interval was normal in the ECG. NGS revealed a heterozygous mutation in the ANK2 gene which was also identified at his sister. Last case was a 13 year old girl, whom applied for a medical report for performing exercise. Long QT was coincidentally recognised in her ECG. NGS revealed pathogenic mutation in KCNQ1 gene. Long QT syndrome may not always be symptomatic but the consequences may be dramatic. Absence of family history and asymptomatic state does not rule out this condition. Family members with long QT syndrome should be screened. In addition, statement of health reports to approve sportive activity should be given with caution to prevent suddent death due to sportive.

KEYWORDS: Long QT Syndrome, Sudden Death, Genetic Conselling, KCNQ1 , Family History

S-74 - An Interesting Translocation Pattern With Phenotypically Normal Family; A Daughter Inherited t(5,18) From The Mother With Two Independent Translocation t(1,2) t(5,18)

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Introduction and Aim: Double translocation is a rare chromosomal abnormality. Carriers have a high risk of having offspring with unstable translocation. The identification of these translocations is quite important for accurate genetic counseling. Material and Method: High resolution chromosome analysis was performed from the peripheral blood of the individuals in three generations of a Turkish family. G banding was used to identify structural abnormalities. Twenty cells were counted at least for each patient. Results: We found de novo reciprocal double translocation t(5,18) t(1,2) in the mother. The family study revealed that she transmitted only one of balanced translocation t(5,18) to her daughter. Discussion: Two independent reciprocal translocations found in a carrier are a subset of complex chromosomal rearrangement, although some authors define as multiple chromosomal rearrangements. Such two-way exchanges are rare and mostly de novo chromosomal aberrations. The phenotype of offspring of carriers may vary from normal to severe defects depending on the segregation mode. Therefore, being aware of such chromosomal rearrangements prior to pregnancy is very important in terms of genetic counseling and correct orientation of the process.

KEYWORDS: Double Translocation, Complex Chromosomal Rearrangement, Genetic Counseling

S-75 - EFFECTS OF ETANERCEPT ON CELL PROLIFERATION IN HUVEC CELL LINES

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Introduction And Aim: Tumor necrosis factor (TNF) is a proinflammatory cytokine secreted by many cell types. In recent years, anti-TNF drugs, antagonizing the biological effects of TNFa, have begun to be used in the treatment of rheumatic diseases. Etanersept is a medicine that treats autoimmune diseases by acting as a TNF inhibitor and combining with TNF. The aim of the study, was to investigate effects of etanersept in dose and time depending manner on proliferation factors in HUVEC(Human Umbilical Vein Endothelial Cells) cell lines. aterial& eth ds: In the st dy, etanerse t determinant d ses were identi ied in rder t st dy its ‘e e t on 24 and 48 hours HUVEC cell index using xCELLigence system. The effect of Etanercept on expression levels of FGF1, MYC 204; NFKB1, VEGF, CDK4 genes were evaluated by quantitative PCR. Experiments were studied in duplicate for each dose and compared with the control group. Results: The effect of etanercept on expression of genes was analyzed. Significant increases were observed in in VEGF, CDK4 and FGF gene expression levels, which have an effect on cell growth and differentiation, in specific doses compared to the control group. In the results, it was remarkable that there were increases in different genes, times and doses. Discussion: Results shows that etanercept, which has anti-TNF effect, may induce cell proliferation and may lead to formations of tumors and malignancy due to prolonged use. These results regarding the effect of etanercept are pioneer results and should be considered as the groundwork for the future researches.

KEYWORDS: Etanersept, TNF-a, anti-TNF, RA, cell proliferation

S-76 - Identification of IFN-beta-1a therapy related biomarkers in T cells of multiple sclerosis patients

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Introduction and Aim Relapsing-remitting multiple sclerosis (RRMS) is an inflammatory and degenerative disease characterized by autoimmune demyelination in the central nervous system. Although interferon-β-1a (IFN-β-1a) have been used to treat RRMS patients, this goal can not be attained in some individuals. The aim of this study is to investigate specific biomarkers which are related with different IFN-β-1a therapeutic responses in RRMS patients. Material and Method Forty-two RRMS patients were recruited to the study. CD4+ T (helper) cells were isolated from peripheral blood and characterized by flow cytometry. CD4+CD25+ regulatory (Treg) T cells were isolated from T helper cells by fluorescence-activated cell sorting (FACS), then characterized. Cells were cultured and cytotoxicity assay was performed for 4, 16, 24 and 48 hours to determine optimum drug concentrations affecting cell viability. Gene expression levels of IL-6, IL-10, IL-17, IL-23 and FOXP3 were analyzed in drug-treated cells and control cells by using qRT-PCR. Results were evaluated statistically. Results FOXP3 gene expression level was decreased approximately 1.7 fold after 16 hours in CD4+ T helper cells following treatment, however, it was upregulated in controls after 24 hours. FOXP3 showed an increase over the period, while the expression of IL-10 decreased by time compared to the controls in Tregs. Discussion FOXP3 and IL-10 may be used as biomarkers for Treg cells. The results obtained from the study may help to understand the molecular mechanisms regarding to MS and to develop a personalized treatment method. This study was funded by TUBITAK 1002 funding programme (Project number:216S828).

KEYWORDS: Multiple sclerosis, MS, IFN-beta, CD4+ T cells, biomarker

S-77 - Diagnostic Approach in Hydrops Fetalis: Discussion of Three Cases

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Introduction and Aim Diagnosis of hydrops fetalis (HF) is a comprehensive approach in the prenatal period. The prior investigation should rule out non-genetic etiologies, including immune hydrops, infection, Rh and blood group incompatibilities, structural cardiac abnormality, fetal cardiac arrhythmia, tumor, lung mass, twin-twin transfusion, and maternal factors. An array of different Mendelian conditions may underlie the HF, such as peroxisome biosynthesis and lysosomal storage disorders, mucopolysaccharidosis, RASopathy, hemoglobinopathy, and disruption of lymphatic system development. Material and Method Patients were referred to the medical genetics department upon suspicion of HF caused by an inherited disorder. Their conditions were noted in the 2nd-trimester obstetric ultrasonography screen. All three fetuses were products of consanguine s marriages. ther's ages were between 35- 40 years old. DNA was isolated from parental peripheral blood or amniocytes. Whole exome/clinical exome sequencing was performed. Genes related to HF (OMIM, ClinVar, panels of various certified laboratories) were screened. Sanger sequencing was implemented in confirmation of a variant found in exome sequencing. Results Patient-1 was a carrier of c.401_404del p.(Val134AlafsTer71) mutation in PIEZO1 gene (Lymphatic malformation 6, AR), his spouse was a carrier for the same mutation, too. For patients -2 and -3, we have scheduled clinical exome sequencing, which comprises >80% of the HF genes listed in Genomics England. Discussion Genetic screening should be considered when there are one or more HF incidents in consanguineous parents, where other laboratory investigations do not reveal causation. Whole exome or clinical exome sequencing is time and money saving over targeted gene sequencing approach.

KEYWORDS: Hydrops fetalis, whole exome sequencing, clinical exome sequencing, PIEZO1

S-78 - Prenatal management and pregnancy outcomes in fetuses with cystic hygroma

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Introduction and Aim Cystic hygroma (CH), is defined as congenital lymphatic system abnormality characterized by abnormal fluid accumulation in the fetal neck and may be related to aneuploidies, major congenital anomalies, pregnancy loss and developmental disorders. Trisomy 21, 18 and Turner syndrome are the most common numerical chromosomal anomalies associated with CH, but major structural anomalies can be detected in one third of fetuses having normal karyotype. Our aim was to determine the prenatal management and pregnancy outcomes in our series of fetuses with CH. Materials and Methods This retrospective study was undertaken between January 2013 and February 2019 in the Perinatology Unit of Trakya University, Turkey. All medical records were collected from Obstetrics&Gynecology and Genetic Departments. After the diagnosis was made,all future parents were informed about the prenatal management options and possible unfavorable course of CH. Genetic counseling and fetal karyotyping were recommended. Chorionic villus sampling or amniocentesis was performed according to gestational age. Detailed ultrasound examination was also performed to detect concomitant structural anomalies. Results The study included fifty fetuses with CH. Chromosomal anomalies were present in 15 fetuses(30%), and the most common aneuploidy was Trisomy 21(14%). Turner syndrome was also diagnosed frequently(10%). Other chromosomal abnormalities were Trisomy 18(4%) and Trisomy 13(2%). Major cardiac anomalies constituted the most common additional structural anomaly(18%). One fetus had a diaphragmatic hernia whereas two coexisted with omphalocele. Discussion Since CH is a major anomaly associated with aneuploidies and structural anomalies, genetic counseling, fetal karyotyping together with detailed ultrasound examination should be performed.

KEYWORDS: Cystic hygroma, prenatal diagnosis, aneuploidies, structural anomaly, first trimester

POSTERS

P-001 - Investigation of 3p and other chromosome abnormalities in peripheral lymphocytes in adenocarcinoma and small cell lung cancer

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3p deletions are prominent cytogenetic findings in tumor tissue of small cell (SCLC), and non-small cell lung cancers (NSCLC). These abnormalities have been reported rarely in peripheral lymphoctes of SCLC patients. Since peripheral lymphocytes are easy to collect and processed, they would be valuable source for predicting cancer development, prognosis and future metastasis if cancer related chromosome abnormalities can be scanned in this tissue. To evaluate this, we analyzed peripheral lymphocytes of untreated 24 SCLC and 30 lung adenocarcinoma cases, and 20 healthy control subjects. 72h. lymphocyte culture procedure and GTL banding was applied, and metaphases were evaluated according to ISCN 2016. 100 metaphases were examined each of 18 SCLC, 25 adenocarcinoma and 20 control subjects that we obtain good quality metaphases. Monosomies of all chromosomes were observed in both patient groups and were the most prominent abnormalities. -19 and -22 were the most frequent abnormalities, observed in 34 cases each. Monosomy 3 was noted in 16 SCLC (%64), and 8 (%44) adenocarcinoma cases. All monosomies except X were significantly higher than control group, whereas there wasn't signi i ant di eren e between st dy gr s. del(18)(11) (4 aden a,2 SCLC), del(6)(q15q21) (3 adenoca,1 SCLC), and del(22)(q12) (1 adenoca,1 SCLC) were our recurrent structural anomalies. Structural chromosome 3 abnormalities were detected in only 2 (1 adenocarcinoma,1 SCLC) patients. Although there were significantly more chromosome abnormalities in patients than controls, 3p abn rmalities weren't req ent and, we n l ded that being time and e rt ns ming, yt geneti analysis peripheral lymphocytes to predict prognosis or metastasis is not recommendable.

KEYWORDS: Chromosome abnormalities, Lung cancer, small cell lung cancer, adenocarcinoma, cytogenetics

P-02 - Mosaic Trisomy 9 Presenting With Congenital Diaphragmatic Hernia And Facial Dysmorphism

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Introduction: Mosaic trisomy 9 is a rare disorder that characterized by intrauterine growth restriction, mental retardation, hypotonia congenital heart defects, facial dysmorphism, musculoskeletal, genital and renal anomalies. Aim:The current report was aimed to compare the methodological based techniques in the diagnosis of mosaic trisomy 9 case with multiple congenital anomalities. Materials and Methods: Newborn baby with non-consanguineous marriage was referred us because of multiple congenital anomalies. Clinical examination showed hypotonia, facial dysmorphism, short neck, bilateral undescended testes and camptodactyly. At second trimester of gestation, level II ultrasound showed congenital diaphragmatic hernia .The parents elected to terminate the pregnancy. Patient was analyzed by comparing methods of chromosamal analyses,FISH analyses and Microarray-CGH (Agilent 180 K platform,US) Results: The cytogenetic analyses of patient was 47,XY,+9[2]/46,XY[13] indicating %13 (2/15) mosaicism for trisomy 9. Fluorescence in situ hybridization (FISH) analysis of cultured cells showed three signals in 10 out of 31 interphase/metaphase cells and two signals in the remaining 13 interphase/metaphase cells indicating 32% (10/31) mosaicism for trisomy 9. Array comparative genomic hybridization (aCGH) analysis of the genomic DNAs from peripheral blood-EDTA using oligonucleotide-based aCGH revealed genomic imbalance and %30 gene dosage increase in chromosome 9. Discussion: Mosaic trisomy 9 is a rare disorder and associated symptoms may vary greatly in range and severity, depending on the percentage of cells with the extra chromosome. The current results showed us the important eficiacy of FISH and MicroArray-CGH techniques in the definitive diagnosis of mosaic trisomy 9 cases

KEYWORDS: Mosaic trisomy 9, congenital diaphragmatic hernia, Microarray-CGH

P-03 - A PGD outcome of the intronic mutation of the ABCC8 gene linked to congenital hyperinsulinism

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Introduction and Aim: Congenital hyperinsulinism (CHI) is characterized by the drawbacks in the insulin secretion by the pancreatic beta-cells and the most common reason of the persistent hypoglycemia in infancy (OMIM#256450). CHI has been revealed to be inherited in an autosomal recessive or dominant pattern, and associated with the mutations in the several genes including ABCC8, defecting ATP-potassium channel function. Here, we present a preimplantation genetic diagnosis (PGD) case where exclusion of an intronic mutation (c.2041-25G>A) with the evaluation of variant of uncertain significance, which was heterozygous in each parent and homozygous in an affected child who was applied whole exome sequencing method to identify the phenotype-associated mutations, prevented CHI in the newborn. Material and Method: Oocytes were picked up by antagonist protocol. After in vitro fertilization (IVF), eight blastomere cells were analyzed for wild type cells by ABCC8-linked STR markers as well as linkage analysis at day three, and normal cells were transferred to the mother via frozen embryo transfer (FET). Results and Discussion: PGD analyses of eight blastomere cells showed that four of the cells carried the related mutation; three of them were the wild type; and one of them was technically unusable. The normal cells were transferred to mother and the newborn individual was healthy. This study underlines the possible role of the intronic mutations with uncertain significance in CHI. Moreover, PGD may be a protocol to confirm the potential affect the uncertain mutations in the presence of appropriate consents of the parents.

KEYWORDS: Congenital hyperinsulinism, Preimplantation genetic diagnosis, ABCC8

P-04 - TWO NOVEL MUTATIONS IN THREE DIFFERENT GENES ASSOCIATED WITH RETINITIS PIGMENTOSA/LEBER CONGENITAL AMAROSIS IN ONE PATIENT

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Introduction: Inherited retinal dystrophies are one of the most common causes of blindness in the world, affecting approximately 1 in 3000 individuals. A majority of the defects are in genes that are expressed in photoreceptors or the retinal pigment epithelium. Retinitis Pigmentosa(RP) and Leber Congenital Amarosis(LCA) are both characterized with severe retinal dystrophy affecting the photoreceptors. Herein we present a family with Leber Congenital Amaurosis with 3 different genes inherited in homozygous state in one member of the family. Methods: After DNA isolation from peripheral venous blood all exons and exon-intron boundaries were sequenced using Agilent SureSelect V5 kit in Illumina NovaSeq platform and Sophia DDM database analysis. Identified mutations from proband were analyzed at other family members via Sanger sequence analysis confirmation. Case: Twenty-seven years old male patient referred to our clinic with congenital nystagmus and dark-blindness. He had afebrile seizure at one year old. After WES data analyses, we found two novel homozygous mutations at three different genes associated with RP and LCA. One of the novel mutations was in RPE65 gene(p.Tyr466*), other novel mutation was in AIPL1 gene(p.Ala289_Pro292del) and his known mutation was in ARHGEF18 gene(p.Gly23Arg). After these results, we consulted eye examination for him in order to figure out the differential diagnosis between RP and LCA. With his genetic results, he got diagnosed as LCA. Conclusion: We have reported our patient to expand the spectrum of mutations in RP/ LCA related genes and implicate the importance of genetic analysis for patients to get the right

KEYWORDS: Retinitis Pigmentosa(RP), Leber Congenital Amarosis(LCA), AIPL1, ARHGEF18, RPE65

P-05 - Hypoxia induced HIF1α and NOS3 Expression Profiles in JAK2V617F Positive Cancer Stem Cells of Polycythemia Vera

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Introduction: Polycythemia vera (PV, MIM #263300) is a myeloproliferative neoplasm. Caused by somatic mutations in hematopoietic stem cells (HSC). The most common found genetic variant is p.V617F in JAK2. We hy thesized that xygen level and rea tive xygen s e ies might reg late HIF1α and NOS3 ex ressi ns in JAK2 mutated cancer stem cells. Material and Methods: In this study, we aimed to find the role of hypoxia on cancer stem cell (CD34+ /-) and m n n lear ells (NC) by dete ting HIF1α and NOS3 gene ex ressi n profiles in JAK2V617F positive PV. Blood samples have been collected from 10 patients with PV, MNCs isolated by using ficoll-gradient centrifugation and sorted with cell sorter by using CD34 antibodies. CD34+/- m artments were rther lt red at 37°C in n rm xi (20% O2), hy xi (1% O2) and an xi (0% O2) conditions by using Cellasic ONIX instrument. DNA and RNA isolations were performed for the assessment of p.V617F mutation and hy xia related gene ex ressi n r ile. es lts: In l w xygen n entrati n, HIF1α gene expressions were increased in CD34+/- compartments while NOS3 gene expressions were insignificant. Only 7 out of 10 RNA isolates were appropriate for expression analysis. Dis ssi n: HIF1α were nd t demonstrate higher expression profile in PV CD34+ /- as anticipated. More experiments are required in order to provide the role and the significance of hypoxia on cancer stem cell function.

KEYWORDS: Hypoxia, Polycythemia Vera, Cancer Stem Cell, JAK2V617F, Myeloproliferative Neoplasm

P-06 - A novel homozygous frameshift SPTBN2 gene mutation associated with Spinocerebellar Ataxia-14

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Spinocerebellar ataxia-14 caused by a homozygous mutation in the SPTBN2 gene, is a neurologic disorder characterized by delayed psychomotor development, severe early-onset gait ataxia, eye movement abnormalities, cerebellar atrophy on brain imaging, and intellectual disability. Unlike many other spinocerebellar ataxia, it is infantile onset. Whole-Exom Sequencing is performed by using an isolated DNA from peripheral blood sample of a female patient who had psychomotor retardation, behavior anomalies, delayed speech and cerebellar atrophy on cranial MR. We detected a homozygous frameshift deletion, c.3427delC, also confirmed via Sanger squencing, on SPTBN2 gene. This variant was also observed heterozygous state in her mother and father who had relationship between them.As far as we know, this frameshift deletion is not found any clinical databases (ClinVar or Human Genome Database HGMD ect.). It could alter gene function by causing an early termination of gene expression. According to the guideline of Ameri an C llege edi al Geneti s (AC G) (PVS1, P 2, PP3) it is lassi ied as ' ath geni '. As a conclusion, with this mutation that we found, we added a new one to the variants detected in the SPTBN2 gene. Functional studies are needed to contribute to the determination of the pathogenicity of this variant.

KEYWORDS: Spinocerebellar Ataxia, SPTBN2 gene, c.3427delC, Next Generation Sequencing

P-07 - CYTOTOXIC T-LYMPHOCYTE ANTIGEN-4 GENE POLYMORPHISM IS NOT ASSOCIATED WITH INCREASED RISK FOR CHRONIC LYMPHOCYTIC LEUKEMIA IN MACEDONIA POPULATION

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CYTOTOXIC T-LYMPHOCYTE ANTIGEN-4 GENE POLYMORPHISM IS NOT ASSOCIATED WITH INCREASED RISK FOR CHRONIC LYMPHOCYTIC LEUKEMIA IN MACEDONIA POPULATION Elena Arangelovic, Marica Pavkovic, Rosica Angelovic, Sanja Trajkova, Slobodanka Terziev-Trpkovska, Irina Panovska-Stavridis, Sonja Genadieva-Stavric, Aleksandar Stojanovic. University Clinic for Hematology, Medical Faculty, Skopje, Republic of Macedonia. INTRODUCTION: Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a glycoprotein molecule that is highly homologous to CD28 and reacts with higher affinity to B7.1/ B7.2 on antigen-presenting cells. It is transiently expressed on the surface of activated T-cells and delivers an inhibitory signal to the T cell. An A to G polymorphism at position 49 of the CTLA-4 first exon, has been associated with several autoimmune dis rders like Graves' disease, Hashim t thyr iditis,Ty e 1 Diabetes mellitus. Some studies have reported association of this CTLA-4 polymorphism with the higher risk and susceptibility for Non Hodgkin Lymphoma(NHL) and Chronic Lymphocytic Leukemia(CLL). The aim of our study was to investigate a possible association of this CTLA-4 polymorphism with the risk for CLL in our population. METHODS: We have examined this CTLA-4 polymorphism in 130 CLL patients and 100 healthy controls. In our series, 30 of these 130 CLL patients had a prior history of autoimmune hemolytic anemia(AIHA). RESULTS: Our results did not demonstrate significantly different CTLA-4 genotypes distribution in patients with CLL (G/G=16, A/G=53, A/A=61) comparing with controls (G/G=10, A/G=39, A/A=51), p=0.777. A strong correlation was observed between the presence of the CTLA-4 G allele and the development of AIHA (CLL with AIHA, A/A=8, G/A=20, G/G=2, versus CLL without AIHA, A/A=53, G/A=33, G/G=14; p=0.004). Interestingly, this correlation was less significant when we compared DAT positive and DAT negative CLL patients, regardless of the presence of AIHA (p=0.021). Our data indicate that the G allele of CTLA-4 gene is more frequent in CLL patients with AIHA and/or anti-erythrocytes antibodies.

KEYWORDS:

P-08 - Family Based GWAS for Colorectal Cancer Identifies Five Susceptibility and Twelve Prognosis Related Loci in Turkish Population

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Introduction: In Turkey colorectal cancer (CRC) incidence is in the 3rd place among other cancers. We have conducted the validation study of the first GWAS for CRC conducted in Turkish population. Material and Methods: Family based GWAS was conducted (Affymetrix 250K-Nsp1) for 51 trios. Validation of 75 candidate SNP was performed using KASP (kompetitive allele spesific PCR) on 1019 sporadic CRC cases and 948 controls. SNPs were excluded if their minor allele frequency was <5%, or if the p-value of Hardy-Weinberg equilibrium test was <10-6 or if the linkage disequilibrium measurement, r2>0,8. Multiple logistic regression was used for additive, dominant, and recessive models. Odds ratios were adjusted for gender and the first principal component based on observed data for genomic control of population stratification (inflation fa t r, λ=0,903). F rther analysis is vered t lassi y the atients by their stat s metastasis, an er ty e, stage, grade, and tumor location. Results and Discussion: A total of 5 SNPs, rs635833, rs3007737, rs6826441, rs10067633, rs16829831, were found to be significantly associated with CRC risk ($p<0.05$). rs6826441, rs16829831, rs10067633 and rs3007737 were significantly associated with CRC stage. rs878250 and rs635833 showed association with disease grade. Meanwhile, rs1797710, rs17082506 and rs4283324 conferred risk for metastasis. In addition, rs17082506 and rs635833 were significantly associated with mucinous CRC. Whereas, rs6928177, rs16954516 and rs7516468 were associated with tumour location To the best of our knowledge, this is the first GWAS and its validation reporting predisposition to sporadic CRC in Turkish population. This study is supported by TUBITAK project no. 112S634.

KEYWORDS: Colorectal Cancer, GWAS, SNP

P-09 - Epigenetic Analysis Of BNC1, SCUBE3, SFRP1 and PCDH8 Candidate Tumor Suppressor Genes In Renal Cell Carcinoma

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Cancer, affected by environmental factors, is a process formed by the results of genetic and epigenetic changes. Methylation is the leading type of these epigenetic changes. Many researches in the field emphasized that some genes hypermetylation are efficient on the formation of many cancer types. Renal cell carcinoma (RCC) is the most common tumor of the kidney. Renal cell carcinoma (RCC) accounts for 2-3% of all cancers. The highest incidence is seen in developed countries. The incidence of the disease is increasing by about 2% annually in the whole world and in Europe. RCC is the most common massive lesion in the kidney. The aim of this study was to determine the methylation status of BNC1, SCUBE3, SFRP1, and PCDH8 genes in pRCC patients. After bisulfite conversion of DNAs isolated from paraffine embedded tumor and adjacent normal tissues of 24 patients. As a result; it can be thought that promoter methylation in BNC1, SCUBE3, SFRP1, and PCDH8 genes may have a role in the pathogenesis of RCC. However, further studies by using different molecular techniques are needed to clarify these results.

KEYWORDS: Renal Cell Carcinoma(RCC), BNC1, SCUBE3, SFRP1, PCDH8

P-10 - Clinical characteristics of 3p26.3p25.3 deletions and 19p13.3 duplication

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Clinical characteristics of 3p26.3p25.3 deletions and 19p13.3 duplication Introduction We report a 12-year-old female patient with growth failure, dysmorphic facial appearance, developmental delay, intellectual disability and seizures. Molecular cytogenetic analysis showed 9,2Mb deletion of the 3p26.3p25.3 and 5,9Mb duplication of 19p13.3. While there are several reports in the literature about each of these chromosomal regions rearranged by other chromosome partners, this is the first case with partial monosomy 3p and partial trisomy 19p. Material and Methods: A standard protocol was used for conventional karyotyping. Subtelomeric FISH analysis was performed for only 3p-3q and 19p-19q in index atient a rding t man a t rer's protocols. Genomic DNA was extra ted sing asterP re™ C m lete DNA P ri i ati n Kit. Chr m s mal mi r array analysis (CytoScan 750K Array, Affymetrix) was performed. Results: Chromosome analysis showed 46,XX,der(3)t(3;19)(p25,p13.3) in index patient. Subtelomeric deletion of 3p and duplication of 19p were nd by FISH analysis. The atient's kary ty e revealed nbalan ed transl ati n: 46,XX.ish der(3)t(3;19)(p25-,p13.3+)(D3S4559-,129F16/SP6+). Father was found to be carrier of a balanced translocation t(3;19)(p25,p13.3) by G-banding. Array CGH analysis results were consistent with 9,2Mb deletion of the 3p26.3p25.3 and 5,9Mb duplication of 19p13.3. Discussion: 3pter-p25 deletion syndrome is a rare condition. Microduplication syndrome of 19p13.3 was reported recently. We present the first patient with combination of partial monosomy 3p and partial trisomy 19p. This case is further a good example for combined effect of partial monosomy 3p and partial trisomy 19p. Functional analysis of the genes in this region can give more information about gene dose effects on the phenotype.

KEYWORDS: deletion 3p, duplication 19p, partial trisomy 19p, partial monosomy 3p

P-11 - Comparison of a patient with 9p deletion and 15q duplication to another with 9p duplication and 15q deletion

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Introduction Distal deletion and distal duplication of 15q are rare chromosomal disorders characterized by prenatal and postnatal growth retardation or overgrowth respectively. Intellectual disability and craniofacial malformations are seen in both. 9p copy number variations especially 9p deletion syndrome is characterized by intellectual disability, trigonocephaly, dysmorphic features. Distal deletions of 9p have also been reported to cause 46,XY sex reversal. Here we present a patient with 9p deletion and 15q duplication due to maternal balanced reciprocal translocation, and another patient with a de novo 9p duplication and 15q deletion. Patient 1 In the neonatal period, the patient was consulted because of ambiguous genitalia and hypoglycemia. Chromosome analysis showed a 46,XY,der(9)t(9;15)(p23;q23) and microarray analysis revealed a deletion on 9p24.3p24.1 and a duplication on 15q24.2q26.3. Patient 2 The 11-year-old male patient who referred due to short stature and mild intellectual disability. Microarray analysis was performed and detected a 9p24.3p24.2 duplication and a 15q26.3 deletion. Discussion The IGF1R gene is located on 15q26.3 and deletions and mutations of this gene were associated with microcephaly, growth retardation and intellectual disability. Overgrowth is also related to a dosage excess of the IGF1R. Consistent with this, in the follow-up, the first patient had overgrowth and the second had growth retardation. Besides the DMRT genes in the 9p region were associated with XY gonadal dysgenesis. The deletion in the 9p region detected in patient 1 included these genes. The present cases contributes to the continuing delineation of phenotype-genotype correlations of chromosome 9p and 15q copy number variations.

KEYWORDS: 9p deletion and duplication, 15q deletion and duplication, t(9;15), IGF1R, DMRT genes

P-12 - THE PRESENCE OF EZH2 AND EZH2-TARGETED GENES IN EXOSOMES OF DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of aggressive lymphoma, and accounts for approximately 30-40% of Non-Hodgkin's Lymphomas. Although recent advances in diagnosis and treatment of DLBCL, the pathogenesis still remains to be elucidated. It is well known that exosomes derived from cancer cells are able to transfer important modulators for tumor formation and progression. In this respect, this study was designed to evaluate if transcriptional changes in EZH2 and EZH2-targeted genes in primary tumor are also observed in circulating exosomes. This study included 21 healthy volunteers and 21 DLBCL patients and then plasma exosomes were isolated. After RNA isolation from the exosomes and primary tumor tissue samples, we determined whether exosomes and primary tumor tissue samples contained transcripts of the genes. EZH2 transcript was found in all primary tumor samples of DLBCL patients but not in the exosome counterpart. CDKN1A and CDKN2A transcripts were determined in 12 (57%) and 9 (43%) of the FFPE tumor samples, respectively, whereas these transcripts were not found in the exosomes. CDKN1B transcript was determined in all FFPE tumor samples while CDKN2B transcript was determined in 3(14%) of the tumor samples. In the exosome counterpart, the presence of CDKN1B transcript was observed in 38% of the samples while there was no transcript for CDKN2B. We thought that specific target molecules were preferentially sorted into plasma exosomes in DLBCL and plasma exosomes may contibute to lymphomagenesis, at least in part, by pathogenic pathways including CDKN1B.

KEYWORDS: DLBCL, exosome, EZH2

P-13 - Ten patients with single gene disorders diagnosed by chromosomal microarray

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Introduction: Chromosomal microarray is an important diagnostic tool that can detect genomic copy number variations (CNV) in patients with intellectual disability (ID)/developmental delay and/or multiple organ anomalies. However, CMA also contributes to the diagnosis of rare single-gene disorders. Methods: Array CGH analysis (Agilent-ISCA-8x60K) were performed in 1000 patients with ID and/or different clinical findings. Results: In ten patients (1%), CNVs of the genes that cause single gene disorder were found. Clinical findings of the patients and the results were summarized in the Table. Discussion: The results of the patients indicate that CMA is not only a tool which can detect contiguous gene deletions/duplications but also contributes to the diagnosis of single gene disorders. Major deletions and duplications, which are including whole or part of the gene related to single-gene disorders, should be considered in patients who cannot be diagnosed, especially by sequence analysis. In such cases, microarray methods that can easily scan the whole genome and relatively inexpensive, and thus can be preferable.

Table: CNVs in Patients

Patient No	Gene	Syndrome	Deletion/ Duplication	Clinical findings of the patients
1	GLRA1	Hyperekplexia	Deletion	Gait disturbance
2	RUNX2	Cleidocranial dysplasia	Duplication	Teeth anomalies
3	SOX9	Campomelic dysplasia	Deletion	Bowing of long bones
6	SOX9	46,XX Testicular Disorders	Duplication	Ambiguous genitalia
4	SOX3	Panhypopituitarism	Deletion	ID, panhypopituitarism
5	SCN1A	Dravet syndrome	Deletion	Dravet syndrome
6	ARID1B	Coffin-Siris syndrome	Deletion	Developmental delay
8	IL1RAPL1	Mental retardation, X-linked	Duplication	ID
9	RYR2	Ventricular tachycardia, catecholaminergic	Deletion	Epilepsy
10	NIPBL	Cornelia-de-Lange syndrome	Deletion	Growth retardation

KEYWORDS: Chromosomal microarray, single gene disorders

P-14 - A case of Basal Cell Nevus Syndrome with a new PTCH1 gene mutation: c.592A>T

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Introduction and Aim: Basal Cell Nevus (Gorlin-Goltz) Syndrome (BCNS) is a dominantly inherited multisystem disorder, affecting skin, endocrine system, nervous system, eyes, and bones. It is characterised by multiple jaw keratocytes, multiple basal cell carcinomas and shows high penetrance and variable expressivity. Lamellar calcification of the falx cerebri, jaw keratocyte, palmar/plantar pits, multiple basal cell carcinomas, first-degree relative with basal cell nevus syndrome are major diagnostic criterias. BCNS is caused by mutations mostly in the PTCH, or SUFU genes. Material and Method: Our patient is a 9 years old girl, referred by dental surgery clinic with multiple odontogenic keratocytes. Physical examination showed macrocephaly, synophrys, telecanthus, long palpebral fissure, prominent supraorbital ridge, short nose, broad nasal root, midface hypoplasia, mild prognatism, high arched palate, microstomia. Patient history revealed palmar/plantar pits, after she soaked her hands and feet in warm water for up to ten minutes. There was no family history. Chest / skull X-rays, brain MRI; dermatological and ophtalmic clinical evaluations were normal. For molecular genetic diagnosis 2 ml of peripheral venous blood was taken, after DNA isolation multistep pathogenic variant detection protocol based on exon sequence analysis was performed. Results: Heterozyg s " lass 2" .592A>T, p.Lys198Ter mutation in exon 4 of PTCH1 (protein patched homolog 1) gene has been detected with mutation surveyor programme. No mutation was found in her parents. Discussion: The mutation was considered as de novo. To our knowledge this is the first report of PTCH1 gene c.592A>T mutation1. 1. Human Gene Mutation Database: http://www.hgmd.cf.ac.uk/ac/index.php, accessed March, 2019

KEYWORDS: Basal Cell Nevus Syndrome, PTCH1, mutation, de novo, jaw keratocyte

P-15 - A new patient with dual diagnosis: not as rare as assumed

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Introduction: The patients with multisystem involvement could have molecular pathologies for more than one Mendelian disease. Here we present a case with a molecular diagnosis for both Bardet-Biedl syndrome (BBS) and otopalatodigital syndrome (OPD). Materials and methods: A male patient whose parents have 7th-degree consanguinity and weight was 11 kg (50-75th centile), height was 77 cm (25-50th centile), and head circumference was 44.3 cm (<3rd centile) when he was 1-year-old was referred to and followed by our clinic. In his physical examination; neurodevelopmental delay, hypertelorism, micro-retrognathia, cleft palate, postaxial polydactyly, brachydactyly, clinodactyly, broad hallux, hypospadias, and cryptorchidism were observed during the follow up. In abdominal ultrasonography, a parapelvic cyst was found in his left kidney. Array CGH and WES analysis were performed for molecular diagnosis. Results and Discussion: Array CGH analysis revealed a heterozygous deletion on chromosome 9 including TRIM32 gene causing BBS11. WES analyses resulted in homozygous c.563C>A and c.1907C>T missense mutations in BBS10 gene and hemizygous c.486G>C missense mutation in FLNA gene. All mutations were confirmed by Sanger sequencing. Two or more disease loci involvements have been reported in approximately 5% of the patients who had been referred to a clinical diagnostic laboratory for WES (NEJM 376.1(2017):21-31). It is assumed that neurodevelopmental delay, genitalia problems and postaxial polydactyly in the patient may be caused by the common clinical aspects of OPD and BBS, facial dysmorphism features, head, and hand-foot abnormalities have arisen from OPD, and finally renal cyst has arisen from BBS.

KEYWORDS: dual diagnosis, WES analysis, array CGH, Bardet Biedl syndrome, Otopalatodigital syndrome

P-16 - GENETIC ASPECTS OF PREDICTIVE MEDICINE

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GENETIC ASPECTS OF PREDICTIVE MEDICINE Sevdalina Alekova**, Borislav Popov *, Veselina Petrova-Tacheva * *Department of Molecular Biology, Immunology and Medical Genetics, Faculty of Medicine **Department of internal Diseases and General medicine, Faculty of Medicine Trakia University,11 Armejska str., Stara Zagora, Bulgaria Introduction: Predictive medicine is a relatively new and modern branch of medicine, which has occurred mainly through the development in the field of genetics and genomics. It applies individual approach as it explores hereditary characteristics and predisposition to a disease in each person individually. Goal: To determine genomic and genetic aspects of application of predictive medicine, hence existing probabilities of occurrence of morally - ethical, legal cases and dilemmas. Material and Methods: To realize the goal, we have examined and analyzed the publications and reports of local and foreign experts, data from independent surveys and expert assessments. Results: The ability to prevent diseases, to treat patients before they become sick, and to encourage them to change unhealthy lifestyles make predictive medicine highly appealing for many people. Predictive medicine acts as the medicine of individuality. However, there are also a number of complex questions about the use of genetic tests and results. A genetic test can only indicate a susceptibility to the disease with no certainty of the illness developing. Despite much research, genetic susceptibility to complex diseases such as heart disease, cancer and obesity has proved difficult to identify, with many poorly reproducible results. Therefore applying genetic tests to predict disease, one can never negate the role of the environment, individual risk behavior and lifestyle. Further, when it comes to genetic testing to predict disease, cost and ethics are also of major concern. Conclusion: Predictive medicine has a major role to play in twenty-first-century health care. Although there are several scientific disciplines dealing with the concept of predictive medicine, genomics, that is the study of the human genome, is certainly the one with the biggest potential. However, predictive medicine requires not only the progress of fundamental scientific research but also the ability of health professionals and patients to enhance the availability and use of individual risk information, particularly genetic, and to be aware of the limitations and / or disadvantages associated with this new situation. References: 1. Khera, A. V. et al. Nature Genet. 50, 1219–1224 (2018). 2. C. arz ill , C. De Vit , E. D'Andrea, A. ss , P. Villari; Predictive genetic testing for complex diseases: a public health perspective, QJM: An International Journal of Medicine, Volume 107, Issue 2, 1 February 2014, Pages 93–97, https://doi.org/10.1093/qjmed/hct190 3. Nikpay, M. et al. Nature Genet. 47, 1121–1130 (2015). 4. Jen MY, Varacallo M. Predictive Medicine. [Updated 2019 Jan 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441941/ 5. Tikkanen, E., Havulinna, A. S., Palotie, A., Salomaa, V. & Ripatti, S. Arterioscler. Throm. Vasc. Biol. 33, 2261–2266 (2013). 6. Warren M. The approach to predictive medicine that is taking genomics research by storm. Nature. 2018 Oct;562(7726):181-183. [PubMed] 7. Bin P, Capasso E, Paternoster M, Fedeli P, Policino F, Casella C, Conti A. Genetic Risk in Insurance Field. Open Med (Wars). 2018;13:294-297. [PMC free article] [PubMed] 8. P. et al. JAMA Oncol. 2, 1295–1302 (2016). 9. Lee, J. J. et al. Nature Genet. 50, 1112–1121 (2018) 10. Baranov VS. Genome paths: a way to personalized and predictive medicine. Acta Naturae. 2009;1(3):70-80.

KEYWORDS: genetic and genomic aspects, predictive medicine, individual approach

P-17 - Molecular Genetic Results of Patients with Parkinson Disease from Turkey

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Introduction: Parkinson's disease (PD) is classified as juvenile-PD (<20 years), early-onset-PD(<50 years) and late-onset-PD (>50 years). Familial inheritance is seen in 15% of the patients. Material and Method: 75 PD cases (3 Juvenile, 52 early-onset, 20 late-onset) are reffered for genetic investigation and counseling. Sequence variants using in-house designed dementia-gene-panel (Ion Torrent platform) and deletion/duplication by MLPA (P051-052)have been applied. Results:MLPA in 12%, gene-panel in 8% and additive methods in 2.6% of the cases revealed 15 different pathogenic variants in 33 alleles of 17 patients (23.8%).Mutation detection rates for juvenile, early-onset and late-onset PD patients were 33.3%, 29%, and 5%, respectively. Mutations were found in PARK2 (12%), SNCA (4%), FBXO7 (2.6%) and PARK7 (1.3%) genes. Discussion: Sporadic cases are built up the highest percentage of late-onset PD patients. Multifactorial components may render them with complexities and lead to the least beneficiaries from the genetic testing in those patients. Our study was in agreement with this knowledge. Neverthless, identification of pathogenic variantsin PD not only benefits families for counseling and strategies of future therapeutic options but also for the collection of data on the mutation specific disease progressions. Rational testing strategy for PD should be recommended to start with PARK2, SNCA, FBXO7 and PARK7 analysis and using MLPA as the initial test followed by the sequencing of the associated genes before more expensive methodologies (whole geneome or exome sequencing) are applied. This work was supported in part by Istanbul University Research Fund (Project No: TDK-2016-20253)

KEYWORDS: Parkinson's Disease, Parkin, Panel Based Next Generation Sequencing, MLPA, Genetic Counselling

P-18 - Compound Heterozygous Mutation in MYO5B Gene Causing Microvillus Inclusion Disease: A Case Report

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Introduction: Microvillus inclusion disease (MVID) was defined in infants with congenital enteropathy characterized by persistent severe watery diarrhea, malabsorbtion, failure to thrive and at last death. Due to its ele tr n mi r s i examinati n inding ‘ yt lasmi in l si ns with br sh b rder mi r villi n their side’; disease named as microvillus inclusion disease. In the last decade genetic abnormalities causing MVID were defined. First, MYO5B mutations were identified in MVID patients and MVID was confirmed as an autosomal recessive disease. MYO5B encodes the myosin 5b protein, controlling the intracellular traffic. Recently, two more genes (STX3 and STXBP2) that functionally related to MYO5B were also identified as causing MVID. Although there is a late onset (around the age of 3 months) MVID is generally starts during neonatal period. Here we report an infant died because of MVID in her first year of life. Method and results: Her mother and father admitted to our outpatient clinic with her MYO5B gene mutation result for genetic counseling after her death. She was compound heterozygote for MYO5B gene mutations (c.1463T>C and c.1355_1363dup). We performed Sanger sequencing in mother and father for the mutations defined. Mother was found heterozygote for c.1463T>C and father was found heterozygote for c.1355_1363dup. After all, we informed family for prenatal testing and pre-implantation genetic testing. Discussion: MVID is a life-threatening disease starting especially during neonatal period. Although it is mostly seen in consanguineous marriages; it is also possible in non-consanguineous parents for compound heterozygosity and locus heterogeneity. Because of rareness, genotype-phenotype correlation is not available yet.

KEYWORDS: Microvillus inclusion disease, MYO5B

P-19 - Is this a fetus with monosomy X or with a de novo chromosomal rearrangement? An unusual phenomenon due the cytotrophoblastic and the mesenchymal tissues.

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Introduction and Aim: Chromosomal alterations due to the early mitotic or meiotic errors, confined to placenta and/or fetus is still a dilemma of prenatal diagnosis. Here we report a prenatal case, who has variable distribution of abnormal cell line in chorionic villi (CV) sample. Material and Method: Invasive procedure was performed at 14th weeks of gestation because of advanced maternal age. Fluorescence in situ Hybridization (FISH) analyses, and the long term tissue cultures (LTC), and array Comparative Genomic Hybridization (aCGH) analyses of CV materials were performed. The techniques were reapplied to the amniocytes. Results: FISH analyses of cytotrophoblast revealed monosomy X, cytogenetic analyses of mesenchyme tissue and amniocytes (LTC) revealed one normal, and one short arm derived X chromosome (derXp). Partial long arm of chromosome 12, was found located on derXp via FISH and aCGH analysis (partial trisomy of chromosome 12q, and partial monosomy of Xp). Discussion: The most probable mechanism of the existence of an aneuploidy, and a chromosomal rearrangement at the same fetus is the lost of derX at trophectoderm stage and the remaining of derX at the inner cell mass, which is divided to hypoblast (mesenchyme) and epiblast (amniocytes). Karyotype of the amniocytes was confirmed this hypothesis. Genetic information of variable phenotype of partial trisomy 12q due to X inactivation process, and the variant monosomy X findings, was told to the parents. References: 1- J Clin Med. 2014 Sep; 3(3): 809–837 DOI: 10.3390/jcm3030809 2- Prenat Diagn 2005; 25: 470–474. DOI: 10.1002/pd.1164

KEYWORDS: Amniocyte, Array Comparative Genomic Hybridization, Chorionic Villi Sample, Chromosomal Rearrangement, Cytotrophoblast

P-20 - Expanding the Phenotypic and Genetic Spectrum of RUSAT-2: Definition of A Novel Mutation in the MECOM Gene

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Congenital hypoplastic bone marrow failure is a rare condition in neonates and often suspected to be inherited. Radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSAT) is an inherited bone marrow failure syndrome, including thrombocytopenia and congenital fusion of the radius and ulna. Majority of RUSAT syndromes are caused by HOXA11 mutations (RUSAT-1), but MECOM gene mutations are also involved in etiology in RUSAT (RUSAT-2). MECOM gene mutations clinical spectrum varies from isolated radioulnar synostosis to severe bone marrow failure without skeletal abnormalities. Here we present a clinical and molecular characterization of a patient with MECOM gene mutation. A 1-month-old boy was consulted to Medical Genetics Clinic because of congenital adenoid malformation, prematurity and congenital bone marrow failure. The case was first born male of nonconsanguineous parents, who presented at birth with ecchymoses. He did not have distinct facial dysmorphism, visible skeletal abnormalities, or organomegaly. Biochemical investigations revealed pancytopenia (platelet count 7x103/uL, hemoglobin of 3.9 g/dL, white blood cells 2.2x103/uL). Whole exome sequencing revealed a novel heterozygous frameshift variation (c.1242dupT(p.Thr538fs)) in exon 8 of the MECOM gene. Variation validated by Sanger sequencing. Parents were also analyzed and the variation was not detected. This variation was evaluated as pathogenic according to ACMG 2015 criteria. In this report, we present a RUSAT-2 patient and we describe a novel, de novo pathogenic variant in MECOM gene.

KEYWORDS: MECOM, mutation, RUSAT-2

P-21 - An Inherited Novel FGFR2 Variant: A Case Report

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Introduction: Crouzon syndrome is the most common craniosynostosis syndrome with a prevalence of 16 per million. Its phenotypic severity ranges from very mild to lethal. We report a family with Crouzon syndrome in two generations. Case Report: An 18 years old male patient directed to our clinic because of a syndromic face and dental problems. He had ocular hypertelorism, proptosis, midface hypoplasia, a small beaked nose, and crowded teeth. His vision, hearing, and intelligence were normal. His hands and feet had no abnormality. He also claimed that his mother, brother, sister and an uncle had the same a ial a earan e. He didn't have aesthetic complaints. He was clinically diagnosed with an FGFR-related craniosynostosis syndrome. A skeletal dysplasia next generation panel test which includes FGFR1, FGFR2 and FGFR3 was ordered. Results showed the heterozygous novel missense c.185G>T p.C62F FGFR2 variant which was predicted to be pathogenic. Mother, sisters and the uncle were also tested to be positive for the variant. Conclusions: Here, in this case, we see that patients with mild phenotypes do not directly seek a genetic explanation for their condition unless they are consulted.

KEYWORDS: craniosynostosis, Crouzon, familial,

P-021 - A rare case report of SMARD1 (SPINAL MUSCULAR ATROPHY WITH RESPIRATORY DISTRESS 1) syndrome.

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SMARD 1 syndrome (Spinal muscular atrophy with respiratory distress1) is a rare autosomal genetic neuromuscular disorder characterized by progressive decrease of motor function and respiratuar failure which might cause death in early life. Responsible gene for this disease IGHMBP2, localized on chromosome 11q13. General symptoms of this diseases include devolopmental delay, tachypnea, diagraphma paralysis, recurrent apnea, weak cry, contractures of distal extremities and pes eqiunovarus. In the literature, homozygous / combined heterozygote mutation in the IGHMBP2 gene was reported in 47 cases. 5 days old male patient reffered to us with diagraphma eventration, triangular face, weak cry, hypotonia and foot deformity. IGHMBP2 gene was sequenced for SMARD1 syndrome as differential diagnosis. Test revealed c.1894_1910delCAGCATGGGGAAGTACG (p.Gln632Hisfs*4) pathogenic heterozygous and c.707T>G (p.Leu236*) likely pathogenic variants which considered as compound heterozygous. After Sanger sequencing we confirmed these hanges in atient's DNA and we nd ather and m ther heter zyg s arriers r c.1894_1910delCAGCATGGGGAAGTACG (p.Gln632Hisfs*4), c.707T>G (p.Leu236*) variants,respectively. Detailed genetic counseling has been given to family. Preimplantation Genetic Diagnosis and prenatal diagnosis is recommended for the next pregnancy.

KEYWORDS: SMA, SMARD1, IGHMBP2 gene, rare diseases, neuromuscular diseases

P-22 - Mitochondrial DNA analysis in a patient with complex neurological symptoms

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Introduction: Most studies indicate that mitochondrial DNA (mtDNA) sequence variation is a risk factor in the pathogenesis of migraine headache, diabetes mellitus, Leber Hereditary Optic Neuropathy. The aim of this study is to investigate mitochondrial changes in a 49-year-old woman with various symptoms. Methods:Mitochondrial DNA was isolated from the blood sample of the patient and mitochondrial DNA Sequence analysis was performed by Sanger sequencing method. Results: A 49-year-old female patient was referred to us with right-sided headache accompanied by nausea and vomiting and bilateral loss of vision. Her right eye had photosensitivity, discharge, itching and blurred vision;15 days later, the same situation was revealed in the le t eye. She had a ty e 2 diabetes mellit s and en valve erati n hist ry. Her arents didn't have consangenious marriage, her mother have type2 Diabetes mellitus too. In the eye examination, the VEP (visual evoked potentials) P100 res nse ldn't be btained r m b th eyes. In the mit h ndrial DNA analysis, it was found that the m.8836A>G (M104V) in the ATP6 locus, m.16390 G>A in the CR locus, m.16176C>G in the CR locus variants were homoplasmic. Discussion: The m.8836A> G (M104V) variation is known a cause of Leber's of Hereditary Optic Neuropathy. The m.16390G>A change is associated with POAG (potential for association), may be with type 2 DM. There is no associated disease with m.16176C>G variant in the CR locus; The m.16176C>T exchange is associated Cyclic Vomiting Syndrome with Migraine. Our atient's migraine diagn sis and the h m lasmi hange in the same siti n an be related.

KEYWORDS: Neurologic, Symptoms, Mitochondrial, DNA

P-024 - Investigation of the polymorphisms rs1800012 in collagen type I alpha 1 (COL1A1) in cyclists

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It has been reported that the single nucleotide polymorphism (SNP) rs1800012 in COL1A1 gene, which encode the alpha-1 chain of type I collagen, have an effect on performance of athletes. But the data from different studies are not consistent. Here we attempted to identify the association between the rs1800012 SNP and cyclists performance. Genomic DNA was isolated from oral epithelium of 38 cyclists. Genotypes of COL1A1 rs1800012 SNP were conducted. Estimation of allele frequencies were performed. Our results indicated the differences of distribution of COL1A1 rs1800012 SNP between on cyclists. The numbers and percentages of CC, AC and AA genotypes for rs1800012 polymorphism that we obtained were 24 (63%), 13 (34%) and 1 (3%), respectively. The distributions of C and A alleles were as 61 (80%) and 15 (20%). There was a significant difference in the genotype and also allele distribution between cyclists. Carriers of a C allele as compared to carriers of the allele A are more prone to cyclism.

KEYWORDS: COL1A1, SNP, cyclists, genotype, allele frequency

P-25 - DETECTION OF FUSION ABL-BCR GENE IN PEDIATRIC PATIENTS WITH LEUKEMIA

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DETECTION OF FUSION ABL-BCR GENE IN PEDIATRIC PATIENTS WITH LEUKEMIA Liljana Tasevska-Rmus1, Rosica Angelkovik2, Vesna Vankovska1, 1University Children's H s ital, edi al S h l Skopje, Macedonia 2Department of Hematology, Medical School, Skopje, Macedonia Introduction: The Philadelphia chromosome or Philadelphia translocation is an acquired abnormality of chromosome 22 which is most commonly associated with chronic myelogeneous leukemia (CML). It is the product of a reciprocal translocation between chromosome 9 and chromosome 22 [t(9;22)(q34;q11)] and this gives rise to a fusion gene bcr-abl, that juxtaposes the Abl1 gene on chromosome 9 (region q34) to a part of the BCR ("breakpoint cluster region") gene on chromosome 22 (region q11). The presence of this translocation is found in 95% of people with CML. The presence of the Philadelphia (Ph) chromosome is not sufficiently specific to diagnose CML, since it is also found in acute lymphoblastic leukemia (ALL, 25–30% in adult and 2–10% in pediatric patients) and occasionally in acute myelogenous leukemia (AML). Patients and methods: Pediatric patients with acute and chronic lymphoblastic and myelogeneous leukemia were tested for the presence of the fusion bcr-abl gene. RNA isolation from leukocytes from fresh bone marrow and peripheral blood samples was performed by Trizol extraction per manufacturer's protocol. The principle of RT-PCR is reverse transcription of mRNA from complementary DNA (cDNA) with subsequent amplification. The final result is bcr-abl fused gene detected on the 1% agarose gel as a 450bp band. Results: During the ten year period (2002-2015) 266 pediatric patients with various forms of leukemia were tested for presence of fusion gene bcr-abl gene. It was found in 7 patients (2.6%). Six patients had CML while the seventh patient with microBCR had rare Ph+ chronic neutrophilic leukemia. Conclusion: RT-PCR method is useful for detection of fusion bcr-abl gene. This is an accurate investigation, relatively cheap and the result is issued within two days. Poster Presentation Liljana Tasevska 'm s University Children's H s ital 17 V dnjanska 1000 Sk je, a ed nia Tel.+389-76- 443-396 E-mail

KEYWORDS: RNA , BCR, RT-PCR,CML.ALL

P-26 - MOLECULAR DETECTION OF HERPES SIMPLEX VIRUS TYPE 1, HERPES SIMPLEX VIRUS TYPE 2, CYTOMEGALOVIRUS AND EPSTEIN-BARR VIRUS IN SUBGINGIVAL DENTAL PLAQUE IN PATIENTS WITH PERIODONTAL DISEASE

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Introduction: Pathogenesis and some clinical features of periodontal disease cannot be explained with bacterial etiology alone. Aim: To determine the presence of the herpes simplex virus (HSV-1 and HSV-2), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) in subgingival dental plaque in patients with the periodontal disease, as well as to examine the correlation between the presence of these viruses and the level of periodontal destruction. Material and methods: Molecular analysis of the HSV-1, HSV-2, EBV and CMV was performed in a total of 89 patients with chronic periodontal disease (54 had moderate stage and 35 had advanced stage of the disease) using multiplex polymerase chain reaction (PCR). Results: In the patients with chronic periodontal disease, the most prevalent was EBV (13.5%), followed by HSV-1 found in 6.7%, HSV-2 in 3.4% and CMV found in 2.2% of patients. The molecular analysis shown presence of the viruses in 11/54 (20.4%) of the patients with moderate stage and in 15/35 (42.9%) of the patients with advanced stage of chronic periodontal disease. There was a significant difference in the presence of viruses in subgingival plaque between the patients with moderate and advanced stage of periodontal disease ($p = 0.02$). Significantly lower probability for detection of viruses in the subgingival plaque in the patients with moderate stage of the disease compared to patients with advanced stage of periodontal disease was observed (OR = 0.34 /0.13-0.88/). Conclusions: Our findings support the role of the herpes simplex viruses in the progression of the periodontal disease.

KEYWORDS: chronic periodontal disease, herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, epstein-barr virus

P-27 - Potential diagnostic value of circulating miR-1183 and its target gene in early-onset preeclampsia

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Introduction and Aim: Identification of patients with an increased risk for preeclampsia (PE) is one of the most important goals in obstetrics. The differential expression of circulating microRNAs (miRs) were reported in maternal plasma of pregnant women and they could be stabilized in blood plasma. The aim of this study was to characterize the molecular mechanism of PE development through circulating miR-1183 and its target gene expression profiles. Material and Method: Expression of circulating miR-1183 and Churchill containing domain 1 (CHURC1) mRNA was detected by RT-qPCR. The interaction between miR-1183 and CHURC1 was demonstrated by bioinformatics analysis. Results: Circulating miR-1183 was highly expressed in blood plasma of preeclamptic women with PE ($p=0.002$). Further bioinformatics investigation revealed that CHURC1 was a target of miR-1183. In contrast to the miR-1183, expression levels of CHURC1 were dramatically decreased in PE cases compared to controls ($p<0.001$). Pearson correlation between miR-1183 and CHURC1 expression levels shows an r-value of -0.37, suggesting a moderate inverse relationship between the two parameters. The accuracy levels of miR-1183 and CHURC1 according to receiver operating curve (ROC) analysis were done: the area under the curve (AUC) were: 0.79; (95% CI: 0.62-0.91) and 0.96; (95% CI: 0.78-0.99), respectively. Discussion: The overexpression of circulating miR-1183 and the suppression of its target gene CHURC1 biomarkers suggested to manipulate preeclampsia specific biological process such as trophoblast invasion and presenting a novel molecular mechanism in PE pathogenesis. This study was funded by the Research Fund of Istanbul University (Project no: 25666).

KEYWORDS: Preeclampsia, circulating miR-1183, biomarker

P-28 - Coronal Synostosis Syndrome (Muenke Syndrome)

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Coranal Synostosis Syndrome (Muenke syndrome) Neslihan Cinkara1 , Çiğdem Yü e Kahraman 1, Pelin Er şk n1, Ömer Yakar1, Abdulgani Tatar1 1Department of Medical Genetics, Ataturk University, Erzurum Introduction and Aim: Muenke syndrome (MS) (OMIM 602849) was first described in 1997, is an autosomal dominant disorder with craniosynostosis due to FGFR3 mutation (p.250Arg) [1, 2]. MS has an incidence of 1 in 30,000 births[3]. Material and Method: A three-year-old girl was referred to us with strabismus, dymorphic face and anormal shape of head. We examined the patient and planned NGS skeletal displasia panel. Results Dymorphological features were; brachycephaly, narrow forehead, temporal bossing, midface hypoplasia, bilateral exotropia and proptosis. Skull examination revealed ridged coronal sutures bilaterally. MRI showed an arachnoid cyst and partial empty sella. Moleculer testing revealed a heterozygous mutation in FGFR3 gene (.749C>G .P250A). Dis ssi n: S generally resents a rematüre si n sk ll b nes al ng the r nal suture that results anormal shape of the head and face[4]. Phenotype of patients is variable even within the same family. Patients with MS have a uni or bicoronal synostosis, synostosis of other sutures, hearing loss, macrocephaly, developmental delays [4]. Neurologic abnormalities, ocular anomalies, limb finding such as brachydactyly, carpal/tarsal fusion and cone-shaped epiphyses may occur. This case report may contribute to the literatüre. Key w rds: enke syndr me, FGF 3 related rani syn st sis, rani syn st sis e eren es: 1. Muenke M, Gripp KW, McDonald-McGinn DM, et al. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. Am J Hum Genet 1997;60:555Y564 2. P. Kruszka, Y.A. Addissie, C.M. Yarnell, D.W. Hadley, M.J. Guillen Sacoto, P.Platte, et al.Muenke syndrome: an international multicenter natural history study Am J Med Genet A, 170A (2016), pp. 918-929

KEYWORDS: Muenke Syndrome, FGFR3 related crasiosynostosis, craniosynostosis

P-29 - Two siblings with Infantile-onset multisystem neurologic, endocrine, and pancreatic disease, IMNEPD: a case report

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Introduction: Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD; MIM 616263) is a very rare disorder caused by homozygous mutation in PTRH2 gene (608625) on chromosome 17q23. Here we report two siblings diagnosed by IMNEPD and carrying novel homozygous mutations in PTRH2 gene. Material Method: A 15-year-old male patient whose parents have 3rd-degree consanguinity applied to our clinic because of intellectual disability, motor delay and polyneuropathy findings. Microbrachycephaly, narrow forehead and bilateral proximally placed thumbs detected on dysmorphic examination. He had hypothyroidism, bilateral severe sensorineural hearing loss, chronic sensorimotor demyelinating polyneuropathy and generalized epileptiform abnormality. His cranial MRI and metabolic test were normal. His 5-year-old sister displayed similar clinical features. Chromosome and array CGH analysis were performed for both siblings and WES analysis was performed for the only male patient. Results: Chromosome and array CGH analyses did not reveal clinically significant abnormalities. A homozygous c.269_270del(p.A90fs) mutation was detected in PTRH2 gene by WES analyses. His sister was also homozygous and his parents were heterozygous state for the same mutation. Discussion: IMNEPD is a very rare and newly identified disorder. Only four patients from two families have been reported up to date. Microcephaly, motor delay, hearing loss, progressive ataxia and sensorimotor polyneuropathy were common features in all patients. Exocrine pancreatic insufficiency was reported for only two patients in one family and not detected our cases. The present study enhances the literature by reporting additional proof for the mutation and the phenotypic spectrum.

KEYWORDS: IMNEPD, polyneuropathy, deafness, motor delay

P-30 - Genetic analysis of two Turkish patients with Brugada Syndrome

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Introduction and Aim: Brugada syndrome (BrS) is an autosomal dominant inherited disorder with incomplete penetrance and characterized by lethal ventricular fibrillation and right precordial ST segment elevation on ECG. We aimed to investigate the association of gene variants in the candidate ion channel genes with abnormal cardiac excitation in BrS. Material and Methods: Two male patients (19 years old and 45 years old) with type 1 Brugada ECG pattern who had ST elevation in V1-V2 leads were included in study. After the informed consent form was obtained, exome sequencing was performed using the TrueSight One Panel (Illumina, San Diego, USA) that includes 4,813 genes. Variant predictions were made using in silico analysis: Mutation Taster, Polyphen2 and SIFT. The human gene mutation database (HGMD), 1000 genomes database and ExAC browser were used to data interpretations. Results and Discussion: Several single nucleotide variants of the ion channel genes previously associated with BrS and cardiac arrhythmia were identified in patient samples. Three missense variants in SCN5A gene were predicted to be pathogenic with in silico analysis and were found in the HGMD database. V1405M pathogenic variant (CM100715) in SCN5A gene and D601E (CM103389) modifier variant in CACNB2 gene, which was known to have a phenotypic effect was found in the 45-year-old patient. The 19-year-old patient was found to have G1158S and E1784K compound heterozygous variants in the SCN5A gene (respectively, CM146082 and CM991128). In conclusion, identification of pathogenic variants in patients with BrS may benefit both in clinical follow-up and in predicting disease risk of family members.

KEYWORDS: Brugada syndrome, candidate genes, variant analysis

P-31 - A PGD outcome of the PSD3 gene mutation putatively linked to APS

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Introduction and Aim: Antecubital pytergium is a syndrome inherited in an autosomal dominant pattern and is characterized by antecubital webbing and limitation of full elbow extension (OMIM 178200). Since the reported cases are limited, the molecular genetics of the syndrome is not deciphered yet. Still, a recent study in Turkish patients revealed a heterozygous missense PSD3 variant (c.437T>C; p.Ile146Thr) in three affected kindred with antecubital pterygium syndrome (APS) by whole exome sequencing (WES) analyses and emphasizing that further molecular studies were needed to prove the proposed association (J Clin Invest. 2016;126(2):762-78). Here, we present a preimplantation genetic diagnosis (PGD) case where exclusion of the related variant prevented APS in the newborn in the family reported in the given reference. Material and Method: Oocytes were picked up by antagonist protocol. After in vitro fertilization (IVF), eight blastomere cells were analyzed for wild type cells by PSD3-linked STR markers as well as linkage analysis at day three, and normal cells were transferred to the mother via frozen embryo transfer (FET). Results and Discussion: PGD analyses of eight blastomere cells showed that four of the cells carried the related mutation; two of them were the wild type; one of them had monosomy 8; and one of them was with uniparental disomy. The normal cells were transferred to mother and the newborn individual was healthy. This healthy infant was the first child of the family. This study may support the association of PSD3 with the APS as previously proposed.

KEYWORDS: Antecubital pytergium, Preimplantation genetic diagnosis, Linkage analyses, PSD3

P-32 - FREQUENCY OF DETECTED GENOTYPES IN PATIENTS WITH SALT-WASTING FORM OF 21-HYDROXYLASE DEFICIENCY

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Introduction: Steroid 21-hydroxylase deficiency is a most frequent cause of congenital adrenal hyperplasia (CAH), due to mutations in the CYP21A2 gene. Nine pseudogene-derived CYP21A2 point mutations account for about 80% of all CYP21A2 defects. Classical CAH can present as severe salt-wasting (SW) and simple virilizing (SV) form. Materials and Methods: We have performed molecular diagnosis of the nine common CYP21A2 point mutations in 24 Macedonian patients with clinical and laboratory signs of severe SW form of CAH, evaluated at Department of Endocrinology and Genetics, University Pediatric Clinic, Skopje, Republic of Macedonia, using differential PCR/ACRS. Results: In 91.7% (22/24) of the SW patients complete genotype was detected. Seventeen (77.3%) patients were homozygous, and five (22.7%) were compound heterozygotes. Two patients harboured none of the tested mutations. The most common genotype was IVS2/IVS2 found in 14/22 (63.6%) patients, followed by Q318X/Q318X and IVS2/Q318X observed in 2/22 (9.1%) patients, each. Other genotypes Del8ntG110/Del8ntG110, R356W/Del8ntG110, IVS2/V281L+Q318X+R356W and Q318X/Del9nt(c.1271_1279) were observed in only one patient, each. No phenotypic differences in SW patients were detected based on genotype. Conclusion: The most prevalent genotype among the Macedonian patients with SW form of CAH was IVS2/IVS2. Our results support the role of the IVS2 splice mutation in the SW phenotype of the disease.

KEYWORDS: congenital adrenal hyperplasia, salt-wasting form, CYP21A2 gene, point mutations, steroid 21-hydroxylase

P-33 - Familial Mediterranean Fever Severity in Patients with Complex Genotypes

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Introduction and Aim: Familial Mediterranean Fever (FMF) is a chronic auto-inflammatory disorder. Severity can differ between patients; according to the heterozygosity / homozygosity status and to the type of variation of the individual. Aim of this study is to understand whether there is a difference between patients with 2 pathogenic variations and complex genotypes (more than 2 variants), including at least 1 R202Q variation. Material and Methods: Medical records of the patients were screened retrospectively. Patient files were reviewed and updated by the same physician. Routine laboratory analysis including complete blood count, CRP and Erithrocyte Sedimentation Rate were assessed using standard laboratory methods. To evaluate the severity in an objective fashion, International Severity Scoring System for Mediterranean Fever (ISSF) was used. Results: 16 patients with complex genotypes were enrolled in the study. Out of 16, 13 had 6 points or higher from ISSF scoring system (thus classified as severe disease). All were clinically diagnosed with FMF according to the Tel Hashomer Criteria. Discussion: When compared with ISSF trial results (91 of 152 patients were severe among children and 58/119 in adults), this data shows the severity of FMF might be correlated with number of harbored variants, and patients with complex genotypes including R202Q mostly have severe disease. With larger datasets and variation - based comparisons, disease status of patients with complex genotypes will be further enlightened.

KEYWORDS: Familial Mediterranean Fever, Complex Genotype, Severity

P-34 - TRANSITIONAL p.Arg802His POINT MUTATION IN A2ML1 GENE IN TWO SISTERS OF NOONAN-LIKE SYNDROME WITH VARIOUS CLINICAL FINDINGS

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Introduction: Noonan syndrome (NS) is an autosomal dominant disorder that characterized by short stature, failure to thrive, typical dysmorphic facial features, congenital heart defects, loose anagen hair, and various chest wall deformities. Aim: We present this case of Noonan-Like Syndrome with missense mutation at A2 L1 gene in rder t ntrib te t the literatüre aterials and eth ds: Tw sisters r m a amily with t a consanguineous marriage were evaluated for their short stature. One is 14 years old and showed hypertelorism, epicanthus, broad high forehead, widely spaced nipples and broad thorax in the clinical examination. The second 13 years old sister with the same clinical findings was also examined in the current report. The elder sister has ne a é-au-lait spot and pectus excavatum. We performed a multigene panel which includes A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1, SPRED1 genes by using NGS. Results: We found a missense point mutation in A2ML1 gene [c.2405G>A, (p. Arg802His)] in both probands which is at a highly conserved residue and it has been considered as a VUS variant based on ACMG 2015 criteria. Discussion: Two affected individuals of NLS from one family with the missense point mutation in A2ML1 gene were examined in the current report with extremely different hen ty i ex ressi n, in arti lar n erning with a é-au-lait spot and pectus excavatum phenotypes. This report gives further support for the molecular confirmation of A2ML1 gene function in NLS etiology.

KEYWORDS: A2ML1 gene, Noonan-Like Syndrome, c.2405G>A; p.Arg802His

P-35 - Von Hippel Lindau Patients

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Introduction-Aim: Von Hippel Lindau Syndrome(VHL) is an autosomal dominant tumor-prone disease characterized by hemangioblastomas, renal cell carcinoma, and pheochromocytoma.VHL occurs by the mutation in the VHL gene on chromosome 3p25.3. The aim of this study is to discuss genotype-phenotype correlations in a Turkish VHL cohort. Material-Method: Sixteen patients (7 unrelated families) with a diagnosis of VHL were included in this study. After DNA isolation from peripheral blood lymphocytes, VHL gene all exons and exon-intron boundaries of VHL were sequenced. Results: Six of 16 (37,5%) patients had cerebellar hemangioblastoma and pheochromocytoma, five patients (31%) had retinal hemangioblastoma, multiple pancreatic cysts, and bilateral renal cysts. Pancreatic neuroendocrine tumors (12,5%), were also seen in our patients. We detected five distinct known missense mutations (p.Arg167Gln, p.Ser65Pro, p.Arg167Trp, p.Ser68Pro, p.Pro86Leu), one novel frameshift mutation (p.Glu70AspfsX88). In one family no mutation was detected in the VHL gene but copy number variations were not excluded. Two patients had no family history of whi h ne's m tati n was sh wn t be de n v . Dis ssi n: VHL gene single n le tide variants (SNVs) and copy number variations (CNVs) are responsible respectively from 90% to 10% of VHL patients. In 6/7 families we detected SNVs of which two were at codon167 which is hotspot region. Also, Arg167Trp mutation related to high risk of pheochromocytoma was found in four of six patients who had pheochromocytoma. Although exon 3 mutations are related to high risk of pancreatic neuroendocrine tumors(PNET) in literature, in our one patient who had PNET has exon 1 mutation.

KEYWORDS: VHL, Von Hippel Lindau syndrome, hemangioblastoma, pheochromocytoma

P-36 - Marfan Syndrome: Genotype-Phenotype Correlations

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Introduction: Marfan Syndrome (MFS) is an autosomal dominant inherited disorder of fibrous connective tissue which shows striking pleiotropism and clinical variability. The cardinal features occur in three systems: skeletal, ocular, and cardiovascular. A phenotype is characterized by tall stature, arachnodactyly, scoliosis, ectopia lentis, cardiac and pectus anomalies. It is caused by mutations in the FBN1 gene. Approximately 90% of classic MFS patients have an FBN1 mutation that can be identified by gene sequencing. Here we analyzed genotype-phenotype correlations in patients with Marfan syndrome. Cases: From 2015 to 2019 sixty-seven patients were referred to our medical genetics clinic for genetic analysis of Marfan Syndrome phenotype. Next Generation Sequencing of FBN1 gene identified ten patients with mutations in the FBN1 gene. Of these two were classified as novel (c.5700T>G (p.Cys1900Trp), c.3620G>A(p.Gly1207Asp) and (c.3058A>G(p.Thr1020Ala) were VUS (Variant of uncertain significance) . Six were known mutations (c.5417G>C(p.Cys1806Ser) (2/6), c.7828G>A(p.Glu2610Lys) (2/6), c.2113+2T>G (1/6) and c.7364G>A(p.Cys2455Tyr) (1/6)). In these patients, mitral valve prolapsus was the most common cardiac anomaly. Pectus carinatum was more frequently seen than pectus excavatum. Ectopia lentis was seen in a patient with a known mutation. Conclusion: We have reported our patients to contribute to genotype-phenotype correlations in Marfan syndrome.

KEYWORDS: Marfan syndrome, FBN1, mitral valve prolapsus, ectopia lentis, pectus carinatum

P-37 - Conventional Cytogenetics Results of 355 Multipl Myeloma Cases

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We present the cytogenetic results of 355 (168 female/187 male) multipl myeloma cases (ages between 16-84; median: 60). We obtained metaphases from unstimulated bone marrow cultures of 317 patients (89.29%), and evaluated the GTL banded metaphases according to ISCN 2016. There were numerical and/or structural chromosome abnormailities in 104 cases (29%). 22 cases (21%) had complex karyotype. There were hypodiploid cells in 72 of cases, while hyperdiploidy in 12 and both hypo- and hyperdiploid cells in 5 cases. Recurrent numerical abnormaities were -21 (15 cases), -Y (14 cases), -18 (12 cases), -15 (10 cases) -20 (9 cases), -13 and -22 (8 cases each), -19 (7 cases), -17 and +3 (6 cases), -X, +1, +2, -5, -8, -14, +14, -16 (5 cases each), -2 (4 cases), -1, -10, +10, -11 (3 cases each), -4, +4, +6, -9, -12, +13, +19, +20 (2 cases each). And +Y, -6, -7, +7, +11, +12, +16, +17, +21 and +22 were observed in one case each. The most prominent structural abnormalities were deletions or additions of 6q (13 cases). Although each of the specific structural abnormalities was observed in only one patient, the chromosomes involved in structural abnormalities other than chromosome 6 were chromosome 1 (10 cases), chromosome 9 (9 cases), chromosomes 10 and 16 (5 cases each), chromosomes 4, 7 and 11 (4 cases each), chromosomes 12, 14 and 19 (3 cases each), chromosomes 13 and 17 (2 cases each), and chromosomes 5 and 15 (1 cases each).

KEYWORDS: Multipl Myeloma, Cytogenetics, Chromosome Abnormality, Cancer

P-38 - Unexpected WES result of a fetal MCD case; the complexity of prenatal management

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Introduction and Aim: Lissencephaly forms the major group of malformations of cortical development (MCDs) that can cause severe intellectual and motor disability and epilepsy in children. Early and accurate prenatal diagnosis is one of the most challenging areas of MCD management and is important for genetic counselling and antenatal care. Here we report a fetus with unrelated parents presenting with asymmetrically dilated ventricles, simplified gyration, mega cisterna magna, tricuspid regurgitation and premature atrial contractions. The pregnancy was terminated at the 28th GWs due to poor expected neurological outcome. Postmortem clinical examination revealed craniofacial dysmorphism and normal growth. Material and Method: Chromosomal abnormalities and LIS1, DCX and TUBA1A related phenotypes were ruled out by the karyotype, array-CGH and Sanger sequencing of the respective genes and WES-trio analysis was performed. Result: As the parents were unrelated we focused on the de novo variant-list including 256 genes and a de novo pathogenic variant on IDH2 (c.G419A, p.R140Q) associated with D-2-hydroxyglutaric aciduria (D-2-HGA) type II was detected. Discussion: D-2-HGA type II is a rare metabolic disorder characterized by psychomotor retardation, seizures and brain abnormalities including posteriorly diminished white matter, cortical atrophy and simplified gyration. This is the first report of a D-2-HGA2 case presenting with cortical abnormalities in the antenatal period. The case presented manifests how NGS methods provide a new perspective in prenatal management of complex MCD phenotypes with clinical variability.

KEYWORDS: D2-HGA2, malformations of cortical development, WES, prenatal management

P-39 - Assessment of Rhesus D and Sex-specific Genotyping with cell free Fetal DNA from Maternal Blood

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Determination of the fetus Rh type is critical for the Rhesus (Rh) factor negative (-) pregnants considering the development of Erythroblastosis Fetalis. In recent years, detection of cell free fetal DNA (cffDNA) derived from maternal blood has enabled the development of important techniques in prenatal diagnosis. In our study, fetal Rh and sex-specific genotyping were performed by utilizing cffDNA obtained from peripheral blood of 100 Rh(-) pregnant women. Real-time polymerase chain reaction(PCR) was performed with specific primers for S Y and hD genes. The mean age at s e imen lle ti n was 28.5±5.5(years±SD) in whi h 11 ases were 21 years and nder, 10 ases were 35 years and lder. The mean gestati nal age was 25.81±9.02 weeks. The resulting cfDNA concentrations were between 2.9-106.3 ng/µL and the mean was 15.72±17.08 ng/µL. The results were further compared with the New Born Follow up System of the hospital. So far, 54 of the 100 cases were delivered their babies. The comparison of the analysis revealed the false negative results in 3/54 of cases in the Rh D, and 1/54 case in SRY analyses. The PCRs of the remaining 46 cases were completed and will be confirmed when the system is updated with new born babies. According to these results, the use of this technique could be easily applied as an early diagnostic test as well as an early assessment of the treatment modalities considering Congenital Adrenal Hyperplasia in Turkish laboratories. Therefore, the unnecessary stress, treatment and the cost to the patient could be prevented.

KEYWORDS: Cell free DNA, Erythroblastosis Fetalis, Rh D, SRY, Congenital Adrenal Hyperplasia

P-40 **- silindi**

P-41 - BCL11B gene may be a candidate gene for mastocytosis in a patient with partial trisomy of distal 14q

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INTRODUCTION:Mastocytosis is a spectrum of rare diseases characterized by expansion and accumulation of clonal mast cells in the skin and various internal organs. Although the disease is thought to be caused by activating mutations of KIT gene, recent studies have shown that mutations in other genes may also be determined. AIM:Here we report a patient diagnosed with diffuse cutaneous mastocytosis (DCM) and had a large duplication in the long arm of chromosome 14 including BCL11B gene. CASE REPORT: A 32 months-old girl was referred to our medical genetic oupatient clinic because of DCM and stuttering. Her growth and neuromotor development was normal. Karyotype analysis revealed 46,XX normal chromosomal constitution. The Array-CGH analysis showed a de novo 7,7 Mb duplication in 14q32.2-q32.33 region that contains 15 m rbid O **I** genes whi h ne them is BCL11B gene. DISCUSSION :In the literatüre; d li ati n in the 14q32.2-qter region was reported to be associated with primordial short stature, mild developmental delay and distinct facial dysmorphism that were absent in our patient. But absence of BCL11B gene located in this region was reported to be associated with atopic dermatitis (AD)-like skin inflammation and extensive infiltration of immune cells including mast cells in adult mice skin, as well as systemic immune responses that share similarity with human AD patients, consistent with DCM clinic of our patient. (1). We suggested that BCL11B gene can be a candidate gene for mastocytosis.

KEYWORDS: BCL11B, duplication of chromosome 14, mastocytosis

P-42 - De novo nbalanced translocation resulting in 6q26-qter monosomy and 12q24 partial trisomy

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Terminal 6q deletions and partial trisomy of 12q24 have been rarely described and both have variable phenotypes. Both syndromes consist of similar clinical findings such as craniofacial abnormalities, developmental delay, growth retardation, central nervous system (CNS), cardiovascular and urogenital malformations. In this study we report on a 15-month-old patient with developmental delay and intractable seizures carrying a de novo unbalanced translocation of der(6)t(6;12)(q26;q24.31). Phenotypic evaluation revealed brachycephaly, low hairline, anteverted ears, narrow palpebral fissures, bilateral epicantus, broad nasal bridge and short neck. Cranial MRI demonstrated corpus callosum agenesis, periventricular heterotopia (PVH) and col e haly. O htalm l gi examinati n res lted in 5' hy er ia. **i** r array analysis sing A ymetrix Cytoscan Optima platform revealed 8,6 Mb deletion on 6q26q27 and 10,1 Mb duplication on 12q24.31q24.33. The arents' FISH and array st dies were all n rmal. Previous studies show that 6q27 terminal region contains 4 genes, THBS2, DLL1, PHF10, C6Orf70 that play a critical role during CNS morphogenesis and neuronal migration. Thus structural CNS anomalies, particularly PVH seen in our patient is compatible with the hypothesis that the contiguous gene deletion of this region may result in neuronal migration defects. To our knowledge this is the first report of a liveborn with a de novo translocation of t(6;12) with various congenital anomalies. Nevertheless further studies are required to elucidate the functional characteristics of the genes in this region that may relate to genotype-phenotype correlation in 6q monosomy/12q trisomy syndromes.

KEYWORDS: 6q monosomy, 12q trisomy, periventricular nodular heterotopia, C6Orf70, microarray

P-43 - A Novel Candidate Frameshift Mutation For Leigh Syndrome

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Leigh syndrome (LS) is progressive neurodegenerative mitochondrial disorder which is characterized by focal, symmetrical, and necrotic lesions in the thalamus, the brain stem and the columns of the spinal cord. SURF1 gene, one of the genes responsible for Leigh syndrome, is located at chromosome 9p34 which encodes a protein localized to the inner mitochondrial membrane. This protein is involved in the biogenesis of cytochrome c oxidase complex. A couple who have consanguinity between them have been admitted to our department due to the fact that they have 3 children who died with the suspicion of mitochondrial disease. Their two children died at the age of 3 and one at the age of 9. Children had similar findings such as difficulty swallowing, tremor, hypotonia, difficulty breathing and severe psychomotor retardation. Mitochondrial genome analysis of one of them was normal. We planned the Whole-Exome Sequencing for the detection of common heterozygous variants. In both father and mother, we identified a novel heterozygous deletion in SURF1 (NM_003172.3) gene c.252delG which is not found in clinical databases such as ClinVar or Human Genome Database (HGMD). According to American College of Medical Genetics (ACMG) criteria (PVS1, PM2, PP3) it is classified as 'pathogenic'. We also determined the same variant as homozygous in their passed away child with Sanger sequencing. With this mutation, we added a new one to the variants detected in the SURF1 gene. Functional studies are needed to contribute to the determination of the pathogenicity of this variant.

KEYWORDS: Leigh syndrome, c.252delG, SURF1 gene, Whole Exom Sequencing

P-44 - A Novel Truncating Mutation in LIG4 Gene

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Introduction: LIG4 syndrome (OMIM 606593) is a rare autosomal recessive disorder resulting from mutations of LIG4 gene which is a part of the non-homologous end joining mechanism. The syndrome is characterized with mi r e haly, 'bird like' a earan e the a e, rim rdial gr wth ail re, imm n de i ien y, pancytopenia and skin manifestations (1). We report a patient with a novel stop gain mutation on LIG4 gene. Material and Method: Genomic DNA was isolated from peripheral blood samples of the patient and his parents. The only coding exon and exon-intron boundaries of LIG4 gene was sequenced. Results: The patient was a 3,5 old boy with microcephaly, severe growth retardation, dysmorphic features and pancytopenia. His parents were first cousins. The pregnancy was complicated with IUGR and he was born at 37th week with C/S. When he was two, he developed perioral petechial lesions and complete blood count revealed thrombocytopenia and anemia. He was tested as negative for Fanconi anemia, Nijmegen breakage syndrome and DiGeorge syndrome. c.428T>G (p.Leu143*) homozygous mutation was found in the proband. Parents were heterozygous for the same mutation. The patient deceased at the age of 5 due to bone marrow failure. Discussion: The variant was found neither in ExAC nor 1000G. The mutation leads to a truncated protein and was predicted as disease causing by MutationTaster. DNA ligase IV protein was not detected by western blot immunoassay, supporting the pathogenicity of the mutation. 1. Altmann, T., & Gennery, A. R. (2016). DNA ligase IV syndrome; a review. Orphanet journal of rare diseases, 11(1), 137.

KEYWORDS: LIG4 syndrome, novel mutation, rare diseases, DNA ligase IV deficiency

P-45 - A Case of CHARGE Syndrome Diagnosed with Antenatal Left Ventricular Minority and Syndromic Appearance

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CHARGE syndrome is a rare autosomal dominant syndrome characterized by cardiac defect, coloboma, koanal atresia, growth and developmental retardation, genital hypoplasia and ear anomalies. The CHD7 gene is responsible for the disease. Here, we present a case with the diagnosis of CHARGE syndrome, which was observed for syndromic manifestation and polyhydramnios. The male baby borned from a 27 years old mother via C/S at the end of 34+4 weeks gestation period as being the 2nd live birth among four pregnancies was referred to our polyclinics with the indications of syndromic appereance (micrognathia, nasal radix depression, square face), polyhydramnios in prenatal term, small left ventricule, one artery one vein in umblical cord. Physical examination revealed hypotonia, lower extremity immobility, congenital bronchopneumonia and microgenitalia. In the karyotype analysis, chromosome establishment was found as 46, XY. The region of c.2572C>T (p.Arg858Ter), which is localized in CHD7 gene 8q12.2 related to Charge syndrome, was analyzed by PCR-DNA sequence analysis. As a result of the analysis, it was observed that the CHD7 gene was carrying heterozygous c.2572C>T (p.Arg858Ter). It was explained that the change in the children was compatible with the disease and genetic counseling was given. The family planned to have a preimplantation genetic diagnosis for their next pregnancy. As a result, multidisciplinary approach is essential for CHARGE association patients. It should be evaluated especially in terms of koanal atresia, cardiac anomalies, eye and hearing abnormalities. Early diagnosis will be life-saving for early intervention in congenital malformations.

KEYWORDS: CHARGE Syndrome, Rare Disease, CHD7 Gene

P-46 - The importance of extended genomic analysis in the differential diagnosis of patients with pediatric lung diseases and discovery of novel disease-causing genetic variants and genes

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Introduction and Aims: Primary ciliary dyskinesia (PCD) is a rare disorder that affects the lungs, reproductive organs and the internal organs laterality. The disease is inherited in autosomal recessive or X-linked manner. PCD is clinically and genetically heterogeneous disorder with overlapping symptoms with other pediatric lung diseases. The aim of the study was genomic profiling of suspected PCD patients in order to establish the genetic background of PCD in our patients, to confirm clinical diagnosis, and to design a strategy for differential diagnosis of PCD patients among patients with similar clinical presentation. Material and Method: Using Clinical-Exome Sequencing Panel, we analysed 93 genes related to PCD and other pediatric lung diseases in a cohort of 21 Serbian patients with clinically suspected PCD. Results: Analysis of obtained results revealed genetic variants in CCDC40, DNAI1, DNAL1, DNAH5, DNAH11 and LRRC6 genes, and pointed SPAG16 and SPAG17 as possible novel PCD candidate genes. Eighteen variants in these genes were pathogenic, of which twelve (66.67%) were novel. The PCD diagnosis was established in 52.38% of patients. Analysis of genes related to individual symptoms of PCD, revealed 6 pathogenic variants in ABCA3, CFTR, MUC2, SCNN1A, and SLC26A9 genes, of which 5 (83.33%) were novel. This enabled the diagnosis for additional 28.57% patients. Discussion: The analysis of extended list of genes enables mutation detection rate of 95.23% (20/21 patients), while the rate of established diagnosis reached 80.95% (17/21 patients). This work was funded by the MESTD, Republic of Serbia (grant no. III 41004)

KEYWORDS: Primary ciliary dyskinesia, NGS approach, novel mutations, novel candidate genes, pediatric lung diseases

P-47 - The Frequency and Clinical Findings of IDH mutations in Acute Myeloid Leukemia Patients

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Isocitrate dehydrogenase (IDH) is one of the enzymes in the citric acid cycle. IDH1 and IDH 2 are involved in conversion of isocitrate to alpha-keto glutarate. In the presence of IDH mutations, this step does not occur. Instead, 2-hydroxyglutarate (R 2-HG) is formed. (R) 2-HG may lead to changes in DNA methylation; leads to differentiation in myeloid series. Mutant IDH1 and IDH2 enzymes causes an increase of the oncometabolite, (R)-2-HG. IDH mutations are seen in AML between % 7-14. In this context we aimed to assess the frequency of IDH mutations in de novo acute myeloid leukemia patients with clinic and pathological features. The data of 30 patients who were diagnosed with acute myeloid leukemia by the Department of Hematology Trakya University Faculty of Medicine between 11.08.2017 and 31.12.2018 were evaluated retrospectively. Mutations in IDH1 (IDH1R132) and IDH2 (IDH2R172) were assessed by Real Time PCR. IDH1 mutations were found in three patients and one patient had IDH2 mutation. Three were male and one patient was female. Three patient had de novo acute myeloid leukemia and one patient was transformed from myelofibrosis. Mean age of patients with IDH mutations were 65,25. All four patients had monosomal karyotype and negative for FLT3-ITD mutations. IDH mutations increase in frequency with older ages and in our data all patients with IDH mutations are above sixty. Mutations in IDH2 are more common found than IDH1 but in our analysis we found IDH1 mutations more common this may be due to our lack of sample size.

KEYWORDS: Acute Myeloid Leukemia, IDH Mutations, Oncometabolite

P-48 - A novel HPSE2 gene mutation associated with Ochoa Syndrome

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Introduction and Aim: The Ochoa Syndrome (UFS1,Urofacial syndrome-1) is a rare disease characterized by early-onset form of dysfunctional urinary voiding and characteristic facial grimace which is most obvious during smiling. It is inherited as an autosomal recessive manner due to the mutations of HPSE2 gene localized on chromosome 10q24. Here, we report a 6-year-old girl with urinary incontinence, recurrent urinary tract infections, peculiar facial expression mainly when smiling, hypertelorism, constipation and incomplete closing of the eyelids during sleeping. Material and Method: The DNA was extracted from the patient and her family members using MagnaPure LC DNA Isolation Kit-Large Volume and MagnaPURE LC instrument. HPSE2 gene was analyzed in proband by Next Generation Sequencing [Miseq Illumina]. The variant found with NGS was confirmed in the proband and the other family members were screened for this mutation by Sanger sequencing. Results: We found a novel homozygous c.755delA (p.Lys252SerfsTer23) mutation causing a premature stop codon. His parents and one brother were found to be carrier for the same mutation. The impact of the mutation on HPSE2 function was predicted as damaging by in silico analysis. Discussion: The mutation nd in the atient has n t been des ribed in the literat re s ar. Alth gh we didn't er rm n ti nal st dy, this homozygos mutation is predicted to lead to a truncated nonfunctional protein. Furthermore, a probable nonsense mediated decay may lead to complete loss of the protein. UFS1 should be considered in patients with renal manifestations and characteristic facial findings since patients highly benefit from early treatment.

KEYWORDS: Ochoa Syndrome , UFS1 , HPSE2

P-49 - RSPO4-related nonsyndromic congenital nail disorder: Anonychia congenita

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Introduction: Anonychia congenita (OMIM 206800) is a rare autosomal recessive condition in which the only presenting phenotype is the absence or severe hypoplasia of all fingernails and toenails. After determining responsible gene: R-spondin 4 (RSPO4), approximately 10 familes have been reported hitherto. Here, we present two individuals from the same family with extremely rare nail development anomaly, anoychia congenita. Case presentation: 15-year-old male patient was consulted to Pediatric Genetics Clinic because of the total absence of fingernails and toenails. It was learned that he was born without fingernails and toenails. His parents were consanguineous and his one brother had same condition. He had normal head and body hair, rudimentary nail plates and total absence of the nails. X-rays of hands and feet showed normal structures with no dysplasia or hypoplasia. The patient diagnosed as anonychia congenita when specific clinical findings and recessive genetic inheritance patern were taken in consideration. Method of genetic analysis: Exon 1-5 and the corresponding exon-intron boundaries of the RSPO4 gene were amplified by polymerase chain reaction and analyzed by direct sequencing. Resulting sequencing data were compared with the reference sequence NM_001029871.3. Result: The homozygous splite site mutation c.79+1G>A in exon 1 of RSPO4 was detected in the patient. Conclusion: RSPO4 has a key role in the later phases of only embryonic nail development and possibly maintenance during adult life. The heredity pattern, the absence of development defects of other ectodermal components or bone dysplasia is supportive in the differential diagnosis for RSPO4-related anoychia congenita.

KEYWORDS: Anoychia congenita, RSPO4, nail development anomaly

P-50 - A novel frameshift mutation in the KAL1 gene in Kallmann syndrome: A case report

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Kallmann syndrome is a genetically heterogeneous developmental disease of congenital hypogonadotropic hypogonadism with a defective sense of smell (hyposmia or anosmia). It can be inherited X chromosome-linked recessive, autosomal recessive, autosomal dominant with incomplete penetrance and most probably digenic/oligogenic inheritance. The mutations in various genes were found related to the pathogenesis of hypogonadotropic hypogonadism with Kallmann syndrome. So far, there has not been detected any mutations in about 40% of Kallmann patients by carrying out genetic tests. However, KAL1 gene mutations which inherited by X-linked are accepted as a most frequent one among the known mutations. In this study, we report a novel frameshift mutation in KAL1 gene. An 18-years-old male with referred to our department with anosmia and hypogonadotropic hypogonadism history. The cytogenetic analysis was 46,XY, inv(9)(p11q13). FISH analysis with KAL1 and STS genes (locus spesific probe) on the X chromosome confirmed. The novel hemizygous mutation p.Arg282Valfs*28 (c.844delC) in KAL1 gene was determined using NGS analysis. The results were confirmed by Sanger sequence analysis which is ongoing to determine the paternal origin. p.Arg282Valfs*28 (c.844delC) mutation in KAL1 gene has not been previously reported in the literature. This novel frame shift mutation may be associated with Kallman syndrome.

KEYWORDS: KAL1 gene, novel mutation, Kallman syndrome.

P-51 - A novel missense variant in the homogentisate 1,2-dioxygenase (HGD) gene in a patient with clinical symptoms of alkaptonuria.

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Introduction Alkaptonuria is an autosomal recessive metabolic disorder caused by accumulation of homogentisic acid (HGA) in different types of connective tissue, mainly in cartilage. The patients usually have darkened urine, ochronosis, arthritis of the spine and larger joints, and heart valve damage. Prevalence of the disease is approximately 1/111,000 -1/1,000,000. In individuals with alkaptonuria is determined deficiency of homogentisate 1,2-dioxygenase, an enzyme that is involved in conversion of HGA to 4-maleylacetoacetic acid. Alkaptonuria is suspected in the patients with above mentioned symptoms and elevated HGA in the urine is a significant finding of the disease. The diagnosis is confirmed by identification of homozygous or compound heterozygous pathogenic variants in HGD gene on molecular genetic testing. Case A 50-year-old male patient with knee arthritis, black urine and aortic stenosis was referred to our clinic from rheumatology division preliminary diagnosed as alkaptonuria. A novel homozygous variant (HGD, NM_000187:c.709C>G, .Arg237Gly) that hadn't been revi sly re rted, was determined in the next generation sequencing (NGS). The variant was considered as likely pathogenic according to ACMG guideline. Conclusion 90 pathogenic missense variants in HGD gene were classified in UniProt and ClinVar to date. With developing genetic diagnostic techniques novel pathogenic variants are more often determined as in our case. Consequently, the clinical symptoms of our patient can occur due to novel missense HGD mutation, R237G. References 1. Wendy J. Introne, William A. Gahl. Alkaptonuria. 2016, GeneReviews. 2. Thierry Vilboux et al. Mutation spectrum of homogentisic acid oxidase (HGD) in alkaptonuria. Hum.Mutat. 2009 Dec; 30 (12): 1611-1619

KEYWORDS: Alkaptonuria, ochronosis. missense variant, homogentisic acid

P-52 - Genotoxic effects of new organoruthenium complexes measured by the comet assay in lymphocytes

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Aim: The medical applications of organoruthenium complexes have been attention attracted by chemists in decades. Organoruthenium complexes are used to be as alternative chemo-preventive agents of medical treatments including anti-tumor activity and the attenuation of reperfusion damage and infarct size but the molecular mechanisms behind of these chemicals genotoxic or antigenotoxic are still not clearly understood. Material and methods: In this study, 4-vinylbenzyl and 2-m r h lin ethyl s bstit ted (NHC) (II)(η6-p-cymene) complexes (1a-b, 2a-b) were synthesized and we characterized the genotoxic/antigenotoxic activity of different amounts of these chemicals by prevention of DNA damage induced by hydrogen peroxide (H_2O_2, 100 μ) sing the alkaline met assay in h man lym h yte ells. es lts: teni m m nds sh wed genotoxic effect as altering the median % DNAT (except the Rut-1b: 1,81μ and t-1b: 3,61 μ concentrations) compared to untreated control. According to the changes in the studied parameters within the experimental groups, there were a dose-dependent relationship only between maximum dosages of Rut-1b, Rut-2a and Rut-2b and other dosages of these groups. Conclusions: Our results suggest that higher doses of these compounds gave genotoxic effects, but the antigenotoxic potential could be obtained with the use lower doses.

KEYWORDS: Organoruthenium complexes, Genotoxicity, Comet assay, Lymphocytes

P-53 - Application of Multiplex PCR Method For Genetic Diagnosis of FHL Disease by Using HCC1143 BL and NCI-BL 1184 Cell Lines

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Introduction and Aim Familial Hemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive disease characterized by uncontrolled activation of immune system cells. FHL has five subtypes and is caused by mutations in four different genes, except FHL1. These are the genes PRF1 (FHL2), UNC13D (FHL3), STX11 (FHL4), STXBP2 (FHL5). The genetic diagnosis of FHL is based on some molecular genetic tests which are performed by sequencing and deletion/duplication analysis of related genes. Multiplex PCR is a type of PCR that allows the amplification of multiple target sites using multiple primer pairs in the same reaction. Multiplex PCR is also a suitable method for NGS-based targeted sequencing for mutation analysis because it is fast and cost-effective compared to uniplex / traditional PCR. In our study, it was aimed to develop NGS-based targeted sequencing with multiplex PCR. Materials and Method In our study, DNA isolation was performed from HCC1143 BL and NCI-BL 1184 cell line cultures. The primers designed using bioinformatics tools were controlled by MFEprimer program for multiplex PCR. After PCR, PCR products were sequenced by Illumina MiniSeq platform. Results and Discussion Detection of mutations in PRF1, STX11, UNC13D, STXBP2 genes is possible by sequencing. Prior to sequencing, PCR should be applied for amplification of the target regions. The design of multiplex PCR for these genes is thought to be a time-saving and cost-effective PCR method. In our study, multiplex PCR design was performed for related genes and it was observed to be successful in NGS analysis.

KEYWORDS: FHL, multiplex PCR, NGS, molecular genetic diagnosis

P-54 - Interstitial microdeletion of 17q22 in a patient with de novo apparently balanced t(1;17)

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Introduction and Aim: Cryptic deletions have been reported in approximately 30% to 50% of phenotypically abnormal patients with apparently balanced chromosomal abnormalities. 17q22 contiguous microdeletion syndrome is rare, recently described chromosomal disorder (1). Clinical features of affected individuals are heterogeneous because of variable deletion sizes. Here, we report a case presented with large-posteriorly rotated ears, prominent nasal bridge, high-arched palate, thin upper lip, short neck, proximally placed thumbs, delayed psychomotor development, hypopituitarism and vesicoureteral reflux. Material and method: Peripheral blood lymphocyte culture followed by metaphase preparation was performed according to standard protocols. Furthermore, chromosomal microarray analyses (CMA) was performed (Affymetrix Cytoscan Optima Chips (315k) (hg19)). Results: Cytogenetics revealed a balanced structural abnormality, 46,XY,t(1;17)(p22;q22). We tested possible parental transmission and his arents' kary ty es were n rmal. The C A identi ied a 1.53 b microdeletion at the 17q22 chromosome band (chr17:56012009_57541627) in the proband. The deletion was confirmed with FISH (D17S2151, Kreatech). Discussion: Because of this detected deletion, 17 OMIM genes have nly ne y in r atient's gen me. The DYNLL2, PO, BZ AP1, T 4, SEPT4 and T I 37 genes that are deleted in our patient are expressed in the brain and may explain the psychomotor retardation and hypopituitarism of our patient. In our knowledge, there are very few cases with interstitial 17q22 deletions in the literature. As the reported cases increase, we believe that genotype-phenotype correlation will be better illuminated. Reference 1) Laurell, Tobias, et al. "Molecular and clinical delineation of the 17q22 microdeletion phenotype." European Journal of Human Genetics 21.10 (2013): 1085.

KEYWORDS: 17q22, cryptic, deletion, chromosome

P-55 - Investigation of the PTEN Gene in the Bronchial Lavage of Non-Small Cell Lung Cancer Patients with Fluorescent Insitu Hybridization"

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Introduction and Purpose: The prognosis in patients with lung cancer is related to the stage at the time of diagnosis. Lung cancers are divided into two main groups as small cell lung cancer and non-small cell lung cancer (NSCLC). The detection of cancer cells in the sputum and bronchoscopic samples of lung cancer patients are important in terms of investigating specific anomalies and markers. In our study, it was aimed to determine the PTEN gene by using interphase fluorescent in situ hybridization (iFISH) method in bronchial lavage materials of patients with NSCLC Methods: In our study, 30 patients diagnosed with NSCLC from bronchial lavage material and 10 control subjects without any malignancy were used. PTEN gene detected with the iFISH method. The results were statistically analyzed. Conclusion: We observed by iFISH method that PTEN deletion increased in patients with NSCLC, compared to the control group and according to the signal characteristics of the cells in iFISH analysis we performed using the PTEN probe, compared to the number of cells in normal NSCLC patients. We have firstly identified bronchial lavage specimens with a significant decrease in the number of cells with biallic deletion, monoallelic deletions, monosomic cells, and atypical signals. In our study, we found that the number of cells with monoallelic deletion, monosomic cell and atypical signal were decreased significantly compared to normal signaled cells according to the signal characteristics in the iFISH analysis results of the cells of the control group we used for comparison with the patient.

KEYWORDS: Non-small Cell Lung Cancer, PTEN, Fluorescence in-situ Hybridization.

P-56 - Clinical characteristics, identification and in silico analysis of a de novo SLC6A1 gene mutation in Myoclonic-atonic epilepsy phenotype

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Introduction and Aim: Myoclonic-atonic epilepsy (MAE) (#616421) is a rare epilepsy syndrome of childhood and characterized by onset of absence and myoclonic seizures and show varying degrees of intellectual disability following seizure onset. Impulsivity, aggregation and autistic like behavior have been noted in some. MAE is an autosomal dominant disease which is located at 3p25.3. Mutations in the SLC6A1 gene contribute to epilepsy with myoclonic-atonic seizures. Here in, we report a 11 years old male patient with the symptoms of MAE. He had autism, delayed motor development, focal seizures, severe intellectual disability, bruxism, hand biting and abnormal eyelid movement. He uses antiepilectic medications. Also, his mother has adult onset epilepsy (at 18 year). Material and Method: Whole exome sequencing was performed to investigate the possible presence of SLC6A1 mutations in the patient as well as in his relatives. Results: Heterozygous c.1648G>A (p.Gly550Arg) mutation on SLC6A1 (NM_003042.3) gene was detected. This variant was not detected in parents so this was de novo in the index patient. According to the HGMD this variant (rs886042046) classified as a Class 2 and was reported as a pathogenic in dbSNP, SIFT, MutationTaster and ClinVar databases. Conclusion: To the our knowledge, c.1648G>A (p.Gly550Arg) mutation on SLC6A1 gene was associated with MAE. Most patients carrying pathogenic SLC6A1 variants have an MAE phenotype with language delay and mild/moderate intellectual disability before epilepsy onset. Our study suggests that psychiatric and autism like symptoms in myoclonic-atonic epilepsy are necessary for clarifying their genetic relation.

KEYWORDS: Myoclonic-atonic epilepsy, mutation, autism

P-57 - NOVEL MUTATIONS OF CHD7 GENE IN TURKISH PATIENTS WITH CHARGE SYNDROME

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CHARGE syndrome (CS) is an autosomal dominant genetic condition caused by a mutation in the CHD7 (chromodomain helicase DNA binding protein 7) gene characterized by ocular coloboma, heart defects, atresia of the choanae, retardation of growth, genital hypoplasia, and ear malformations (hearing loss, vestibular dys n ti n). We re rt n vel m tatı ns CHD7 gene in three atıents wıth Charge syndr me The irst ase is a 13-years-old girl referred us owing to congenital heart defects, short stature, choroid coloboma, and hearing loss. Physical examination revealed a round face, low posterior hairline, curled ear, and bulbous nose. The second case is a 6 months-old girl presented choanal atresia, bilateral coloboma and hearing loss. On physical examination; she had deep-set eyes, long philtrum, and dysmorphic ears. The third case is a 2-month-old girl presented choanal atresia, bilateral coloboma and hearing loss. Physical examination revealed unilateral microphthalmia, micrognathia and dysmorphic ears. None of them are consanguineous at family history. The atients' DNA seq en ing analyses CHD 7 gene were res e tively; heter zyg s ath geni n vel m tati n in intron 7 (c.2498+2T>G), a heterozygous pathogenic novel mutation in exon 34 (c.7307_7308insA), a heterozygous pathogenic novel mutation in exon 2 (c.1281T>G). Mutations were searched in varsome, pubmed, clinvar, centoMD databases. Mutations in the CHD7 gene are responsible for 65-70.0 % cases of CHARGE syndrome, with cases fully meet the formal diagnostic criteria the incidence scaled up 90.0-95 %. We report three cases diagnosed with Charge syndrome with novel mutations in the CHD7 gene.

KEYWORDS: Charge syndrome, Coloboma, CHD7 gene

P-58 - DETERMINATION OF MONOSOMY 7 IN ANEMIA APLASTICA USING FLUORESCENCE IN SITU HYBRIDIZATION

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Background: Aplastic anemia (AA) is a hematologic disorder characterized with peripheral blood pancytopenia and hypocellular bone marrow. Bone marrow transplantation and immunosuppressive therapy are standard treatment strategies for severe AA. Monosomy 7 (del 7q) is the most common chromosomal aberration in aplastic anemia. Presence of this aberration is crucial for the therapy. Materials and Methods: A boy with clinical signs of pancytopenia was diagnosed at the Department of Hematology, University Pediatric Clinic, Skopje, Macedonia, according to standard criteria. We performed standard G-banded karyotype from bone marrow and fluorescence in situ hybridization (FISH) on interphase nuclei using del 7q deletion probe LPH 025 (Cytocell). Standard protocols for karyotyping and FISH were used. Results: The karyotype in this case was unsuccessful since the bone marrow was poor in cells. The FISH analysis, using del 7q deletion probe, showed presence of two signals in the interphase nuclei on 10% of cells, which indicates monosomy 7. This finding was key factor for further treatment strategy for the patient. It was decided antithymocyte globulin not to be given, and hematopoietic stem cell transplantation was performed. After transplantation the patient started with normal cell production. Conclusion: Fluorescence in situ hybridization analysis is rapid, sensitive and reliable tool for detection of chromosomal aberrations especially in cases when standard karyotype is unsuccessful .

KEYWORDS: Aplastic anemia, karyotype, FISH, monosomy 7

P-59 - Evolution of chromosomal aberrations in patients with bladder cancer: from blood to bladder tumors

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Introduction: Urinary bladder cancer is still a socially significant healthcare problem, rating 7-th most common cancer worldwide. Aim: The aim of our study is to identify the chromosomal imbalances in the blood, normal and neoplastic tissue of patients, suffering from bladder cancer. Materials & Methods: Tumor samples from 20 B lgarian atients, staged r m Ta t T3 were investigated. CNV's 20 uroepithelial neoplastic samples, 10 blood and 3 normal tissue samples (Infinium OncoArray-500K BeadChip, Illumina) were performed. Data was analyzed by Karyostudio 1.4.3.0. Results and discussion: Blood sample analysis reveal mainly loss of the 6p21.32 chromosomal region, containing HLA-DRB5; HLA DRB4; HLA-DRB1 genes (4 samples) and gain of the nine different chromosomal region, thought to be likely benign variation. Surprisingly five LOH regions were determined: 3q28q29, 5p15.33p15.32p15.31, 6q24.1q24.2q24.3q25.1, 10q11.21q11.22 and 11p11.2p11.12. No variations in chromosomes 7 and 9 were found. The results from the macroscopically normal tissue showed loss of 9p23 only in one sample, LOH in 7q21.3q22.2 only as well as unspecific gain in a numerous of chromosomes. In the tumour samples-deletion in both 9p and9q were the most frequent, but we also saw losses of 4p16.3, 5q34, 6p21.32, 13q21.31 and 18q22.1q22.3. The LOH variant 7q21.3q22.2 from the normal tissue was preserved. No other LOH variants were found. Gaines in different chromosomal regions except for chr.15 and 21 were documented. Acknowledgements: C ntra t D 13/4, 2017 NSF, Д-60/03.05.2018, CMH, U-Sofia, MANU-BAS.

KEYWORDS: bladder cancer, CNV's, SNP array

P-60 - Chromosomal abnormalities in couples that undergo assisted reproduction technologies

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Introduction: Recent progress in reproduction technologies helps many couples in conceiving pregnancy. Considerable portion of pregnancies obtained in this way have an unfavorable outcome, ending up with unsuccessful conception, recurrent miscarriage, stillborn, or birth of a child with certain genetic condition. Many pathogenic mechanisms such as chromosomal instability, single gene mutations, imprinting, and, most likely, idiopathic reproductive loses are underlying factors for poor pregnancy outcome. Among all, chromosomal rearrangement in one of the partners could be found in 2-4% of high-risk couples. Materials and methods: We present several cases where chromosomal changes and polymorphic chromosomal variants were found in couples that had performed some of the assisted reproduction technologies (ART) repeatedly. Results: Balanced reciprocal translocations between variable chromosomes, as well as Robertsonian translocations were detected. Inversion of chromosome 9 was found in infertile couples more frequently that in general population. Despite performing ART, unsuccessful implantation and miscarriage were the most frequent outcomes in these cases. Genetic counseling and the best treatment options were offered in all. Discussion and conclusion: Reciprocal chromosomal breakage could occur between variable chromosomes due to several mechanisms: existence of polypurine/polypirimidine repeats along DNA, microdeletions/duplications, regions where prolonged replication occurs, etc. The size of the chromosomal segment involved in the translocation has a crucial role in unfavorable pregnancy outcome. Karyotype is still the only method that provides diagnosis of balanced chromosomal rearrangements. Although disputed by some authors due to the cost of the analysis, selective kariotyping should be mandatory in high-risk couples.

KEYWORDS: infertility, selective karyotyping

P-61 - Association of vitamin D level and CYP27B1 gene polymorphism with multiple sclerosis in Türkish Population

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Multiple sclerosis (MS) has been associated with low levels of 25-hydroxyvitamin D (25(OH)D). Several genetic polymorphisms of the CYP27B1, of whom rs703842 has functional consequences for receptor protein structure and the immune system, have been studied in relation to MS with variable results. The purpose of our study was to assess an association of the CYP27B1 polymorphism with MS, and to further unravel the interaction of this polymorphism with vitamin D metabolism. Therefore, we genotyped 99 MS patients and 99 healthy controls for the CYP27B1 polymorphism and determined levels of the vitamin D metabolites 25(OH)D. No association of the CYP27B1 polymorphism with MS was found. The C-allele was associated with serum 25(OH)D levels in our MS patients, and with lower 25(OH)D levels in healthy controls. The role of CYP27B1gene polymorphism should be further studied in other populations, and the distribution of other polymorphism, another susceptibility gene for MS and to obtain more adequate strategies for treatment of MS. This should be taken into account in association and ultimately intervention studies on vitamin D and MS.

KEYWORDS: Multiple sclerosis, CYP27B1 gene polymorphism, Vitamin D, Susceptibility gene, Turkish

P-62 - Mechanism of formation a small supernumerary marker chromosome derived from chromosome 8: Constitutional chromothripsis

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Introduction and Aim: Small supernumerary marker chromosomes (sSMC), are characterized by additional centric chromosome fragments which are too small to be classify by cytogenetic banding alone and smaller than or equal to size of chromosome 20 of the same metaphase spread. Chromothripsis is a chromosomal rearrangement, occurred from breaking from one or more chromosome and assembling of surviving chromosome pieces (1). Here, we report a patient presents with slight neutropenia and oral aphthous ulcer. Extra D8Z1 signal was detected in bone marrow cells of the case when investigated for differential diagnosis. Detailed genetic workup revealed a mosaic de novo, sSMC, which was originated from five discontinuous regions of chromosome 8. Material and Method: A standard protocol was used for conventional karyotyping and FISH analysis. Chromosomal microarray analysis was performed Affymetrix, CytoScan 750K SNP microarray platform. Results: GTG karyotyping revealed mos 47,XX,+mar[9]/46,XX[11]. The diagnosis of constitutional was supported by urine and buccal smear FSH analysis. Microarray demonstrates that sSMC originated from five discontinuous regions of chromosome 8. The parents and twin sister had normal results. The atient's inal kary ty e revealed de novo, mosaic, sSMC derivated from chromosome 8. Discussion: Incomplete trisomy rescue triggered by chromothripsis is the most probably explanation of formation of the sSMC. This case is also a good example of importance of conventional karyotyping and examining tissues other than bone marrow in patients with inconsistent genotype and phenotype. References: 1. Kurtas et al. Small supernumerary marker chromosomes: A legacy of trisomy rescue? Hum Mutat. 2019; 40(2):193-200.

KEYWORDS: Small supernumerary marker chromosomes (sSMC), chromothripsis, chromosome 8, trisomy rescue

P-63 - Two SMA families with 2+0 carrier status

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SMA is the most common autosomal recessive and lethal disorder. %95 of patients have homozygous deletion in SMN1 gene, specifically in exon 7. Carrier frequencies vary by ethnicity and panethnic priority risk is 1/54. SMN1 differs from SMN2 by 2 nucleotides in exon 7 and exon 8 and based on these differences several test methods can be used for diagnosis and carrier screening. MLPA is most common used method in the world but can not determine cis carrier status. Recently, detection rate of silent carrier increased by screening specific polymorphisms, albeit the detection rate is not one hundred percent. These specific polymorphisms are more frequent in Ashkenazi jewish and asians, and the frequencies in different populations unknown. 4% of the SMA patients' parents are silent carriers, so determining carrier status of healthy individuals is very important for genetic counselling and management SMA disease. Here we report two SMA families with cis carrier status. Our first patient with homozygous deletion died at 6 months-old. There is no consanguinity. Carrier screening revealed that mother is carrier, father has two SMN1 copies and father's sister is a carrier. We performed family screening and carrier screnning revealed that father's father is a carrier, and mother and brother have three SMN1 copies. We considered father as a cis carrier and genetic counselling was given to family. Our second patient is 5 years old. There is consanguinity in this family. Patient's mother, father and brother's MLPA results were 2,2, and 4 SMN1 copies, respectively. Both parents are cis carriers, and accurate genetic counselling was given to family. Finally, we suggested carrier screening to both families. 4% of SMA families are silent carriers, and MLPA methods can not determine cis status. Therefore, screening healthy population has some challenges. We aimed to remind that cis carrier status must be kept in mind in the case of one or both parents with 2 SMN1 copies and the patients with homozygous deletions, and family screening will be very useful in these families.

KEYWORDS: Cis carrier, silent carrier, 2+0 carrier, SMA, SMN1

P-64 - Reciprocal Translocation 46, XX, t(1; 5) (p13.1; pter)) in Infertile Female

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In this study, we present the results of a cytogenetic analysis performed on a couple, who were referred to our laboratory due to infertility. We found a normal karyotype 46,XY in male, and balanced reciprocal translocation 46, XX,t(1; 5) (p13.1; pter) in the female. To determine the origin of the reciprocal translocation, chromosomal analysis was performed from the parents of the propositis. In addition, the same chromosomal organization was seen in her sister who has two abortions and two living children. A carrier of a balanced reciprocal translocation can produce unbalanced gametes, resulting in zygotes with 50% of partial trisomy or partial monosomy for the defined chromosomal regions, 25% of balanced resiprocal translocation and 25% of normal karyotype. In a study, it has been reported that normal karyotype (46,XX) in female, and balanced reciprocal translocation [46,XY,t(1;5)(p33;qter)] in the male. 5p deletion syndrome and partial trisomy of 5 have same clinical features like microcephaly, micrognathia, developmental delay, mental retardation, congenital heart defects, abdominal muscle hypoplasia and dysmorphic features. Two cases were products of maternal translocations in trisomy of 1p. All the others were de novo intrachromosomal duplications and the large amount of additional genetic material from chromosome 1 leads to a very early termination of pregnancy and poor fetal development. The possibility of partial monosomy and trisomy gamet formation in the infertile may have a large share, and may be due to advanced maternal age and long-term smoking.

KEYWORDS: Infertile, Reciprocal Translocation, Cytogenetic Analysis, t(1; 5)

P-65 - Protective effect of Plantago lanceolata L. extract and luteolin against genotoxic damage induced by H2O2 in human lymphocytes

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Aim: Recently, plant extracts and main their contents are used to be as alternative chemo-preventive agents of medical treatments and have become widespread throughout the world. Plantago lanceolata L. (PL) is plant species that grow widely in Anatolia and is thought to have healing effects for many diseases but the molecular mechanisms behind of this plant genotoxic or antigenotoxic are still not clearly understood. The purpose of this study is to investigate genotoxic and antigenotoxic effect of extracts of this plant and its main flavonoid luteolin against hydr gen er xide (H2O2, 200 μ) ind ed DNA damage by sing met assay in h man lym h yte in vitro. Material and methods: The lymphocytes were incubated with two different concentrations of PL extra t (200 and 500 ng/ml) and three di erent n entrati ns l te lin (10, 20 and 30 μ) al ne and simultaneously with H2O2. Percentage DNA in tail (DNAT) and tail moment on 100 cells per sample (two duplicate sample slides, 50 randomly selected cells scored per slide) was scored using image analysis software. Results: The extract of PL and luteolin alone did not induce significant DNA damage in all the concentrations (exept maximum dosages) compared to negative control. PL+ H2O2and luteolin+ H2O2 treatments significantly reduced DNA damage at all the concentrations compared to H2O2 treatment alone for all comet parameters. Conclusions: Our results suggest that this plant extract and luteolin exhibited chemopreventive activity against DNA damage induced by H2O2 at minimal experimental doses.

KEYWORDS: Plantago lanceolata, Luteolin, H2O2, Genotoxicity, Human Lymphocytes

P-66 - A NOVEL MUTATION IN THE TRANSGLUTAMINASE-1 GENE IN A LAMELLAR ICHTYOSIS PATIENT

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Lamellar ichthyosis is a cornification disorder classified under the category of autosomal recessive congenital ichthyosis. Lamellar ichthyosis is characterized by coarse and brown/dark scaling. Infants are often born with a shiny, taught, transparent collodion membrane. Other findings are ectropion, eclabium, alopecia, palmar and plantar keratoderma. Lamellar ichthyosis is a rare genetic condition that affects the skin. Prevalance is estimated to affect 1 in 100,000 and 300,000 individuals. Mutations in the TGM1 gene are responsible for approximately 90 percent of cases of lamellar ichthyosis. The TGM1 gene is located on chromosome 14q11.2 and has 15 exons. It encodes the transglutaminase 1 enzyme. In this study, Congenital Lameller Ichthyosis case with a novel mutation in the TGM1 gene is presented. A 1 month old girl patient was referred to our clinic with abnormal skin findings. She was the third live born of the consanguineous parents. On the first month of life, she had plate-like tight and dark skin ,covering the whole body surface area. And she had ectropion and eclabium. Molecular analysis revealed a novel homozygous mutation (p.His436Arg(c.1307 A>G)). In conclusion, a novel mutation defined in this study may help to expands the current knowledge about TGM1 mutation spectrum in this rare disorder.

KEYWORDS: Lamellar ichtyosis, TGM1, novel mutation

P-67 - FCGR2A AND FCGR3A POLYMORPHISMS AND RESPONSE TO RITUXIMAB TREATMENT IN PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA

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FCGR2A AND FCGR3A POLYMORPHISMS AND RESPONSE TO RITUXIMAB TREATMENT IN PATIENTS WITH B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA RosicaAngelovic,MaricaPavkovic, Irina Panovska-Stavridis, Elena Arangelovic, SanjaTrajkova, Lazar Cadievski, AleksandarStojanovic. University Clinic for Hematology, Medical Faculty, Skopje, Republic of Macedonia. Purpose:Chronic lymphocytic leukemia(CLL) is the most common form of adult leukemia in Western world. Chemoimmunotherapy with rituximab, fludarabine and cyclophosphamide (R-FC) has prolongedprogression free survival(PFS) and overall survivalin CLL patients.FCGR2A and FCGR3A are polymorphic and have two allelic forms:FCGR2A-H131 allele having a higher affinity for human IgG2, comparing to FCGR2A-R131, while:FCGR3A-158V variant has higher affinity for Fc gamma receptor than 158F variant. These FCGR polymorphisms may influence antibody-dependent cytotoxicity(ADCC), complement-dependent cytotoxicity(CDC) and direct proapoptotic effect.The aim of our study was to investigate a possible association of these two polymorphisms with response to R-FC therapy in CLL patients. Methodology:We have analyzed these polymorphisms in 90 CLL patients treated with R-FC. Median age of our patients was 62.7(36-78) and 63% were male. Average numbers of R-FC cycles were4.3 and median PFS was 35.1 months. Median time of observation after treatment was 3.6 years (range:6 months-8 years). Response was evaluated 2 months after therapy according to National Cancer Institute(NCI) criteria. Complete response(CR) was achieved in 24/90(26.7%), partial response(PR) in 56/90(62.2%) and no response in 10/90 (11.1%). Results:Distribution of genotypes in our patients was: 33% H/H, 49% H/R and 18% R/R for FCGR2A and 43% V/V, 40% V/F and 17% F/F for FCGR3A. Rate of CR and PR were similar irrespective of the FCGR variants and our results did

KEYWORDS: Chronic lymphocytic leukemia,polymorphisms .FCGR2A, FCGR3A chemoimmunotherapy,

P-68 - Effect of the cryopreservation on the viability of Sertoli cells

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Introduction and Aim : Sertoli cells have an important role in the process of spermatogenesis. These cells provide functional and structural support for the differentiation of germ cells in response to endocrine and paracrine factors, especially to FSH and testosterone. Maturation arrest might be associated with the defects of Sertoli cell function in individuals with non-obstructive azoospermia (NOA). Our aim was to investigate the effect of the freezing and storage of Sertoli cells on their viability, which could have a potential for future male infertility treatments. Material and Method: Testicular tissue samples were obtained during the scrotal exploration from OA and NOA patients. Primary Sertoli cell cultures were performed from the testicular tissues. Sertoli cells were cryopreserved using a slow-freezing protocol. In our study, the viability/proliferation and apoptosis of the Sertoli cells were tested with MTT and Annexin-V respectively before freezing and after thawing. Results and Discussion: There was no significant difference between MTT and apoptosis scores before and after cryopreservation. We found that the cell viability (48h; $p=0.695$, 72h; $p=0.937$) and apoptosis (before; %15.28 and after; %16.05, $p>0.05$) comparisons were in normal levels after cell freezing-thawing. As a conclusion, it was found that cryopreservation of Sertoli cells might be an efficient and effective method for in vitro studies.

KEYWORDS: Sertoli Cells, Cryopreservation, Cell viability, Male infertility

P-69 - THE RARE ABNORMALITIES OF CHROMOSOME 1 IN MYELOID MALIGNANCIES

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Introduction-aim: Most of the chromosomal aberrations in myeloid malignancies are determined by cytogenetic analysis. Some abnormalities are rare, thus their clinical significance are not known. Here, we aimed to present the rarely seen chromosome 1 abnormalities that had been revealed in myeloid malignancies. Material-Method: Conventional and molecular cytogenetic tests from bone marrow samples of the patients with myeloid neoplasia were performed. Results: Case1 (myelofibrosis): 46,XX,der(11)t(1;11)(q21;q23) nuc ish(KMT2Ax1)[223/227] Case2 (myelofibrosis): 46,XY,der(6)t(1;6)(q21-23;p22),-6,+der(6)t(1;6)(q21-23;p22) nuc ish(DEKx1, NUP214x2)[147/331] Case3 (MDS) : 46,XX,der(14)t(1;14)(q11-12?;q11?) nuc ish(TP73x2,ABL2x3)[135/200] Case4 (MDS>AML) : 45-48,XX,der(1)t(1;21)(p?;q?),+8,+20 nuc ish(RUNX1T1,RUNX1)x3[85/163],(D20S108x3)[81/190] Case5 (CML) : 46,XY,(1;9;22)(p36.2?;q34;q11) nuc ish(ABL1x3),(BCRx3),(ABL1conBCRx1)[170]/(ABL1x3)(BCRx3),(ABL1conBCRx2)[43]/(ABL,BCR)x2[2] Discussion: According to the literature, the effects of chromosome 1 anomalies on prognosis are variable and generally associated with poor prognosis. We found that the clinical data of myeloid neoplasia patients with chromosome 1 abnormalities were variable. The cases (case no 1,3,4) have poor prognosis. The treatments of cases 1 and 3 have failed, and case 4 have shown transformation from MDS to AML. Although the cases 2 and 5 have responded to treatment. We concluded that although the 2nd and 5th cases have positive responses to treatment, 1st, 3rd, and 4th cases had poor prognosis. The treatment have failed in 1st and 3rd patients whereas transformation from MDS to AML have seen in the 4th case. The chromosome 1 abnormality may have a potential for being a prognostic marker. Additionally we supposed conventional cytogenetic should been studied in all hematological malignancies, thus the prognostic significance of rare chromosomal abnormalities will be clarified.

KEYWORDS: Cytogenetics, FISH, Chromosome 1, Myeloid Malignancies

P-70 - Novel MID1 mutation in a patient with X-linked Opitz G/BBB syndrome

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Intr d ti n and Aim The O itz GBBB syndr me (O İ #300000) is a ngenital midline mal rmati n syndrome characterized by hypertelorism, hypospadias, cleft lip/palate, laryngotracheoesophageal abnormalities, imperforate anus, developmental delay, and cardiac defects. X linked Opitz G/BBB syndrome (XLOS), is caused by pathogenic variants in the midline-1 gene (MID1 – OMIM * 300552) located in the short arm of the X chromosome (Xp22.2). Material and Method A 4 years-old male patient referred us with anal atresia, hypospadias, coarctation of the aorta, patent ductus arteriosus, flat philtrum, epicanthus, bulbous nasal tip. Patients genomic DNA was analysed with Trusight Inherited Disease Panel (Illumina), followed by sequencing on Illumina MiSeq. Chromosome analysis of the patient was performed from peripheral blood cultures. Chromosomal microarray analysis (CMA) was performed using Agilent Technologies 4x180K SurePrint G3 Human CGH+SNP Platform. Microdeletion syndrome mutation screening test was also performed. Results Chromosomal analysis, CMA and microdeletion syndrome analysis were evaluated as normal. The hemizygous ENST00000317552.4 (MID1): c.1507_1511dupAACTT (p.Val506Ter) variation determined in the patient. It was not identified in dbSNP database and the ExAC global allele frequency was not reported. This variation was determined as pathogenic according to ACMG-2015 classification (PVS1, PM1, PM2, PP3, PS2). His mother was normal for this variation and evaluated as de novo and novel. Discussion To date, 90 different pathogenic variants in MID1 have been described. Neverthless the c.1507_1511dupAACTT (p.Val506Ter) mutation that we found was not previously reported in the literature. Therefore, our finding is considered as the first case report of this mutation.

KEYWORDS: X-linked Opitz G/BBB syndrome, MID1 Gene

P-71 - DETECTED GENOTYPES IN MACEDONIAN PATIENTS WITH SIMPLE VIRILIZING FORM OF CONGENITAL ADRENAL HYPERPLASIA

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Introduction: Congenital adrenal hyperplasia (CAH) ranks among one of the most frequent recessive inborn errors of metabolism. Classical simple virilizing (SV) form of CAH, mainly associated with I172N mutation in the CYP21A2 gene, leads to virilization of external genitalia in newborn females and pseudoprecocious puberty in both sexes, due to reactive androgen overproduction. Materials and Methods: Molecular analysis of the nine most common mutations in CYP21A2 gene was performed in 32 Macedonian patients with clinical diagnosis of SV form of CAH, using PCR/ACRS method. Results: Seven different mutations were detected on 87.5% (56/64) of the alleles. Complete genotype was detected in 27/32 SV patients (84.4%). The most prevalent was IVS2/IVS2 genotype found in 7/27 (25.9%) of the patients followed by P30L/I172N found in 5 (18.5%), P30L/IVS2 in 4 (14.8%), P30L/P30L in 3 (11.1%) and I172N/I172N genotype found in 2 (7.4%) of the patients. The genotypes P30L/Q318X, P30L/R356W, P30L+V281L/V281L, IVS2/I172N, I172N/Q318X and Del 8ntG110/V281L were detected in only one patient each. Two of the SV patients had genotype with IVS2 on the one of the alleles with no detected mutation on the second allele. In 3/32 (9.4%) SV patients no mutation was detected. Conclusions: The most prevalent genotype among the Macedonian patients with SV form of CAH was IVS2/IVS2. We observed wide genotypic variability in SV CAH, and low prevalence of I172N mutation in exon 4 which is considered as a typical SV mutation.

KEYWORDS: 21-hydroxylase deficiency, CYP21A2 gene, simple virilizing form

P-72 - A RARE HETEROCHROMATIN POLYMORPHISM OF CHROMOSOME 6 ASSOCIATED WITH RECURRENT MISSCARRIAGE: A CASE REPORT

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INTRODUCTION: Recurrent miscarriage (RM) is defined to be two or more pregnancy losses and a multifactorial condition includes genetic factors as chromosomal abnormalities, single gene defects, balanced parental chromosome abnormalities. Parental chromosomal polymorphisms that including heterochromatin region changes(HRCs) in different chromosomes were reported in RM ethiology. AIM: Here we report a heterochromatin region increase(HRI) of the short arm of chromosome 6, a rare variant, in a 24 years-old woman with RM. CASE REPORT: An Afghan couple was referred to our Medical Genetic oupatient clinic because of three misscarriages in the first trimester. Karyotype analysis after G banding technique showed an increased profile in 6p11 region in the female patient. The enlargement in the short arm of chromosome 6 was identifed as centromeric heterochromatin region increase(HRI) after C banding technique. Array CGH analysis was normal. DISCUSSION :Heterochromatin regions play a key role in chromosome structure, histone modification and gene regulation. HRCs, especially of chromosome 1,9,16 and Y, have been reported to be associated with several conditions include RM and also seen more frequently in general population. But HRC

hr m s me 6 is a very rare nditi n and in the literatüre, H C hr m s me 6 is re rted in atients with premature ovarian failure (POF) and infertility (1). It was conclude that this rare variant of chromosome 6 may nseq ently be a se in r atient. EFE ENCES 1. KÜÇÜK, Halime, et al. The e e ts a heterochromatin polymorphism in chromosome 6 on premature ovarian failure. Asian Pacific Journal of Reproduction, 2015, 4.1: 41-43.

KEYWORDS: Chromosomal heterochromatin; Chromosome 6; C banding; Recurrent miscarriage

P-73 - A case of mosaic idic(Yq) with another cell line with two idic(Yq)

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Background: Isodicentric(idic) Yq is a rare chromosomal abnormality characterized by short stature and disorder of sex development(DSD). Approximately 95% of the idic(Y) carriers have a 45,X cell line with different percentages. Here we present a case of mosaic idic(Yq) with another cell line with two idic(Yq). Materials and Methods: 3.5-month-old female patient referred to our clinic with a complaint of ambiguous genitalia. She is the only child of a non-consanguineous couple with an unremarkable family history. Physical examination revealed closure of fontanelles, and ambiguous genitalia with cliteromegaly. No palpable gonads noted. Her weight, height and head circumference were in the normal range. Results: Karyotype analysis using G-banding resulted as 45,X[88]/46,X,idic(Y)(q10)[9]/47,X,idic(Y)(q10),+ idic(Y)(q10)[3] and FISH (Fluorescence In Situ Hybridisation) analysis using Cytocell Aquarius dual labeled satellite probe (LPE 0XYc) reported as nuc ish (DXZ1x1)[86]/(DXZ1x1)(DYZ3x1)[6]/(DXZ1x1)(DYZ3x2)[8]. Conclusion: 47,X,idic(Y)(q10),+ idic(Y)(q10) cell line in idic(Yq) patients is quite rare. Considering the dosage effect leading the pathogenesis in this group of patients, we believe reporting clinical and cytogenetic findings of a case with a cell line of two isodicentric Y chromosomes will further delineate the genotype-phenotype correlation of idic(Y).

KEYWORDS: idic(Yq), ambiguous genitalia, isodicentric Y, Turner Syndrome, Gonadal Dysgenesis

P-74 - Investigation of HIF3A And IL-6 Genes Promoter DNA Methylation Changes in Childhood Obesity

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Introduction and Aim: Obesity is rapidly growing and is a major health problem threatening the world. Epigenetic changes of genes involved in food intake, energy econsumption and fat metabolism associated with obesity was observed. Methylation of the HIF3A (hypoxia inducible factor 3 alpha subunit) gene is associated with VKI and adiposity. Obesity is a disease with low degree of systemic inflammatory. IL6 (interleukin-6) levels are high in obese patients. Our aim is to investigate the HIF3A and IL6 genes promoter DNA methylation profiles in childhood obesity. Material and Methods: Our study was conducted on 50 obese and 50 non-obese children. According to the percentage calculations, children with obesity diagnosed with body mass index (BMI> 95) were selected for study from pediatric endocrinology clinic. Genomic DNA was isolated from blood leukocytes. DNA methylation status of samples for HIF3A and IL6 genes promoter were detected through methylation spesific PCR. Following the PCR products were then examined using agarose gel electrophoresis and visualised under UV illumination. Results: According to the results , there was no methylation for both obese (47) and non-obese (45) groups for promoter region of the HIF3A gene (p= 0.99). In the IL6 gene promoter, 47 obese and all non-obese (49) samples were methylated, 3 obese were not methylated (p= 0.43) Conclusion: There was no significant difference in the HIF3A and IL6 gene promoter methylation patterns when two groups were compared. If the methylation analysis had been done in adipose tissue instead of blood, different results could be obtained.

KEYWORDS: OBESITY, HIF3A, IL-6, METHYLATION

P-75 - A Case of Klinefelter Syndrome with Immunodeficiency

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Introduction: Klinefelter Syndrome (KS) is the most common sex chromosome aneuploidy. Number of studies investigating the relationship between Klinefelter syndrome and immunodeficiency is quite limited. Here,we present a Klinefelter patient with hypogammaglobulinemia and recurrent upper respiratory tract infections. Matherials and Methods: A six-year-old male patient was consulted from pediatric allergy & immunology department due to his dysmorphological findings accompanying the complaint of recurrent infections. His hypogammaglobulinemia was detected 2 years ago, and he has been receiving IVIG ever since. In physical examination, long face, pointed chin, forward rotated ears, bilateral 5th finger clinodactly in his hands and feet, bilateral nail hypoplasia in his toes and scoliosis were present, and the testes were in the scrotum. A karyotype analysis and a FISH study were performed. Results: Karyotype of the patient was 47,XXY; and FISH study with SRY - Probe was consistent with XXY. All Ig parameters of the patient were low and sex hormone binding globulin (SHBG) levels were increased. Conclusions: The mechanism of hypogammaglobinemia seen in some patients with klinefelter syndrome is still unknown and further investigation is required. Since there is an extra copy of X chromosome in Klinefelter patients, this immunological consequence might be related to the dosage of immunologically active genes on the X chromosome, especially the ones that escape X inactivation.

KEYWORDS: Klinefelter syndrome, immunodeficiency,

P-76 - WHOLE EXOME SEQUENCE ANALYSES IN A CONSANGUINEOUS FAMILY WITH AFFECTED DIZYGOTIC TWINS REVEAL A NOVEL SEPN1 VARIANT ASSOCIATED WITH MULTIMINICORE DISEASE

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INTRODUCTION AND AIM Multiminicore disease (MmD) which is a congenital myopathy associated with multifocal degeneration of muscle fibers(1). Mutations in different genes such as SEPN1, RYR1, MYH7, TTN, MEGF10 and phenotypic heterogeneity due to these different mutations are reported (2, 3). It is aimed to determine the disease-causing variant from the whole exome sequencing (WES) data of a Turkish consanguineous family with affected dizygotic twins with MmD in this study. MATERIAL AND METHOD Affected dizygotic twins were evaluated by a neurologist, detailed clinical and pathological examinatons were performed with axial muscle biopsy, clinical findings such as severe scoliosis and respiratory distress. Sequencing was performed with NextSeq 500 platform (Illumina). Filtering of the detected variants for all homozygous variants shared by the twins was performed upon candidate genes detected in silico tools for mD sing SEQ Plat rm. Sele ted variants were he ked in arents' seq en e res lts r resesive mode of inheritance. The variant was confirmed with Sanger sequencing. RESULT Genetic analyses revealed a novel h m zyg s SEPN1 variant that s ited amilial segregati n. In sili eval ati ns s rted the variant's r le in disease pathognesis. DISCUSSION A novel SEPN1 variant detected in this study provided valuable information to the family for genetic counseling. REFERENCES 1. Ferreiro A, et al, Multi-Minicore Disease–Searching for Boundaries: Phenotype Analysis of 38 Cases. American Neurological Association, 2000 2. Jungbluth H, Multi-minicore Disease. Orphanet J of Rare Diseases, 2007 3. Clarkea N. F, et al: A novel mutation expands the genetic and clinical spectrum of MYH7-related myopathies. Neuromuscular Disorders, 2013

KEYWORDS: multiminicore disease, whole exome sequencing

P-77 - The Unbalanced 1;15 Translocation in the Neonate With Jejunal and İleal Atresia. Familial 1;15 Translocation.

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A reciprocal translocation usually involves breakage of two non-homologous chromosomes with exchange of the fragments. Incidence in the general population is about 1 in 500. A carrier of a balanced reciprocal translocation can produce unbalanced gametes, resulting in zygotes with 50% of partial trisomy or partial monosomy for the defined chromosomal regions, 25% of balanced resiprocal translocation and 25% of normal kary ty e. There are ew ases in literatüre with transl ati n 1;15. A b y has 46,XY,t(1;15)(q41;q21.2) karyotype with multiple abnormalities including severe bilateral microphthalmia, diaphragmatic hernia and Fallot's tetralogy. The other has developmental disabilities, sensorineural hearing loss, muscle hypotonia with 46,XY,del(15) (q22q23) karyotype. In a malformed infant with craniosynostosis was found an interstitial deletion of (15)(q15q21.1). Another case were a mentally retarded dwarf with reciprocal (1p -;15q+), de-novo translocation. In this report an infant with jejunal and ileal atresia has 46, XY, der(15) karyotype. He has an unbalanced translocation derived from mother who was balanced carrier 46,XX,t(1;15)(p36.1;q22) karyotype. Also five individuals were detected with the same balanced translocation in strain. We determined in three generation this balanced translocation 1;15. Only the proband derived from his mother unbalanced translocation and has congenital anomalies.

KEYWORDS: Unbalanced reciprocal translocation, Jejunal atresia, Ileal atresia, der(15).

P-78 - A Family with MECP2 Duplication Syndrome

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MECP2 duplication syndrome (MECP2 DS) is an X-linked disorder characterized by early-onset hypotonia, poor speech development, recurrent respiratory infections, epilepsy and progressive spasticity. The methyl CpG binding protein 2 gene (MECP2) produces a protein of the same name, the level of which is critical for normal brain function. Mutations leading to protein under-expression cause Rett Syndrome while gene duplication causing over-expression lead to MECP2 duplication Syndrome. Here we describe a boy with Xq28 duplication syndrome. A 10-year-old boy was referred to the medical genetic clinic with a preliminary diagnosis of autism. Physical and dysmorphological examination was determineted triangular facial appearance, thin lip, pointed jaw, large ears, bilateral simian line, widely spaced nipples, and wide-based gait. She had limited eye contact, showed stereotypical movements and could not form meaningful words. The patient also had a history of recurrent lung infection and a infection-associated hyperventilation. We identified a 827 kb duplication in our patient at Xq28 using a chromosomal microarray. we found that 34 genes were present in this region of duplication. Duplication of MECP2 gene from these genes was associated with MECP2 duplication syndrome. Also his mother has 816 kb dublication at the same region. However, her mother had normal. This is consistent with X-linked recessive MECP2 syndrome. His father are also normal. The patient was diagnosed with MECP2 duplication syndrome because the findings such as mental retardation, speech problems, retardation, recurrent severe lung infection were consistent with MECP2 duplication syndrome.

KEYWORDS: Syndrome, MECP2, Duplication

P-79 - Cystic fibrosis mutational spectrum in North Macedonia: a step towards personalized therapy

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Introduction and Aim: The m st revalent “rare” disease w rldwide – cystic fibrosis (CF) is an autosomal recessive multisystem disease, caused by mutations in the CFTR gene. The knowledge of CFTR mutations present in certain population is important for designing a simple, fast and cost-effective genetic testing approach, also for better management of CF patients, including the administration of novel targeted therapies. Here we present genetic results of 158 unrelated CF patients from the National CF Registry of the Republic of North Macedonia. Materials and Methods: Initially, patients were screened for 11 most common CF mutations. Additional CF mutations and large deletions/duplications in the CFTR gene were analyzed using commercial kits. If the genotype was undetermined, all CFTR exons were analyzed using Sanger DNA sequencing or next generation sequencing on MiSeq (since 2014). Results: The most common CF mutation - F508del was found in overall incidence of 75.9%. Additionally, 26 other pathogenic variants and three large deletions were identified in the CFTR gene as a genetic cause of CF. Two of them, c.1070C>T (p.Ala357Val) and c.2779_2788dupCTTGCTATGG (p.Gly930AlafsTer48) were novel. Discussion: According to the distribution and prevalence of the pathogenic variants detected among our patients, a fast and cost-effective method, based on single base extension was designed as a first-line CF genetic test with 90% detection rate within our population. Furthermore, the knowledge of CFTR mutation classes among our CF patients represents first step towards personalized therapy for CF in our country.

KEYWORDS: Cystic fibrosis (CF); Mutations; CFTR mutation classes

P-80 - A Challenging Diagnosis: Poikiloderma with Neutropenia

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Poikiloderma with neutropenia(PN) is one of the genodermatoses and has lots of overlapping clinical features especially with Dyskeratosis Congenita(DC) and Rothmund-Thomson Syndrome(RTS).The main clinical characteristics of PN are poikiloderma which appears first in extremities then progresses to trunk and face, chronic neutropenia, recurrent infections, palmar and plantar hyperkeratosis and dystrophic nails. The disease has an autosomal recessive inheritance pattern and responsible gene is USB1. We report on a patient with PN who was previously diagnosed as RTS.The patient was a 25-year-old male who was born to nonconsangineous parents as their sixth child. He had a rash history starting at the age of eight months. Presence of chronic neutropenia, frequent infections of lungs and soft tissue were also learned from his history. He had been followed-up as RTS since 3 years of age. The physical examination findings included sparse eyelashes, eyebrows, absence of beard, small ears, and nose, poikiloderma throughout the body, hyperkeratosis of palmar and plantar surfaces, camptodactyly of fingers and small testicles. He had normal hypophyseal and sex hormon levels with low neutrophil count.The frameshift mutation of USB1 gene was revealed by Sanger sequencing on ABI 3500 series genetic analyzer.Similar clinical findings found in RTS, DC and PN could be challenging for making accurate diagnoses. However, the distinctive features of PN including neutropenia, localization of poikiloderma, recurrent infections could provide a clue. Nevertheless, molecular testing is mandatory to make precise diagnosis of PN as in our patient.

KEYWORDS: Poikiloderma with Neutropenia, Rothmund-Thomson Syndrome, Sanger sequencing, USB1

P-81 - GENE POLYMORPHISMS OF DNA METHYLTRANSFERASES IN WOMEN WITH SPONTANEOUS PRETERM BIRTH

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Aim: The aim of this study was to evaluate the potential association between idiopathic spontaneous PTB (SPTB) and DNA methyltransferase 3B (DNMT3B) gene polymorphisms in Slavic women, and their contribution to clinical characteristics of women with SPTB and their new-borns (family history of PTB, maternal smoking before pregnancy, maternal age, gestational week at delivery and fetal birth weight). Patients and methods: A total of 162 women with SPTB and 162 women with term delivery were included in a case-control study. Genotyping of DNMT3B rs1569686 and DNMT3B rs2424913 single nucleotide polymorphisms was performed using polymerase chain reaction and restriction fragment length polymorphism methods. Results: DNMT3B rs1569686 and rs2424913 minor alleles (T) were significantly more frequent in women with familial PTB than non-familial PTB, and contributed to a 3.30 and 3.54 increased odds for familial PTB under dominant genetic models (95 % CI = 1.53-7.14, P = 0.003 and 95 % CI = 1.56-8.01, P = 0.002). Furthermore, the DNMT3B rs1569686 and rs2424913 T alleles were significantly more frequent in women with SPTB who smoked before pregnancy, reaching the most significant association under additive genetic models (OR = 6.86, 95 % CI = 2.25-20.86, P < 0.001 and O = 3.77, 95 % CI = 1.36-10.52, P = 0.011). Conclusion: The results of our genetic association study indicate that the DNMT3B rs1569686 and rs2424913 gene polymorphisms might be associated with SPTB in Slavic women, especially in women with familial PTB and smokers.

KEYWORDS: DNA methyltransferases; Pregnancy; Preterm birth; Single nucleotide polymorphism

P-82 - Investigation of interchromosomal effect in male carrier with structural chromosomal abnormality by using FISH technique

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Introduction and Aim: Interchromosomal effect (ICE) refers to a confusion of meiosis where rearranged chromosomes effect the segregation of the chromosomes not involved in the structural chromosomal abnormality. The aim of this study is to investigate the existence of ICE on the sperm nuclei of males who have structural chromosomal abnormality. Material and Method: In 9 male carriers of structural chromosomal abnormality (patient group), and 14 male individuals who did not have any chromosomal abnormalities (control group), aneuploidy of chromosome 2, 3, 12, 13, 17, 18, 21, X and Y in the sperm nuclei were investigated by using the fluorescence in situ hybridization (FISH) method. The patient group included 5 Robertsonian translocation (ROB) carriers [rob(13;14), rob(13;14), rob(13;15), rob(14;22) and rob(15;22)], 3 reciprocal translocation (RCP) carriers [t(9;14)(q21;q11), t(6;15)(q23;q24) and t(5;11)(q11.2;p11)], and 1 inversion carrier inv(6)(p22q13). Results: A total of 51921 sperm nuclei were analyzed (19484 from the patient group and 32437 from the control group) While ICE was determined in four of five patients carrier of a Robertsonian translocation and a inversion carrier patient, it was not determined in reciprocal translocation carriers. Discussion:Our results suggest that there was an interchromosomal effect on male individuals carriers with a structural chromosomal abnormality which appears to be translocation, breakpoint, chromosome and patient dependent.

KEYWORDS: Aneuploidy, fluorescence in situ hybridization (FISH), interchromosomal effect, chromosomal translocation, sperm

P-83 - Mosaic trisomy 8: Comparison of clinical findings in prenatal and postnatal cases

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Introduction: Non-mosaic trisomy 8 is incompatible with life and often ends with spontaneous abortion in the first trimester of the pregnancy. It is also known as Warkany syndrome, it is a rare, viable condition, with an estimated prevalence ranging from 1:25000 to 1:50000 in newborns, 5-fold higher in males than females. The clinical phenotype of the trisomy 8 mosaicism is highly variable. The most common features are mental retardation and facial dysmorphisms, including(prominent forehead and occiput, broad nose with a flat bridge, low set ears), dermatoglyphic patterns and congenital malformations including corpus callosum agenesis and renal abnormalities. It is suggested that the wide clinical variability is not related to the level of mosaicism. Material and method: Mosaic trisomy 8 has been found in 8 patients(4 prenatal and 4 postnatal cases), who were referred to our center. Postnatal cases have been investigated due to the multiple congenital anomaly/mental retardation and prenatal cases because of the pathological ultrasound findings in fetuses. Results: Six cases were mosaic for trisomy 8, one case had a ring chromosome derived from chromosome 8, and one case had non-mosaic ring chromosome 11 in addition to mosaic trisomy 8. The mosaicism rate ranged from 12.5% to 66%. In this series, most common finding was corpus callosum agenesis in the prenatal and the intellectual disability in postnatal cases, which was followed by ventriculomegaly, cardiac and renal abnormalities, respectively. Here, we report the clinical and cytogenetic findings, pregnancy outcomes and postnatal follow-up data of 8 cases with trisomy 8 mosaicism.

KEYWORDS: mosaic trisomy 8, warkany syndrome , corpus callosum agenesis

P-085 - SIX NOVEL F8 GENE PATHOGENIC VARIANTS AS A CAUSE OF HEMOPHILIA A IN REPUBLIC OF NORTH MACEDONIA

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Introduction and Aim: Hemophilia A (HA) is a common X-linked bleeding disorder, caused by deficiency of coagulant factor VIII. Genotyping of the F8 gene has become an important tool in management of HA with respect to prediction of the patients' clinical course and safe genetic counseling. Our previous work showed that the most frequent molecular defect is intron-22 inversion, (46%), followed by intron-1 inversion (9%). Among other hemophilia A patients 24 different types of point mutations, small deletions/or insertions dispersed through the whole coding sequence of the F8 gene were determined and all were private. Here we present six novel F8 variants determined during molecular characterization of HA in our group of patients. Material and Method: PCR followed by direct sequencing and lately NGS using TruSight inherited panel on MiSeq-Illumina were used for molecular diagnosis. MLPA-P178 was used for deletion/duplication screening of the F8 gene. Results and Discussion: Six novel variants, not listed in a Hemophilia A mutation database, were as follows: Three missense pathogenic variants: c.1735G>A;p.Asp579Asn in exon 11; c.6520C>A;p.His2174Asn in exon 23; and c.6820A>G;p.Met2274Val in exon 25, two small insertions: c.553insTC;p.Lys185IlefsTer4 in exon 4 and c.3322dupG;p.Ala1108GlyfsTer10 in exon 14 and one large duplication covering exon 15. Classifications of the variants was according to ACMG guidelines. Each novel missense variant occurred at a highly conserved region. Prediction of the functional effects of the nucleotide changes was performed using in-silico analysis. The six novel variants determined, confirm the high heterogeneity of molecular defects within F8 gene. Supported by RCGEB funds

KEYWORDS: Hemophilia A, F8 gene, pathogenic variants,

P-086 - Frequency of JAK2 V617F mutation in patients with myelofibrosis

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Introduction and Aim: Myelofibrosis (MF) is characterized by bone marrow fibrosis with subsequent extramedullary hematopoiesis. About half of the patients with MF and essential thrombocytopenia (ET) have an acquired somatic V617F mutation in JAK2 gene. Our aim is to determine the prevalence of V617F in patients with MF. Materials and methods: DNA samples were isolated from venous blood of patients with various haematological disorders. DNA was amplified by PCR and subsequent restriction analysis was performed using XbaI restrictase. The genotype status was determined on 2% agarose gel. Results: We analyzed 38 patients suspected for MF, ET or other chronic myeloproliferative disorder (MPN). After trepanobiopsy, 20 out of 38 patients were confirmed myelofibrotic (52.6%), 5/38 (13.2%) diagnosed as ET, 1/38 (2.6%) remained MPN, 6/38 (15.8%) polycythemia vera (PV). In 6 patients disease was rejected. Patients with MF were divided into three groups – homozygous for the mutation (3/20 or 15%), heterozygous (9/20 or 45%) and homozygous for the wild type allele (8/20 or 40%). Discussion: The triggering factor of MF is still unknown. It is associated mainly with JAK2 V617F, CALR exon 9 indel and MPL exon 10 mutation. We have proven that carriership of V617F mutation prevailed in the group of patients with MF (60 vs 40%). Previous studies also show that 50% to 60% of people with MF have JAK2 gene mutation within their blood-forming cells. Therefore the risk of evolution to MF could be associated with V617F-mutant allele burden in patients with MPN.

KEYWORDS: myelofibrosis, JAK2 mutation, frequency

P-087 - Molecular monitoring and BCR-ABL Gene Mutations in Imatinib Resistant CML Patients in Our Centre

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Introduction: Introduction of tyrosine kinase inhibitors (TKI) dramatically improves the treatment and survival of patients with chronic myelogenous leukemia (CML). TKI resistance remains an important problem. BCR-ABL gene mutations are among the most significant causes of TKI resistance. Methods: We have analyzed molecular response in 53 patients with CML treated with Imatinib(IM). Only 15 patients were treated with Imatinib as a front-line therapy, while 38 patients were previously treated with hydroxyurea or/and interferon. Median duration of CML is 6 years (3 months-17 years). Median duration of IM treatment is 3 years (3 months-10 years). Forthy six patients (87%) had complete hematological response, 66% had complete cytogenetic response and 55% had major molecular response (MMR). BCR-ABL mutations were analyzed in 16/47(34%) patients with poor or suboptimal molecular response to Imatinib. Results: BCR-ABL mutations were detected in 43% analyzed patients. MMR was achieved in 29/53(55%) patients, 13/53(24,5%) patients had MMR at 4,0-4,5 log and 16/53(30,2%) had MMR at 3,0-4,0 log. We detected 6 different mutations in 7 patients: T315I, M244V, G250E, Y253H, E279G and M318V. T315I mutation was detected in 3 patients, M244V in 2 and all other mutations were detected in one patient. Three patients had double mutations: one patient had M244V&G250E mutations; one had M351T&Y253H; and one had T315I&E279G. Three of these 7 patients (one with T315I, one with M244V, one with double mutation M244V&G250E) died due to disease progression. Four are still alive, but only one patient is in hematological and clinical remission despite the coexistence of two mutations (T351I&279G).

KEYWORDS: BCR-ABL mutation, chronic myeloid leukemia,Imatinib resistance

P-088 - Long noncoding RNA GAS5 as a novel pharmacotranscriptomic marker in glucocorticoid treatment of pediatric acute lymphoblastic leukemia

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Introduction and Aim: Growth arrest specific 5 (GAS5) is a long noncoding RNA that has a role in cell growth arrest and apoptosis. GAS5 also interacts with the glucocorticoid receptor, which makes it a possible pharmacotranscriptomic modulator of glucocorticoid (GC) treatment response. We intended to find correlations between GAS5 expression and GC therapy response in pediatric acute lymphoblastic leukemia (ALL) and elucidate the molecular mechanism of GC effects on the GAS5 signaling pathway. Material and Method: Peripheral blood mononuclear cells were collected from 29 patients on the day of diagnosis (0), day 15 and day 33 of ALL therapy. GAS5 expression was measured using RT-qPCR. HeLa cells were transfected with GAS5 expression vector and NF-κB DNA-binding activity was analyzed using EMSA. Results: In patients with a higher number of blasts on day 8, reflecting poor therapy response, higher GAS5 expression on day 0 (p=0.016) and a lower ratio of day 15/diagnosis expression levels (p=0.009) were detected. Thus, GAS5 expression profile influences GC therapy response in pediatric ALL. The in vitro analysis has shown that GAS5 expression levels change depending on GC dose and that GAS5 modulates the protein complex binding to the NF-κB DNA consensus sequence. Discussion: The results presented in this study suggest that GAS5 could be a promising pharmacotranscriptomic marker of response to GC treatment of pediatric ALL. This work has been funded by MESTD, Republic of Serbia (III41004).

KEYWORDS: GAS5, glucocorticoids, NF-κB, ediatri ALL, harma trans ri t mi s

P-089 - Determining and Classification of Genetics Variants Associated with Juvenile Arrythmia

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Detection etiology of disturbances in normal heart rhythm including Long QT, Short QT, Brugada Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and Arrhythmogenic Right Ventricular Tachycardia (ARVT) is important for specific treatment. Examination of genetic mutations observed and large data obtained with next generation sequencing (NGS) technics, using bioinformatics tools greatly contribute to the ability to establish diagnoses. The aim of this study is to compare the results of clinic databases such as ACMG, HGMD and ClinVar which are used for analyzing datas obtained with NGS. For this aim, a total of 72 individuals, consisting of 42 male individuals and 30 female individuals who are at or below 16 years old, requesting cardiac arrythmia tests in Istanbul Medipol University's Genetic Diagnostics Center were included in the study. As a result, the HGMD, ClinVar and ACMG databases complement each other. The results of this study might be subject to variances in patient clinics, physician's level of experience and the fact that current articles are not yet evaluated using databases. We hope that gradual accumulation of the laboratory's own database results will increase laboratory reliability.

KEYWORDS: Arrythmia, ion channels, next generation sequencing

P-091 - Clinical Spectrum of Mitochondrial Diseases

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Introduction and Aim: Mitochondrial diseases are clinically heterogeneous group of disorders associated with the heteroplasmic rate of the tissues. Majority of the nuclear gene defects are linked with early while pathogenic variants of mtDNA are related to late onset disease. Aim of the study is to search the mitochondrial and nuclear genome variation with an algorithmic approach including biochemical, proteomic, immunohistochemical staining of muscle tissues, radiological imaging and whole exome sequencing (WES) in cases with mitochondrial dysfunction from different age groups. Material and Method: Three cases from two families are included. PATIENT- I: A baby girl born after an unremarkable prenatal history, to consanguineous parents. Following the delivery, she required ventilation due to the metabolic acidosis with an elevated lactate. Echocardiogram showed hypertrophic cardiomyopathy. Bilateral cataract was found in the eye examination. She died from heart failure on 96th day of her birth. PATIENT II-III: Two brothers (20 and 17 years old), offspring of first degree cousins, were presented with muscle weakness, ptosis and elevated CK level. The muscle biopsies of both siblings were consistent with mitochondrial myopathy. Results and Discussion: Our investigation is still continuing. A biochemical diagnosis is critical in the selection of candidate genes for analysis with in-depth patient phenotyping. In congress, we will present phenotypical variability of the mitochondrial diseases on three patients with different clinical and laboratory findings from two families.

KEYWORDS: Mitochondrial disease, clinical findings, diagnosis

P-092 - Predictive medicine and ethical norms

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Predictive medicine and ethical norms Sevdalina Alekova**, Borislav Popov *, Veselina Petrova-Tacheva * *Department of Molecular Biology, Immunology and Medical Genetics, Faculty of Medicine **Department of internal Diseases and General Medicine, Faculty of Medicine Trakia University,11 Armejska str., Stara Zagora, Bulgaria Introduction: Predictive medicine is a field of medicine that entails predicting the probability of disease and applying preventive measures and activities in order to either prevent the development of the disease altogether or significantly reduce impact of disease on the patient. The scientifically medical techniques and assays include Medical bioinformatics, Preconception testing, Diagnostic testing, Newborn screening, Prenatal testing, Carrier testing. The public trust in genetic testing is a key to the success of predictive medicine in the era of intensive scientifically medical innovations and research. Goal: We aimed to study and analyze the personal position of the people on predictive medicine and the importance of implementation ethical principles in the conduct of genetic testing. Material and methods: In our study we surveyed 140 people from Stara Zagora region, and we used the sociological method - direct individual poll with obligatory observance of the principles of anonymity and voluntary. Results: In the most basic terms, predictive medicine utilizes specific laboratory and genetic tests to determine the probability if an individual will develop a disease. Significant part of respondents appreciates the importance, relevance and information of genetic testing and expresses a positive attitude towards Predictive Medicine. Many of respondents think that undergoing a genetic test is a serious stressful situation associated with a number of psycho-emotional and moral ethical factors. It is essential that people are protected from potential misuse of their genetic information. Conclusion: Traditionally, predictive medicine was exclusively confined to the realm of genetics. Genetics and genomics have improved our ability to predict individual risk of disease for patient. Predictive medicine ushers in several ethical and legal questions associated with genetic discrimination, stigma and psychological consequences of reporting the result of a genetic test. So that genetic testing should only be used in carefully controlled circumstances where it is of proven benefit to health. Key words: Predictive medicine, personal opinion, genetic testing, ethics References:
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KEYWORDS: Predictive medicine, personal opinion, genetic testing, ethics

P-093 - A PATIENT WITH FRA16(q22) AND INTERESTING FAMILY HISTORY

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Intr d ti n: Fragile sites are s e ifi hr m s mal regi ns l ated thr gh t the h man gen me that are especially susceptible to DNA breakage. Except the FRAXA, FRAXE and FRA11B, fragile sites are not associated with specific syndromes or clinic conditions. However, some publications report that there is a link between fragile sites and infertility or spontaneous abortions. Materials and methods: A non-relative couple were admitted to our polyclinic with the complaint of abortion. Her mother also had a history of miscarriage and three early age infant death. Karyotype and FISH analysis were performed for the patient, her husband, and her parents. Results: The patient's karyotype was 46,XX[35]/46,XX,fra(16)(q22)[10]/46,XX,del(16)(q22)[5]. Her karyotype result was confirmed by FISH analysis by using 16q subtelomeric probe and the patient's mosaicism for del(16)(q22) was 10%. Karyotype and FISH of the patient's ibr blast sam les was als performed and same results were obtained. Her father was a carrier of the same fragile site, too. Conclusion: Our case had an abortion and her three sisters died due to alveolar capillary dysplasia. Deletions or mutations of FOXF1 gene, located on 16q24.1, are caused alveolar capillary dysplasia with misalignment of pulmonary veins that poor prognosis leading to death in the first month. Our patient has a risk of abortion and having children with alveolar capillary dysplasia. We have presented this case to highlight the importance of fragile sites and to report that the fra16q22 region may cause clinical problems.

KEYWORDS: Fragile sites, 16q22, alveolar capillary dysplasia, FOXF1 gene, abortion

P-94 - Chromosomal microarray analysis in diagnosis of patients with congenital abnormalities, developmental delay, intellectual disability, autism: a one year retrospective analysis

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Introduction and Aim: Genomic disorders result from the loss or gain of chromosomal/DNA material (copy number variations [CNVs]). Using Chromosomal microarray analysis (CMA) has led to detect growing number of CNV variants related to clinically well-de ined hen ty es. Here we re rt r lab rat ry's array data patients with congenital abnormalities, developmental delay intellectual disability, autism. Material and Method: CMA analysis was performed in 657 patients with congenital abnormalities, developmental delay intellectual disability, autism (referred to our laboratory during the period of February 2018 to February 2019). CNVs were classified according to CNV size and type, gene content, mode of inheritance and genotype-phenotype correlation. CMA analysis was performed by Agilent ISCA v2 Human Genome 8x60k oligonucleotide array. Results: In 162 of 657 patients(%24,6), CNVs were detected. %53,4 of CNVs were pathogenic variants(86/162) and %46,9 of CNVs were VUS (variant of unknown significance) variants. %15 of pathogenic variants were incidental findings and %2,3 of them were VISL (Variants in susceptibility loci). The most common VUS size ateg ry was ≤500 kb (50%). st the ath geni variants were >1 b. The smallest size of detected pathogenic variants was 52 kb (deletion) which cause Rubistein Taybi syndrome. %73,2 of pathogenic variants were deletions. Most of the VUS variants were duplications (%56,5). %47,6(41/86) of pathogenic variants were well-defined CNV syndromes (microdeletion/microduplication). Most common CNV syndrome was 22q11 deletion syndrome (Velocardiofacial / DiGeorge syndrome). Discussion: CMA is a powerful diagnostic tool for patients with congenital and developmental abnormalities, intellectual disability, autism especially for unexplained phenotypes.

KEYWORDS: chromosomal microarray, CNV, developmental delay, intellectual disability

P-95 - A Novel Mutation in the PRKRA gene Causes DYT16 in a Turkish Family

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Background: Dystonia 16 (DYT16; OMIM 612067) is a rare monogenic subtype of dystonia caused by homozygous mutation in the PRKRA gene. DYT16 is autosomal recessive, movement disorder characterized by early-onset progressive dystonia, gait abnormalities, involuntary movements, upper limb dystonia and pyramidal signs. Delayed motor and speech development and cognitive impairment can also be seen in some patients. Here, we describe two siblings of early onset dystonia and intellectual disability with novel homozygous mutations in PRKRA identified by whole exome sequencing (WES). Clinical Report: 13-year-old female patient who was the first child of consanguineous healthy parents was referred to our genetics clinic because of her dysmorphic features including triangular face, bilateral pes equinovarus and her neurodevelopmental problems like gait abnormalities, motor retardation, speech delay and mild intellectual disability. Her brother is a 9 year-old-boy also has mental-motor retardation. Both of them have strabismus. Chromosome analysis showed normal karyotype. WES was carried out for further genetic analysis and a novel homozygous missense mutation in PRKRA gene (c.G172C; p.Asp58His) was determined. The parents were found to be carriers of the same mutation. Conclusion: We identified novel homozygous variant in the PRKRA gene in our cases. Very few DYT16 cases have been reported in the literature to date. We present these cases to contribute to the ongoing clinical and genetic characterization of DYT16.

KEYWORDS: PRKRA, DYSTONIA 16, early-onset dystonia-parkinsonism, autosomal recessive, DYT16

P-96 - Novel FGFR2 variant in a Case with Crouzon Syndrome

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Crouzon syndrome (CRS; MIM#123500) is a well-known autosomal dominant craniosynostosis syndromes (CS) with a prevalence of 1:25,000-1:60,000 births. Premature fusion of coronal or sagittal sutures exposes a clinically recognizable crouzonoid face (exophthalmia, beaked nose, mid-facial hypoplasia) in patients. Pathogenic variants of FGFR2, located on 10q26.13, encoding fibroblast growth factor receptor 2, are found in all CRS patients. FGFR2 acts as a cell surface receptor with tyrosine-kinase activity and important for normal development of the skeleton. Presently, 130 pathogenic variants of FGFR2 have been reported in various forms of CS including Apert, Pfeiffer, Jackson-Weiss, Beare-Stevenson syndromes and isolated coronal synostosis patients. In approximately 95% of the pathogenic variants are reported in exon 7 and 8 of FGFR2 gene (NM_000141.4), encoding Immunoglobulin-like III domain in CRS patients. We sequenced 7 patients with CRS and found in 6 pathogenic known variant except one case. Sequencing of FGFR2 gene in a patient with CRS revealed novel missense alteration (insdel c.983_985delATAinsGTT; p.[Tyr328Cys;Ile329Phe] in exon 8, striking the extracellular Ig III domain, altering consequently two amino acids. Our study is important in terms of showing a novel alteration in FGFR2 gene that may contribute to the genetic diagnosis and counseling of CRS patients.

KEYWORDS: FGFR2, Crouzon Syndrome, Craniosynostosis

P-97 - Acute Pancreatitis Severity Related With Macrophage Migration Inhibitory Factor Gene - 173 G/C Polymorphism and Serum MIF Level

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BACKGROUND: At acute pancreatitis (AP) there is a positive relation between the high macrophage Migration Inhibitory Factor (MIF) levels and tissue damage and mortality. Hereby our aim is to evaluate the serum MIF levels and its possible relation with its promoter polymorphism at -173G/C and the severity of acute pancreatitis. METHODS: In this study, 63 AP patients and 83 controls were included. Patients were 35 females and 27 males and their mean age was 51. Serum MIF levels (at 24th hour of attack) and MIF promoter region -173G/C polymorphisms were analyzed. RESULTS: The genotype of patients and controls and -173 allelic distribution were found significant ($p<0.001$; $p=0.03$). The AP severity was mild at 37, moderate at 21 and severe at 4 patients. The aptness of CC genotype and -173 allele frequency being higher at moderate and severe AP and GG genotype being higher at mild AP was detected. The CC genotype and C allele frequency was 88.9% at eight of nine SIRS developed patients. At the 24th hour of their attack, mean MIF serum level was 44.11 26.43 U/l in patients and 31.57 24.99 U/l in controls. Moreover, the mean serum level of MIF was 37.15 U/l among severe AP patients and 29.78 U/l among moderate and mild AP patients. CONCLUSION: According to our results, although the statistical significance of the severity of AP could not be demonsrated, the CC genotype and C allele frequency were found in relation with AP occurance.

KEYWORDS: Macrophage Migration Inhibitory Factor, Acute Pancreatitis, Polymorphism

P-98 - Whole Exome Sequencing Identifies Novel Compound Heterozygous Mutations in CC2D1A Gene in a Turkish Family with Autosomal Recessive Non-Syndromic Mental Retardation

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Mental retardation (MR) is a health problem affecting approximately 1% to 3% of the general population, which can lead to significant problems in self-care, social skills, and social utility. MR can be divided into two parts: Syndromic and non-syndromic. Even in the majority of studies to determine the etiological cause to date, in a significant percentage of children with MR, the underlying cause or associated syndrome cannot be identified and the pedigree is not helpful enough. It has been shown that genetic factors play a role in approximately half of the individuals with MR. To identify causal variants for syndromic and non-syndromic mental retardation (NSMR) Whole Exome Sequencing (WES) has been quite successful in determining the genes responsible for neurodevelopmental diseases in recent years. In this case, we present a novel compound heterozygous mutation in CC2D1A gene detected by Whole Exome Sequencing (WES) analysis in a patient with mental retardation whose parents have consanguinity. Potential pathogenicity of these mutations was supported by co-segregation with the phenotype, low frequency in control populations and the in silico prediction pathogenicity predictions programmes. To the best of our knowledge, these mutations have not yet been published in the scientific literature, and are expanding the spectrum of the autosomal recessive NSMR mutation associated with the TCTN3 gene. This case represents an example that will increase our insights into the mechanisms of formation that may lead to autosomal recessive NSMR.

KEYWORDS: CC2D1A, non-syndromic mental retardation, compound heterozygosity,

P-99 - Partial Chromosome 2q Duplication in Two Siblings with Intellectual Disability and Dysmorphism

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Introduction and Aim Copy number variations (CNVs) are major causes of developmental delay or intellectual disability, autism spectrum disorders and congenital anomalies. Clinical importance of CNVs varies depending on dosage sensitive genes in the region. Here we report two siblings, who were referred to us with mental retardation, neurodevelopmental delay, happy demeanor and craniofacial dysmorphism and in whom chromosome 2(q22.1q24.1) duplication was detected. Materials and Methods: Metaphases obtained from peripheral blood lymphocyte culture were analyzed after GTG banding. Chromosomal microarray analysis were performed with Affymetrix CytoScan Optima (315k) chips from DNA samples of siblings and their father. Data obtained from CHAS 3.1 analysis program were evaluated by using current databases (Pubmed, OMIM, DGV, DECIPHER). Results: While karyotype analysis of the siblings and their mother were found as n rmal, ather's kary ty e analysis revealed a balan ed re i r al transl ati n whi h was re rted as t(2;4)(q22;q34). Father's hr m s mal mi r array analysis was normal. The siblings had nearly 15 Mb duplication of chromosome 2q22.1q24.1 region according to the microarray analysis. Discussion: Phenotypic features of our patients are consistent with previously reported cases with similar duplications. According to the literature, some of 26 genes such as MBD5, EPC2, ZEB2 in this duplicated region are responsible for the phenotype. We can speculate that this duplication occurred due to unequal crossing over between homologous sequences on chromosome 2q and paternal translocation probably predisposed to the rearrangement especially at the 2q22 breakpoint.

KEYWORDS: Chromosome 2q duplication, copy number variations, intellectual disability, dysmorphism

P-100 - A CASE OF NEONATAL MARFAN SYNDROME WITH FBN1 GENE MUTATION

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INTRODUCTION:Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with cardiac, ocular and skeletal involvement.Mutations in the fibrillin-1 (FBN1) gene are known to cause MFS.Neonatal MFS (NFMS) is rare and most severe form of the disease with poor prognosis.Here we report an infant diagnosed as NMFS with FBN1 gene mutation. CASE REPORT:A 3-day old girl consulted to genetic clinic due to facial dysmorphism and arachnodactly.She was born at 34th gestation week with C/S from dichorionic twin pregnancy.Her parents were nonconsangineous.On physical examination her weight, height and head circumference were at 25th, 25th and 25-50th percentiles respectively.She had dolicocephaly, enophtalmus, hypertelorism, crumpled ear, rebundant skin at neck, downslanting palpebral fissures, micrognathia, high arched palate, arachnodactly and joint laxity.Echocardiogram (ECHO) revealed aortic root and ascending aorta dilatation, mitral regurgitation and mitral valve prolapsus.She had no ocular involvement.In the light of clinical and ECHO findings, NMFS was suspected.Molecular analysis revealed heterozygous c.3602G>A (p.Cys1201Tyr) mutation in FBN1 gene.She was died at 2 months of life because of cardiac insufficiency and respiratory failure. DISCUSSION:NMFS is clinically differs from presentation of classical MFS in infants through the severity of cardiac and pulmonary manifestations.NFMS is most severe form with poor prognosis.The majority of cases die within the first year of life and major cause of death was cardiac insufficiency.The mutation that we detected in our patient was reported in an infant who died in a few days of life with severe phenotype like our patient.It's important to recognize and diagnose NMFS for early medical intervention.

KEYWORDS: FBN1, NEONATAL, ARACHNODACTLY

P-101 - Genotype phenotype correlation of 3 siblings with myotonic dystrophy type 1

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Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. The clinical findings, which span a continuum from mild to severe, have been categorized into three somewhat overlapping phenotypes: mild, classic, and congenital. DM1 is caused by expansion of a CTG trinucleotide repeat in the noncoding region of DMPK. The diagnosis of DM1 is suspected in individuals with characteristic muscle weakness and is confirmed by molecular genetic testing of DMPK. CTG repeat length exceeding 34 repeats is abnormal. Molecular genetic testing detects pathogenic variants in nearly 100% of affected individuals. In our study, genotype and phenotype correlations of 3 siblings with increased CTG repeat number in DMPK gene were investigated.

KEYWORDS: Myotonic dystrophy, genotype,pehotype , dynamic mutation

P-102 - Unusual presentation of Muir-Torre syndrome - A case report

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The Muir-Torre syndrome (MTS), a subtype of Lynch syndrome, is characterized by sebaceous skin tumors associated with visceral carcinomas. Usually, visceral cancers affect the gastrointestinal and genitourinary tracts, and skin lesions may appear before or after the occurrence of the visceral neoplasm. MTS is inherited in an autosomal dominant manner, usually caused by inactivating mutations in MLH1 or MSH2 genes coding for the respective DNA mismatch repair proteins. Mutation in just one of these genes generates lifelong increased risk for malignancy. Case report: Thirty-seven years old male was hospitalized at the Clinic for Thoracovascular Surgery for surgical treatment of gynecomastia, with no other complaints and negative family history. The operative material accepted at the Institute of Pathology consisted of fibro-fatty mammary tissue measuring 7.3x6.8x3.4cm (80g) with uniform serial cut surfaces on gross examination. Microscopic examination revealed male breast tissue with duct hyperplasia and focus of Ductal carcinoma in situ (DCIS)(pTis;NG1)with greatest diameter 8mm. Radical mastectomy followed. The specimen consisted of male breast covered with skin (14x4cm) with regular mamilla and areola, para-areolar grey-yellowish discoloration(2,5x1cm)1mm above the skin level, subcutaneous fat 14x9.5x4.3 in continuity with axillary fat. After standard dissection,samples were taken for microscopic analysis which confirmed gynecomastia with no residual neoplastic tissue. The skin lesion showed Nevus sebaceus-Jadassohn. Immunohistochemical staining revealed total loss of MSH2 in the DCIS lesion. The follow-up (almost 3 years) is uneventful so far. This is a rare case of MTS with peculiar combination of skin lesion with male breast DCIS instead of gastrointestinal/genitourinary malignancy.

KEYWORDS: Muir-Torre, Male breast, Ductal carcinoma in situ, MSI, immunohitochemistry

P-103 - Satellite region of chromosome 14 is oriented to the opposite side due to the pericentric inversion of the nearly entire chromosome

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Introduction and Aim: Pericentric inversions lead fertility defects with the gain and the loss of the outside of the inverted segments of the entire chromosome. Pericentric inversion (inv) of chromosome 14 (chr14) involving the satellite containing ribosomal RNA (rRNA) genes, is a seldom phenomen, like the case presented here. Material and Method: Karyotyping was done to the one and a half year married young woman because of primary infertility. Fluorescent in situ hybridization (FISH) technique was applied to the specimen by the usage of probes hybridized to the short arm (p) of all acrocentric chromosomes, and the probes specific to the chromosome 14s. Results: High resolution banding analyses revealed a large inversion (p12q32.1) of chromosome 14, altering the location of satellite DNAs. FISH probes specific to the p arm of acrocentric chromosomes, and to the telomere of the long arm (q) of chr14, were confirmed the newly oriented location of satellite DNA, and original location of the telomeric region, of the derived chr 14, respectively. Discussion: Deleted or duplicated segments with remarkable number of genes of the acrocentric chromosomes, derived from the the large pericentric inversions, are the main cause of discernible reproductive problems. Vice versa the alterations of p arm only consisting rRNA genes, are insignificant phenomen. The patients desiring having a healthy baby should be aware of these information, and prenatal/preimplantation genetic diagnosis should be announced. References: 1. Fertil Steril 2015;104(3):0015-0282. 2. Prenat Diagn 2005;25:612-627.

KEYWORDS: Acrocentric chromosomes, Fluorescent in situ Hybridization, infertility, pericentric inversion, ribosomal RNA

P-104 - Mutational spectrum of TSC1/TSC2 genes among patients with tuberous sclerosis complex in Republic of North Macedonia

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Introduction and Aim: Tuberous sclerosis (TSC) is an autosomal dominant disorder characterized by benign tumor growths in multiple organs. Majority of patients (~80-90%) have germline pathogenic variants within TSC1/TSC2 genes, while others are due to somatic variants or low mosaicism. It is estimated that 2/3 of TSC cases are sporadic. Here we present the spectrum of TSC1/TSC2 pathogenic variants among Macedonian TSC patients. Material and Method: The methodology included MLPA analysis for gross deletions/duplications and NGS using TruSight-Cancer Panel on Illumina MiSeq platform for point mutations. Results and Discussion: Eleven pathogenic variants were determined, eight within TSC2 and three within TSC1 gene. TSC2 variants included four gross deletions, one small nucleotide deletion and three missense mutations, while TSC1 variants included a small nucleotide deletion, a small nucleotide duplication and a missense variant. Two variants were novel: TSC1 c.1363dupA and TSC2 c.1932C>A. All variants have arisen as a de novo event, with an exception of TSC2/PKD1 contiguous gene deletion detected in a newborn manifesting with cardiac defect and multiple neoplasms, inherited from the mildly affected mother with cysts on kidney only, bearing a mosaic form of the deletion. All patients were children (mean age 5) at the time of diagnosis with classical phenotypic signs of TSC with an exception of 37-year-old female presenting with trichofolliculoma and renal angiomiolipoma, who was mosaic (~30%) for the TSC2 c.1932C>A variant. In conclusion, we present the TSC1/TSC2 mutational spectrum, which includes two novel pathogenic variants in tuberous sclerosis patients from North Macedonia. Funded by RCGEB

KEYWORDS: TSC1, TSC2, Tuberous Sclerosis

P-105 - Chromosomal Abnormalities Related to Congenital Diaphragmatic Hernia

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Introduction: Congenital diaphragmatic hernia (CDH) a defect of the diaphragm that results in herniation of the abdominal contents in the thoracic cavity can be diagnosed prenatal ultrasound examination. In the etiology, genetic factors play an important role. Known genetic factors are chromosomal abnormalities (15%), copy number changes (CNVs) (3.5-13%), and single gene mutations (altogether 30%). Some genes such as GATA4, ZFPM2), NR2F2 and WT1 and genes related to retinoic acid signal pathway have been published. It is clear there are unknown causative genes or genomic alterations involved in the etiology and pathogenesis of CDH. Material and Methods: 153 fetuses with diaphragmatic hernia have been investigated cytogenetically for chromosomal anomalies. In 63 fetuses with normal karyotype, array CGH study with Agilent SurePrint G3 CGH+SNP Microarray Kit (4x180K) was performed subsequently. Results: Chromosomal anomalies were detected in 17 cases (11%). These anomalies were trisomy 18 (n:5), trisomy 13, trisomy 16, mosaic trisomy 16, mosaic trisomy 8, 47, XXY, tetrasomy 12p (n:2), 47,XY,+mar (cat eye syndrome), der(18) inv(18)(p11.23q21.1)mat, del(12)(q23.1;q24.11) and der(X)(12pter->12p11::Xp11->Xqter). A-CGH study revealed that deletions of 15q11.2, 5q13.2, 1q21.1 and duplication of 18q23 in 4 patients (6.6%). Discussion: Genetic counselling can be given based on the detected etiological factor. This approach disclosed the etiology of CDH in 17.6% of prenatal cases, on the other hand, the etiology in about 80% of the cases remained undiagnosed.

KEYWORDS: Chromosomal Abnormalities, Congenital Diaphragmatic Hernia

P-106 - A case with deletion of 2q31.1 contributes in refining the genotype-phenotype correlation

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Introduction and Aim: Widespread usage of genome-wide microarrays in clinical diagnostics facilitates high-resolution detection of chromosomal deletions and determination of affected genes or gene groups, which allows for a better genotype-phenotype correlation. 2q31.1 microdeletion is associated with several varying phenotypic features, involving a spectrum of limb anomalies, facial dysmorphic features and several neuropsychiatric manifestations. Here, we present an individual with phenotypic features of 2q31.1 deletion and aim to narrow down the phenotypic contribution of affected genes. Case Report and Method: A 12-year-old girl, born to nonconsanguineous parents, presenting with synpolydactyly of four limbs, camptodactyly, facial dysmorphic features, esotropia and microcephaly was evaluated in Zeynep Kamil Women and Children's Hospital, Medical Genetics Department. The child had moderate neurodevelopmental delay, mild bilateral ventriculomegaly and behavioral problems. Chromosome and microarray analysis was performed to detect chromosome anomalies and copy number variations. Results: The chromosome analysis revealed a de novo deletion, 46,XX,del(2)(q24.3q31.1). Microarray analysis confirmed this and revealed that the deletion spans approximately 11.5Mbp-region in chr2:167,178,891-178,772,345 (hg19). Discussion: The deletion contains the whole HOXD cluster of genes. Monoallelic loss-of-function mutations in HOXD13 is associated with synpolydactyly, explaining the limb anomalies presented here. Deletion shown here also involves the previously suggested critical region for the common facial dysmorphic features of 2q31.1 deletion syndrome. However, ZNF385B, which is suggested as major cause of neurological and behavioral manifestations of the syndrome, is spared in this patient. We suggest that other genes are involved in the neuropsychiatric manifestaions of 2q31.1 microdeletion syndrome.

KEYWORDS: Syndactyly, Polydactyly, Facial dysmorphism, Developmental delay, microdeletion

P-107 - Eight new patients with autosomal recessive hereditary spastic paraplegia diagnosed via WES analysis

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Introduction and Aim Hereditary spastic paraplegia (HSP) is a rare neurogenetic condition with an estimated prevalence of 1.8 per 100.000. Over 75 genes causing HSP have been identified to date. Autosomal Recessive (AR) HSP is found in 25%-30% of all individuals with HSP and is very heterogeneous genetically. New identified subtypes of AR HSP are very rare and may be limited to a single family. Here we aimed to present eigth new patients with AR HSP from five families with their genetic background. Material and Method In the families who were referred to our clinic between 2017-2018 in order to investigate their neurogenetic etiology, the WES analysis was applied to the probands for the diagnosis. The Sanger sequencing method was used to confirm the variants detected in analysis and to evaluate the affected and the unaffected individuals in their families. Results and Discussion Potentially pathogenic mutations were identified in five families, including mutations in five different genes known to be associated with HSP: AP4B1, ARL6IP1, DDHD2, TECPR2, ZFYVE26. WES analysis is an efficient molecular diagnostic tool in patients with a neurogenetic condition, as HSP which is genetically heterogenous, owing to its high diagnostic yield, less time-consuming and cost-effective features. HSP subtypes associated with the ARL6IP1, DDHD2 and TECPR2 genes have been reported in a small number of families while mutations in AP4B1 and ZFYVE26 genes have frequently been reported. Even though the detected variants have been previously reported, the cases presented here are thought to contribute to the literature.

P-108 - Approach to clinical interpretation of sequence variants

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The rapid increase in the number of genes and new variants associated with the disease necessitates the classification of the pathogenicity according to certain criteria like as ACMG standards (Genetics in medicine 2015, 17(5):405). However, the literature review for newly identified genes is quite important, which requires a correct clinical preliminary diagnosis. Also, in variant analysis, analytical accuracy as well as clinical accuracy should be considered. Exon coverage should be evaluated in clinically related genes and Sanger validation should be done for low reading or homopolymer regions. Caution in terms of dual phenotypes; especially for families with consanguineous marriages and subsequent pregnancies with preimplantation genetic diagnosis. The accuracy of variant interpretations in databases should be questioned. The specificity of in silico prediction tools is lower in the interpretation of missense variants. In splicing prediction programs, the rate of false negativity is lower and the rate of false positivity is higher. In the variant evaluation, the type of pathogen variant known should be considered. In disorders with dominant negative mechanisms, null variants may not always be pathogens, but missense variants may not have a clinical effect in diseases caused by truncating mechanism. Also, truncating variants in the downstream of known pathogenic mutations should be considered.

Keywords: Next generation sequencing, interpretation of sequence variants

INDEX

A

A. Kıvanç Cengiz, 89
Aasly JO, 27
Abdulgani Tatar, 63, 136, 143
Abdullah Hanta, 102
Abdullah Sezer, 130, 144, 220
Abdullatif Bakır, 51
Abdülgani Tatar, 2, 7
Adekile AD, 23
Adem Alemdar, 78, 100
Adife Ercan Şençiçek, 208
Aharon-Peretz J, 27
Ahmet Arman, 2, 48, 86, 91, 119, 150, 151
Ahmet Burak Arslan, 148
Ahmet Dursun, 2, 9
Ahmet Ilter Guney, 150
Ahmet Kablan, 49, 78, 79, 99, 100, 137
Ahmet Kaya Bilge, 145
Ahmet Muzaffer Demir, 162
Ahmet Okay Çağlayan, 2, 6
Ahmet Rencuzogulları, 102
Ahmet Uludag, 168
Ajlan Tükün, 2, 4, 58, 125
Akif Ayaz, 121, 158
Akif Selim Yavuz, 120
Alamillo CL, 29
Aleksandar Dimovski, 2, 6, 16
Aleksandar Eftimov, 215
Aleksandar Sovtic, 161
Aleksandar Stojanovic, 122, 182, 201
Ales Maver, 2, 8, 17
Alexandar Yordanov, 200
Ali Benian, 142
Ali Karaman, 219
Ali Ucur, 76
Alparslan Merdin, 72
Alper Gezdirici, 52
Alper Han Çebi, 108
Altuğ Koç, 3, 5, 19, 41, 60, 65, 109
Ambler G, 29
Ana Peterlin, 196
Aneta Atanasovska-Stojanovska, 141
Anheim M, 27
Anıl Biricik, 2, 5, 17
Anıl Kalyoncu, 88
Anita Barišic, 196
Anita Skakic, 161
Annesi G, 27
Arda Çetinkaya, 219
Arda Kebapcı, 111
Arda Kekilli, 60
Aris Cakiris, 111
Arslan Ateş, 2
Arzu Vicdan, 58
Aslı Demirtaş-Tatlıdede, 132
Aslı Ece Solmaz, 95
Aslıhan Sanrı, 107, 213
Asude Durmaz, 2, 8, 50, 135
Asuman Gedikbasi, 204
Asuman Sunguroglu, 183
Atanas Radinov, 200
Atıl Bısgın, 102
Atıl Yüksel, 153, 218
Atil Bisgin, 101
Atilla Buyukgebiz, 91
Ayberk Türkyılmaz, 48, 86, 150, 151
Aybike Sena Ozuynuk, 103
Ayça Aykut, 3, 6, 9, 50, 135
Ayça Yıldız, 65, 109
Aydeniz Aydın Gümüş, 138
Ayfer Alikaşifoğlu, 126
Ayfer Ülgenalp, 2, 83, 172
Ayhan Abacı, 38
Ayhan Deviren, 152, 170
Ayhan Kuzu, 123
Aynur Acar, 2, 8
Aynur Daglar Aday, 76
Ayse Gul Bayrak, 76
Ayse Gul Zamani, 188
Ayse Kartal, 193, 211
Aysegul Yılmaz, 107, 213
Aysel Kalayci Yigin, 106, 165
Ayşe Çırakoğlu, 116, 152
Ayşe Evrim Kömürcü-Bayrak, 191
Ayşe Gül Zamani, 148, 190, 206
Ayşe Gürel, 157
Ayşegül Çetinkaya, 179
Ayşegül Kaymak, 2, 4
Ayşegül Kuşkucu, 81
Ayşegül Özcan, 181

B

Badel Arslan, 192
Balogh I, 32
Banu Nur, 66
Barbosa ER, 27
Barış Balasar, 197
Basak Celtikci, 94
Basar Bilgic, 87

Başak Aslaneli Çakmak, 152
Başak Funda Eken, 139
Başak N, 32
Başar Bilgiç, 132
Baysal E, 23
Berkcan Doğan, 79
Berna Akca, 168
Bertram L, 27
Beste Tacal Aslan, 139
Betül Çelik, 7
Beyhan Durak Aras, 3, 6, 64, 73, 85, 92, 184
Beyhan Tüysüz, 66
Bılgen Bılge Geckınlı, 48, 119, 150, 151
Bırol Guvenc, 75
Bilçağ Akgün, 88, 95
Bilgen Bilge Geçkinli, 86
Biljana Stankovic, 202
Birim Günay Kılıç, 208
Birsen Karaman, 2, 7, 153, 198, 204, 218
Bojan Ristivojevic, 202
Bojan Vujkovac, 8
Boletini E, 23
Borislav Popov, 131, 205
Borut Peterlin, 8, 9, 16, 196
Branka Zukic, 40, 202
Bumin Dundar, 91
Burak Durmaz, 2, 9, 80, 88
Burcu Albuz, 149, 156, 187
Burcu Sağlam, 125
Burçak Vural, 2, 8, 191
Burçin Erkal, 210
Busra E. Cavdartepe, 193
Bülent Demir, 117
Bülent Uyanık, 61
Büşra Eser Çavdartepe, 77
Büşra Yaşa, 154
Büşranur Çavdarlı, 45, 47

C

Cagla Rencuzogulları, 75, 102
Cagri Gulec, 98
Can Kosukcu, 67
Can Veysel Şoroğlu, 120
Canan Türkyılmaz, 130
Carss KJ, 29
Carter TG, 30
Cem Mujde, 101, 102
Cem Yener, 43, 114
Cemal Çavdarlı, 45
Cemil Altunay, 120
Cemre Örnek, 79
Cengiz Yakıcıer, 2, 8
Cenk Sayın, 43
Ceren Alavanda, 48, 86, 119, 150, 151
Ceren Damla Durmaz, 58, 169, 208
Ceren Yılmaz, 65, 172
Chavdar Slavov, 174
Chitty LS, 29
Christopher Konialis, 2, 5, 15
Cıhan Inan, 114
Cigdem Aktuglu Zeybek, 44
Cigdem Yuce Kahraman, 136
Clementina Carestia, 23
Condroyer C, 27
Constantinos Pangalos, 2, 7, 28, 30
Curuk MA, 23

Ç

Çağrı Güleç, 42
Çetin Timur, 82
Çiğdem Yüce Kahraman, 63, 143
Çisem Mail, 43

D

Dalabira E, 32
Damjan Glavac, 2
Damla Eker, 185
Demet Gül, 121, 158
Deniz Karcaaltıncaba, 134
Deniz Kıraç, 112
Deniz Yücel, 112
Derya Beyza Sayın Kocakap, 2, 7, 129
Derya Erçal, 2, 5, 83, 109
Desislava Nesheva, 174
Dicle İskender, 74
Didem Altindirek, 142
Dijana Plaseska-Karanfilska, 1, 2, 4, 5, 6, 9, 18, 194, 199, 201, 217
Dila Koyunoğlu, 54
Dilek Gün Bilgiç, 138
Dilek Güneş, 204
Dilek Pirim, 49, 78, 79, 99, 100
Dilek Uludağ Alkaya, 66
Dilhan Kuru, 152
Dimitriou E, 27
Dimovski AJ, 23
Divoky V, 23
Dokmanovic L, 32
Dominissini S, 27
Draga Toncheva, 2, 6, 15, 16, 33, 174, 200
Dragan Primorac, 2
Dragana Janic, 202
Dragica Nestoroska, 175
Dragica Radojkovic, 2
Dragomora Nikolova, 174, 200
Dupuits C, 27
Durdugül Ayyıldız Emecen, 88

Durif F, 27
Duygu Arican, 80
Duygu Onur Cura, 110
Duygu Yolal Ertural, 179
Dzimiri N, 32

E

E. Ferda Perçin, 2, 128, 130, 220
E. Vevecka, 23
Eberhardt RY, 29
Ebru Arslan, 210
Ebru Erzurumluoğlu Gökalp, 2, 4, 11, 73, 85, 92, 184
Ebru Göncü, 162
Ebru Özkan Oktay, 97
Ecem Buse Yılmaz, 99
Eda Becer, 171
Eda Utine, 2, 7
Edibe Ece Abacı, 123
Edibe Pembegül Yıldız, 209
Elcın Bora, 55
Elena Arangelovic, 122, 182, 201
Elena Sukarova-Angelovska, 173, 175, 186
Eleni Anastasi, 23
Elif Akçay, 208
Elif Uz Yıldırım, 49, 78, 79, 99, 100
Elif Uzay, 50
Elif Ümit, 162
Elif Yilmaz Gulec, 57
Elifcan Taşdelen, 66, 133, 163, 169
Elvin Kazancıoğlu, 130
Emel Ergül, 111
Emıne Ikbal Atlı, 114
Emilija Sukarova-Stefanovska, 194, 217
Emin Karaca, 2, 9, 80, 88
Emine Berrin Yüksel, 2, 7
Emine İkbal Atlı, 3, 8, 43, 185
Emine İpek Ceylan, 135
Emre Can Tüysüz, 81
Emre Tepeli, 168
Emriye Ferda Perçin, 144
Engin Altundag, 107
Engin Atlı, 3, 8, 185
Enis Boletini, 23
Ercan Mıhçı, 2, 6, 66
Erdal Fırat Çaralan, 121, 158, 203
Erdem Kındış, 195
Eren Demir, 179
Eren Gunduz, 73, 184
Erhan Parıltay, 88, 96
Eser Bolat, 129
Esin Bil Tuncay, 116
Esra Arslan Ateş, 4, 48, 70, 86, 150, 151
Esra Isık, 88
Esra Tekcan, 189
Esra Tug, 216
Esra Usluer, 83
Etem Akbaş, 179, 192
Etleva Refatllari, 23
Evda Vevecka, 23
Evrim Komurcu-Bayrak, 145
Evrim Unsal, 207
Ezgi Gizem Berkay, 66
Ezgi Gökpınar İli, 58, 159
Ezgi Susam, 92

F

Fahrettin Duymus, 193, 211
Fahri Akbaş, 124
Farwell K, 29
Fatih Tepgeç, 132
Fatma Sarı Tunel, 191
Fatma Sılan, 117, 149, 156, 187
Ferda Emriye Perçin, 62
Ferda Özkınay, 50, 88
Ferda Perçin, 7
Fethi Sırrı Çam, 2
Feyza Nur Tuncer, 191
Filip Duma, 217
Filiz Yavasoglu, 184
Francesca Di Noce, 23
Friedman JM, 29
Funda Tüzün, 135
Füsun Varol, 43

G

G. Novelli, 23
G. Zoraqi, 23
Gamze Alaylı, 89
Gamze Bilgili, 146
Gamze Bora, 54
Gamze Guven, 87
Gasic V, 32
Gennaro Musollino, 23
Georgitsi M, 31, 32
Gızem Icme, 75
Giuseppina Lacerra, 23
Gizem Urel Demir, 67
Gjorgji Bozhinovski, 199, 217
Goker-Alpan O, 27
Gonul Ogur, 107, 213
Gordana Ilieva, 173, 186
Göbel A, 27
Gökay Bozkurt, 2, 6
Gökçen Şahin, 42
Gökhan Ozan Çetin, 127
Gönül Aydoğan, 82

Gözde Yeşil, 2, 7
Grdana Ilieva, 175
Grigor Zoraqi, 2, 9, 22, 23
Grossi S, 27
Gulcin Gunden, 73, 184
Gulen Eda Utine, 67
Gulsum Kayhan, 128
Guluzar Fusun Varol, 114
Gülden F. Gökçay, 204
Gülen Eda Utine, 126, 157, 195
Gülnihal Bulut, 198, 218
Gülseren Bağcı, 127
Gülsüm Kayhan, 130, 134, 220, 221
Güven Toksoy, 66, 132, 204

H

H. Gül Öngen, 116
Hagnefelt B, 29
Hakan Cangül, 158, 203
Hakan Gürkan, 2, 3, 6, 43, 56, 114, 162, 185
Hakkı Onur Kırkızlar, 162
Halil Gürhan Karabulut, 58, 133, 163
Halil Özbaş, 59, 160
Halim Kosova, 23
Haluk Akın, 2, 6
Haluk Topaloğlu, 2, 7, 13
Hamilton SJ, 29
Hamza Polat, 86, 119, 150
Hande Kulak, 181
Hande Nur Cesur Baltacı, 163
Hande Ozkalaycı, 55
Hanifi Aktas, 168
Hasan Acar, 197
Hasan Baş, 64
Hasan Huseyin Kazan, 118
Haşmet Hanağası, 132
Hatıce Mutlu Albayrak, 213
Hatice Ilgın Ruhi, 2, 6, 58, 159, 169, 177
Hatice Karaca, 129
Hatice Mutlu Albayrak, 164
Hava Uskudar Teke, 73
Havva Sutcu, 114
Havva Sütçü, 43
Haydar Bağış, 2, 8
Hazal Gezmiş, 112
Henriksson E, 29
Hilal Esmanur Yildiz, 216
Hilal Özdağ, 123
Hilal Sahin, 170
Hilal Yücel, 38
Hillman SC, 29
Hilmi Bolat, 95
Hilmi Tozkır, 2, 3, 7, 162, 185
Huisman TH, 23
Hung Bui, 2
Huri Sema Aymelek, 181
Huseyin Per, 53
Huseyin Sahin, 167
Hülya Kayserili, 2, 9
Hüseyin Görkemli, 206
Hüseyin Onay, 95

I

Ibrahim Boga, 101
Ilia Mıikerezi, 2, 8
Ilia Mikerezi, 25
Ingolf Cascorbi, 2, 4, 6, 16
Irina Panovska-Stavridis, 122, 182, 201
Işıl Uzun, 43, 114
Ivana Novakovic, 2, 8, 9, 25

İ

İbrahim Eker, 73, 184
İbrahim Hakan Gürvit, 132
İbrahim Kaplan, 133
İkbal Cansu Barış, 127
İldeniz Uslu Bıçak, 120
İlhan Sezgin, 2
İlter Güney, 2, 3, 4, 5
İnci Şahin, 132
İpek Yılmaz, 210
İsmail Reisli, 190

J

Janic D, 32
Jelena Lazic, 202
Jelena Peric, 40
Jovana Komazec, 161
Jovanovic N, 32

K

Kaan Aydos, 183
Kadri Karaer, 2, 9
Kanay Yararbaş, 2, 4, 219
Karin Writzl, 2, 8
Kasim Bajrovic, 2
Kassela K, 32
Kaya Bilguvar, 208
Kıvanç Cefle, 2, 6, 66
Kıvılcım Gücüyener, 144, 220
Kilby MD, 29
Kilic Aydinli, 142
Kivanc Cefle, 76
Konialis C, 29
Koray Boduroğlu, 67, 126, 195

Korcan Demir, 65
Korkut Ulucan, 139
Kotur N, 32
Kristel Klaassen Ljubicic, 40
Krstovski N, 32
Kubra Baysal, 166
Kumar KR, 27
Kumuthini J, 32
Kuyaş Hekimler Öztürk, 59, 160
Kübra Metli, 206

L

L. Shundi, 23
Lamiya Alıyeva, 137
Lamiya Aliyeva, 49, 78, 79, 99, 100
Lang A, 27
Langlois S, 29
Lazar Cadievski, 182
Lejla Pojskic, 17
Leontari I, 32
Lesage S, 27
Levent Simsek, 188
Leyla Elkanova, 66
Leyla Özer, 94, 129, 207
Leyli Korkmaz, 204
Liang R, 23
Lidija Cevreska, 201
Lidija Dokmanovic, 202
Lila Shundi, 23
Lilakos K, 29
Liljana Tasevska-Rmus, 140
Lindita Zendeli Bedjeti, 141
Lohmann K, 27
Lord J, 29
Lubomir Balabanski, 15, 33, 174
Lwin A, 27
Lyubomir Balabanski, 2, 8

M

Magdalena Bogdanovska-Todorovska, 215
Maher EJ, 29
Maher ER, 29
Mahmut Cerkez Ergoren, 90
Mahmut Selman Yıldırım, 148, 188, 190, 206
Maja Kolak, 196
Maja Stojiljkovic, 40, 161
Makbule Nihan Somuncu, 190
Maria De Angioletti, 23
Marica Pavkovic, 122, 182, 201
Marija Ivanovska- Stojanoska, 141
Marija Terzikj, 194
Marina Andjelkovic, 40, 161
Marras C, 27
Matem Tuncdemir, 170
Mathur VS, 30
McMullan DJ, 29
Mehmet Alı Soylemez, 48, 86, 150, 151
Mehmet Ali Ergün, 1, 3, 5, 62, 146, 220
Mehmet Ali Uzun, 210
Mehmet Alikaşifoğlu, 3, 5, 8, 67, 126, 157, 195
Mehmet Baysal, 162
Mehmet Bugrahan Duz, 44
Mehmet Cihan Balcı, 204
Mehmet Emre Atabek, 188
Mehmet Rasih Sonsoz, 145
Mehmet Sait Okan, 137
Mehmet Seven, 2, 44, 106, 165
Meliha Nalcaci, 76
Melike Ataseven Kulalı, 68
Meltem Cerrah Gunes, 53
Meltem Erdogan, 183
Meltem Söylev Bajin, 2, 7, 15
Menekşe Öztürk, 117, 149, 156, 187
Meral Yirmibeş Karaoğuz, 2, 6, 134, 216
Merve Aydın, 207
Merve Bali, 124
Merve Benzer, 167, 180
Merve Kumrular, 145
Merve Saridal, 91
Metin Tilki, 210
Michelakakis H, 27
Mikail Demir, 181
Milena Gašparovic Krpina, 196
Milena Jakimovska, 194
Milena Jankovic, 2, 6, 26, 27
Milosevic G, 32
Mirjana Kocova, 141, 147, 186
Mirjana Popovska, 141
Misa Vreca, 161
Mizzi C, 32
Moraitou M, 27
Morris S, 29
Muhammed Hamza Muslumanoglu, 168
Muhammet Ensar Dogan, 53, 69, 166
Muhsin Elmas, 176, 214
Muhsin Konuk, 97
Munis Dündar, 2, 5, 53, 69, 166
Murat Aydın, 189
Murat Derya Ercal, 41
Murat Günel, 208
Murat Tombuloglu, 80
Mustafa Gökoğlu, 58, 212
Mustafa Hakan Demirbaş, 144
Mustafa Murat Ozbalak, 76
Mustafa Tarik Alay, 106, 165
Müge Sayitoğlu, 82

N

Naci Çine, 2, 7
Nadide Cemre Randa, 178
Nadir Kocak, 77, 93, 193, 211
Nalls MA, 27
Narmin Bakhshaliyeva, 116
Nassef SA, 30
Natalija Angelkova, 217
Natasa Tosic, 40
Nataša Tul, 196
Naz Guleray Lafci, 67
Nazan Eras, 179, 192
Nazan Sarper, 82
Nese Akcan, 90
Neslıhan Coban, 103
Neslihan Abacı, 111
Neslihan Cinkara, 63, 136, 143
Neslihan Teker, 84
Nıyazı Cenk Sayın, 114
Nikcevic G, 32
Nikola Kotur, 202
Nikolina Zdraveska, 186
Nilay Güneş, 66
Nilay Şen Türk, 127
Nilgün Genç, 203
Nilnur Eyerci, 84
Nina Pereza, 196
Niyazi Kaya, 49, 78, 79, 99, 100
Nur Oguz Davutoglu, 184
Nur Semerci, 2, 9
Nur Sena Uluskan, 168
Nuray Kırmızı, 198
Nurten Kara, 89, 189
Nüket Yürür Kutlay, 58, 125, 177, 208, 212

O

O.Sena Aydos, 183
Oguz Cilingir, 73, 92, 184
Oguzhan Kalyon, 168
Oğuz Çilingir, 64, 85
Olga Antonova, 174
Omer Salih Akar, 107, 213
Omer Yakar, 136
Onur Eroğlu, 2
Onur Yıldız, 156
Orhan Şahin, 154
Orvisky E, 27
Ozan Çetin, 2, 4
Ozge Cumaoğulları, 123
Ozge Sonmezler, 101
Ozlem Acar Dirican, 53
Ozlem Yıldırım, 119, 151
Ozturk Ozdemir, 117, 187

Ö

Ömer Faruk Karaçorlu, 46
Ömer Faruk Karasakal, 97
Ömer Yakar, 63, 143
Özden Hatırnaz Ng, 82
Özgur Çoğulu, 88
Özgür Balasar, 197
Özgür Çoğulu, 2, 6, 50
Özgür Erkal, 178
Özlem Giray Bozkaya, 38, 60, 68, 172
Özlem İlk, 123
Özlem Tüfekçi, 135
Özlem Yıldırım, 86
Öztürk Özdemir, 2, 8, 149, 156

P

Pangalos C, 29
Parthiban V, 29
Patrinos GP, 31
Pavlovic S, 31, 32
Pelin Ercoskun, 136
Pelin Ercoşkun, 63, 143
Pelin Ozyavuz Cubuk, 39, 41
Pelin Özlem Şimşek Kiper, 67, 126, 157, 195
Pelin Teke Kısa, 60
Peric J, 32
Petrucev B, 32
Pınar Ata, 119, 150, 210
Piraye Oflazer, 191
Pollak P, 27
Pourfarzad F, 32
Powis Z, 29
Predrag Minic, 161

Q

Quinlan-Jones E, 29

R

Rabia Tutuncu Toker, 137
Rachel Schot, 153
Radmilovic M, 32
Radoslava Vazharova, 2, 7, 33
Radost Vazharova, 174
Ramirez A, 27
Rasime Kalkan, 104, 171
Rıdvan Seçkin Özen, 2, 4
Rinck G, 29
Robson SC, 29
Romosan G, 29
Rosenbaum H, 27
Rosica Angelovic, 122, 182, 201

Rosica Rosica Angelkovik, 140
Rubens Jovanovic, 215
Rumen Stefanov, 2, 9
Rylander A, 29

S

Sabri Aynacı, 85
Saide Betul Arslan, 53
Saime Füsun Mayda Domaç, 112
Salih Serdar Erturan, 170
Sanja Trajkova, 122, 182
Santamaria R, 27
Sarenur Gökben, 50
Saša Ostojic, 196
Sashka Todorovska, 141
Savina Hadjidekova, 2, 7, 20, 174
Sebnem Ozemri Sag, 78
Sebnem Özemri Sag, 90
Seda Salman Yılmaz, 191
Sedanur Karaman Gülsaran, 162
Sedar Kasakyan, 125
Sefa Murat Şahin, 208
Seher Basaran, 153
Seher Başaran, 2, 5, 42, 132, 198, 204, 209, 218
Sehime G. Temel, 78
Sehime Gulsun Temel, 90
Selçuk Sözer Tokdemir, 120, 154
Selen Gursoy Erzıncan, 114
Selma Demir, 3, 8, 185
Selvihan Artan, 4
Sema Arayıcı, 117
Sema Berk Ocak, 210
Sema Sırma Ekmekçi, 111
Semih Aşıkovalı, 95
Semih Tangal, 94
Sengul Yuksel, 167, 180
Senol Citli, 93
Serap Sivri, 8
Serap Tutgun Onrat, 214
Serhat Seyhan, 121, 158
Sevcan Alkan Kayaoğlu, 210
Sevcan Tug Bozdogan, 75, 102
Sevcan Tuğ Bozdoğan, 2, 9
Sevdalina Todorova, 131, 205
Sevgi Isik, 73, 184
Sevil Zencir, 127
Sevilhan Artan, 2, 5, 11, 64, 73, 85, 92, 184
Sezen Güntekin Ergün, 62
Sezin Canbek, 61
Shahmirzadi L, 29
Sınan Ates, 114
Sınan Ozkavukcu, 183
Sırrı Çam, 138
Sibel Ersoy Evans, 195
Sibel Hacıoğlu, 127
Sibel Uğur İşeri, 2, 9
Sidransky E, 27
Simeon Rangelov, 174
Sinan Ateş, 43
Sinem Kocagil, 64, 85, 92
Sinem Yalcintepe, 56
Sinem Yalçıntepe, 3, 8, 185
Slavica Kostadinova-Kunovska, 215
Slobodanka Terziev - Trpkovska, 122
Somayyeh Heidargholizadeh, 218
Soner Senel, 166
Sonja Genadieva-Stavric, 122, 201
Sonja Pavlovic, 2, 6, 30, 32, 33, 40, 161, 202
Stankovic B, 32
Stojiljkovic M, 31, 32
Stojka Fustik, 194
Stover SR, 30
Sukru Ozturk, 76
Sukru Palanduz, 76
Suleyman Aktuna, 207
Sulgun Charyyeva, 123
Sumeyra Oguz, 67
Süleyman Atar, 157
Sümeyra Oğuz, 126
Süreyya Demir, 117
Svetel M, 27
Svetlana Koceva, 173
Svobodiva M, 23

Ş

Şahin Zeteroğlu, 146
Şebnem Özemri Sağ, 79, 99, 100, 137
Şebnem Sağ, 49
Şehime Gülsün Temel, 49, 79, 99, 100, 137
Şehime Temel, 2, 9
Şengül Tural, 89
Şeniz Öngören Aydın, 152
Şiar Dursun, 121
Şule Altıner, 58, 105, 125, 169, 177, 212
Şükriye Yılmaz, 152
Şükrü Öztürk, 66
Şükrü Palandüz, 66

T

Tabrizi SJ, 27
Taha Bahsi, 3, 9, 71
Tahir Atik, 50, 88
Taner Karakaya, 187
Tanja Hristova-Dimkovska, 175
Tansu Doran, 112
Tarkan Kalkan, 178
Tatjana Jakovska, 194

Tayfun Çinleti, 109
The-Hung BUI, 5, 34
Timur Tuncalı, 2, 4, 58
Tiraje Celkan, 82
Togneri FS, 29
Tolga Ecemiş, 118
Tommaso Beccari, 2, 5, 16
Tosic N, 32
Tuba Gunel, 142
Tufan Cankaya, 110
Tuğba Kalaycı, 66, 153, 209
Tuğba Kaman, 97, 139
Tuğçe Sudutan, 82
Tulin Cora, 193
Tunay Dogan, 210
Turocy J, 29
Tülün Cora, 211
Türkan Yiğitbaşı, 203

U

Ufuk Demirci, 162
Ugur Gumus, 106, 165
Uğur Özbek, 2, 3, 4, 9
Uğur Sezerman, 2, 9
Ulviyya Kazimli, 166
Umit Yuksel, 90
Ummet Abur, 107, 213
Umut Altunoğlu, 66, 153, 198, 209, 218
Umut Tekin, 129
Urosevic J, 32

V

V. Falbo, 23
Valentin L, 29
Vangelis G. Manolopoulos, 2, 4, 6, 14
Vehap Topçu, 113, 163
Vera Damyanova, 200
Verhoef T, 29
Veselina Petrova- Tacheva, 131, 205
Vesna Sabolic-Avramovska, 217
Vesna Spasovski, 161
Vesna Vankovska, 140
Vicha A, 32
Vildan Caner, 127
Violeta Anastasovska, 141, 147, 173, 175, 186
Violeta Dejanova-Ilijevska, 199
Vladimir Gašic, 202
Volkan Baltacı, 2, 207
Volkan Baş, 162
Volkan Karaman, 66, 209
Volkan Tuzcu, 203

W

Wellesley DG, 29
Weltmer EC, 29
Westerfield LE, 30

Y

Yakicier Mustafa Cengiz, 13
Yakup Sari, 167
Yaman Sağlam, 118
Yang Y, 30
Yasemin Alanay, 2, 7, 67
Yasemin Özen, 185
Yasemin Saygideger, 101
Yazgı Yücel, 121
Yelda Tarkan Argüden, 116, 152
Yunus Yukselten, 183
Yusuf Tunca, 2
Yusuf Ozkul, 166
Yusuf Tunca, 9
Yücel Erbilgin, 82

Z

Z. Betül Çelik, 89
Zehra Oya Uyguner, 3, 5, 42, 66, 132, 153, 204, 209
Zerrin Orbak, 63
Zeynep Doğru, 121, 158
Zeynep Karakaş, 82
Zeynep Tüfekçioğlu, 132
Zihni Ekim Taskiran, 67
Zora Hammoudeh, 174
Zorica Trajkova-Antevska, 199
Zuhal Bayramoğlu, 66
Zukic B, 31, 32
Zulal Keles, 41