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14th Balkan Congress of Human Genetics
& 9th Rare Disease SEE Meeting 2023

Skopje, October 05-07, 2023

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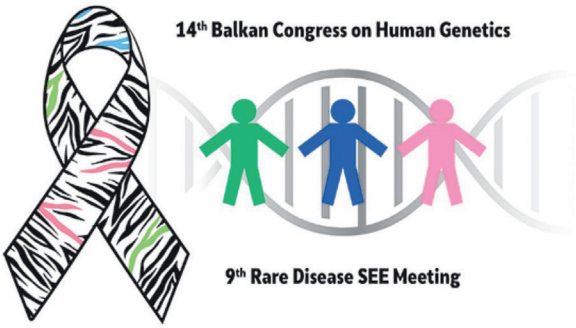

ABSTRACT BOOK

14th Balkan Congress of Human Genetics and 9th Rare Disease SEE Meeting

"Genetic Diseases from Diagnostics to Prevention and Therapy"

October 05-07, 2023
Hotel "DoubleTree by Hilton"
Skopje, North Macedonia

Balkan Journal of Medical Genetics
Vol. 26, 2023
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Disclaimer

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Organizers:

Македонско здружение за хумана генетика
МЗХГ
Macedonian Society of Human Genetics (MSHG)

Macedonian Society for Rare Diseases

LIFE with CHALLENGES
Life is a puzzle, collect it.

РЕТКО Е ДА СИ РЕДОК
RRALLË ËSHTË TË JESH I RRALLË
RARE IS TO BE RARE

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Stojiljkovic Maja, Serbia
Streata Ioana, Romania
Syrrou Maria, Greece
Trajkova Slavica, Italy
Xhetani Merita, Albania

Welcome Address

Dear Colleagues, Friends, Guests,

It is indeed a great honor and pleasure for me to extend you all a very warm welcome, on behalf of the Organizing Committee of the 14th Balkan Congress of Human Genetics and the 9th Rare Disease SEE Meeting. This joint conference brings together leading scientists, researchers, clinicians, and industry professionals from the Balkan region and wider to share their latest findings and developments in the fields of genetics and rare diseases and to exchange experiences.

The conference bears the general designation "Genetic diseases – from diagnostics to prevention and therapy" and covers various areas related to the stated topics in rare diseases as well as in complex diseases influenced by genetic factors. The conference aims to promote knowledge exchange and collaboration between experts in the field, and to provide a platform for discussing the latest advances and challenges in genetic research. It is primarily dedicated to professionals in the field of human genetics, including but not limited to the fields of pediatrics, neurology, cardiology, hematology, oncology, obstetrics and gynecology, and rare diseases.

The program is arranged in a multidisciplinary manner in order to allow delegates to both explore issues pertinent to their own area of interest and to interact with other professionals outside of their specialty. The conference features plenary lectures given by renowned European experts, invited lectures given by leading scientists from the Balkan countries, oral and poster presentations, as well as satellite symposia providing ample opportunities for attendees to network, learn, and share their research. In addition, there is a rich commercial exhibition, where the latest genetic technologies, products, and services are showcased.

The abstracts of the conference have been published in a Supplement of the Balkan Journal of Medical Genetics, an international journal published by the Macedonian Academy of Sciences and Arts, which is cited in all major medical and scientific databases, including PubMed, Web of Science and others.

The conference is dedicated to the patients and especially to those with rare diseases. Indeed, patients' organizations for rare diseases from our country have been our partners in the organization of this event.

To conclude, I would like to thank each and every one of you for attending this conference. I am confident that you will have an exciting, stimulating, and productive meeting. Nevertheless, I also hope that you have planned some extra time to enjoy our culture, food, tradition and hospitality.

Добредојдовте! Welcome!

Prof. Dr. *Dijana Plaseska-Karanfilska*
President of the Organizing Committee

General Information

Venue:
Platinum Conference Room
Hotel "DoubleTree" by Hilton
Blvd "ASNOM" 17,
1000 Skopje
North Macedonia

Registration desk:

Reception desk is organized in front of the Platinum Conference Room (1 and 2) at the Hotel "DoubleTree" by Hilton and will be open for information and registration from 10:00am 05.10.2023

Language:

The official language of the Congress is English.

Oral presentations

Facilities will be available for Microsoft PowerPoint (ppt or pptx) slides, in 16:9 format. Speakers are kindly requested to hand their presentations to the designated technician in the Conference room in the morning or during the breaks, but at least 1 hour before the start of the session.

Please, take in consideration the allocated time for effective presentation of your presentation.

Poster presentations

Posters will be presented on three 65" TV Monitors, according the detailed Program in two Poster sessions. Authors must be present at the boards for the duration of their scheduled poster session. Posters will be on display for the duration of the Conference (Thursday, October 5th, 2023 at 12:00, till Saturday, October 7th, 2023 till 15:00).

Registration Fee

Registration fee covers the Program, access to the Scientific sessions, Opening Ceremony, Get together Party, Coffee brakes, Lunch.

PDF version of the Abstract bookis available on the Event web-site.

Certificate for Attendance will be available at the event web-site (https://mzhg.org.mk) with appropriate log-in.

SCIENTIFIC PROGRAM

October 05, 2023 (Thursday)

10:00	Registration open
12:30 – 14:30	PharmGenHUB Pre-congress Workshop ***Pharmacogenomics***
14:30 – 15:00	**Coffee break**
15:00 – 15:30	**Conference Opening / Welcome** *Speakers: Fatmir Mexhiti, Ministry of Health* *Kalina Stardelova, President of Medical Chamber* *Dijana Plaseska-Karanfilska, President of the Macedonian Society of Human Genetics, and President of the Organizing Committee* *Zoran Gucev, President of the Macedonian Society of Rare Diseases* *Vesna Aleksovska, Life with Challenges (Patients' organization)* *Elizabeta Gjorgievska, First Lady of North Macedonia*
Plenary lectures	*Chairs: Dijana Plaseska-Karanfilska, North Macedonia; Aleksandar Dimovski, North Macedonia*
15:30 – 16:00	**PL-1. Han Brunner, The Netherlands** *Why we have the disorders we have*
16:00 – 16:30	**PL-2. Detlef Bockenhauer, Belgium** *Diagnosis of uncertain significance: the challenge of genetic variant interpretation*
16:30 – 17:00	**PL-3. Borut Peterlin, Slovenia** *Rare diseases to Public Health Genomics: a health system perspective*
17:00 – 17:30	**Coffee break / Poster viewing**
17:30 – 18:00	ELTA 90mm Satellite Symposium ***"Introduction to VeriSeq NIPT v2 solution"***
Session 1:	**Reproductive genetics I** *Chairs: Han Brunner, The Netherlands; Velibor Tasic, North Macedonia*
18:10 – 18:30	**IL-1. Svetlana Madjunkova, Canada** *The Art of ART: Preimplantation genetic testing as a treatment of genetic onditions*
18:30 - 18:50	**IL-2. Maria Syrrou, Greece** *Genetic and epigenetic signatures in low birth weight neonates and future health risks*
18:50 – 19:10	**IL-3. Savina Hadzydekova, Bulgaria** *It's time for extensive reproductive carrier screening*
19:20 – 19:50	Pfizer Satellite Symposium ***"Genetic aspectss of hereditary transthyretin amyloidosis"***
20:00 - 22:00	**Get together party**

October 06, 2023 (Friday)

Session 2:	**Rare diseases/Novel treatments** *Chairs: Stojka Fustic, North Macedonia; Danijela Radivojevic, Serbia*
08:30 – 08:50	**IL-4. Staettemayer Albert Friedrich, Austria** *Wilson disease*
08:50 – 09:10	**IL-5. Stojka Fustic, North Macedonia** *Cystic fibrosis in the era of highly effective CFTR modulators*
09:10 – 09:30	**IL-6. Ioana Streata, Romania** *Romanian activities within European Reference Networks for Rare Diseases*
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09:40 – 09:50	**OP-2. Milos Brkusanin, Serbia** *Outcome of a Serbian pilot initiative: spinal muscular atrophy newborn screening over a 16-month period*
10:00 – 10:30	CeGaT Satellite symposium ***"Latest advancements in exome diagnostics"***
10:30 – 11:00	**Coffee break / Poster viewing**
Session 3:	**Diagnosing rare diseases using NGS** *Chairs: Borut Peterlin, Slovenia; Emilija Sukarova Stefanovska, North Macedonia*
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11:20 – 11:40	**IL-8. Alexandros Onoufriadis, Greece** *Delineating rare diseases using NGS technologies*
11:40 – 12:00	**IL-9. Ales Maver, Slovenia** *The challenging path to diagnosis in human monogenic disorders - lessons from exome and genome sequencing in over 10,000 individuals*
Selected oral presentations	
12:00 – 12:10	**OP-3. Engin Atli, Turkey** *MtDNA NGS results in mitochondrial disorders of Trakya University*
12:10 – 12:20	**OP-4. Meri Kirijas, North Macedonia** *Diagnostic utility of next-generation sequencing gene panel in the diagnosis of systemic autoinflammatory diseases*
12:30 – 13:00	ELTA 90mm Satellite Symposium **"Advancing cancer care with Comprehensive Genomic Profiling"**

13:00 – 14:00	**Lunch**
14:00 – 14:30	GENESIS BIOPHARMA Satellite Symposium ***"Primary hyperoxaluria type 1: novel siRNA-based treatment options"***
Session 4:	**Cancer genetics** *Chairs: Nadica Matevska-Geskovska, North Macedonia; Ljiljana Sherman, Croatia*
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16:00 – 16:45	AstraZeneca Satellite Symposium ***"Rare genetic diseases - a meeting point between laboratory and clinics"***
16:55 – 17:55	**Parallel poster sessions 1 to 3** **Poster sessions 1.** **Rare Diseases/Population genetics/Genetic technologies (MONITOR 1)** *Moderator: Ales Maver, Slovenia* *Posters PP-1 to PP-13* **Poster sessions 2.** **Rare Diseases /Neurogenetics (MONITOR 2)** *Moderator: Slavica Trajkovska, Italy* *Posters PP-14 to PP-26* **Poster sessions 3.** **Cancer genetics/Other thopics (MONITOR 3)** *Moderator: Rijad Konjhodžić, Bosnia and Herzegovina* *Posters PP-27 to PP-39*
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18:00 – 18:20	**IL-12. Olivera Miljanovic, Monte Negro** *Maternal folate metabolism gene polymorphisms and risk of aneuploidy*
18:20 – 18:40	**IL-13. Merita Xhetani, Albania** *Genetic testing of miscarriages using a QF-PCR and MLPA strategy: 2 years experience from Albania*

Selected oral presentations

18:40 – 18:50	**OP-6. Marija Volk, Slovenia** *PGT in Slovenia: a 20-year experience in a national health system*
18:50 – 19:00	**OP-7. Leyla Ozer, Turkey** *The value of prenatal exome sequencing in cases with abnormal fetal ultrasonographic findings: a report of 25 cases*
19:00 – 19:10	**OP-8. Marija Terzikj, North Macedonia** *The role of the complex CPLANE1c.1819delT;7817T>A allele in early pregnancy loss*

October 07, 2023 (Saturday)

Session 6:	**Neurogenetics** *Chairs: Sena Karachanak, Bulgaria; Elena Sukarova Angelovska, North Macedonia*
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08:50 – 09:10	**IL-15. Sena Karachanak, Bulgaria** *Genetic profile of Alzheimer's disease, frontotemporal and unspecified dementia based on pooled whole exome and whole genome data*

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09:10 – 09:20	**OP-9. Dijana Perovic, Serbia** *Clinical significance of X chromosome copy number variations*
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10:20 – 10:40	**IL-18. Florin Burada, Romania** *Romanian Network of Medical Genetics - Research & Diagnostic Activities*
10:40 – 11:10	**Coffee break / Poster viewing**

Session 8:	**Genetic & Omics Technologies** *Chairs: Ales Macer, Slovenia; Tihomir Todorov, Bulgaria*
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Selected oral presentations

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11:50 – 12:00	**OP-13. Anja Kovanda, Slovenia** *Value of optical genome mapping for diagnostics of rare diseases*
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14:30 – 14:35	**OP/CR-3. Nikola Gjorgjievski, North Macedonia** *Fabry disease "AD ASTRA PER ASPERA"*
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14:45 – 14:50	**OP/CR-6. Levent Simsek, Turkey** *TERF1: a novel candidate gene for dyskeratosis congenita*
14:50 – 14:55	**OP/CR-7. Katerina Kubelka-Sabit, North Macedonia** *Twin monozygotic early normal and complete molar pregnancy*

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POSTER PRESENTATIONS

October 06, 2023 (Friday)

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PP-05. **Hazal Sezginer Guler, et al., Turkey**
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October 06, 2023 (Friday)

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October 06, 2023 (Friday)

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October 07, 2023 (Saturday)

12:40 – 13:40 **Poster sessions 4. Rare Diseases (MONITOR 1)**
Moderator: Aleksandra Janchevska, North Macedonia
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PP-51. **Ardiana Beqiri-Jashari, et al., North Macedonia**
Dark Urine Key to Early Diagnosis of Alkaptonuria: A Case Report

PP-52. **Elena Mitreska, et al., North Macedonia**
Prenatal Kidney Hyperechogenicity: A Clue to an Early Diagnosis of Bardet-Biedl Syndrome

October 07, 2023 (Saturday)

12:40 – 13:40 **Poster sessions 5. Reproductive genetics (MONITOR 2)**
Moderator: Savina Hadzydekova, Bulgaria
Posters PP-53 to PP-64

PP-53. **Hakan Gürkan, et al., Turkey**
Investigation of the Relationship of NLRP2, NLRP7 and KHDC3L Gene Variations in Patients with Recurrent Pregnancy Loss History

PP-54. **Marija Mijovic, et al., Serbia**
Prenatal Diagnosis of Skeletal Dysplasia – Review of the Literature and Experiences of the Clinical Genetics Service from Belgrade

PP-55. **Ana-Marija Bosilkovska, et al., North Macedonia**
Case Report: Male Patient with Balanced Reciprocal Translocation 46, XY,t(1;8)(p32~34;p21)

PP-56. **Simona Bardakoska, et al., North Macedonia**
Robertsonian Translocations and Infertility

PP-57. **Anđela Stanković, et al., Serbia**
Expanding phenotipic Spectrum of MPDZ gene mutations

PP-58. **Stefan Matiket, et al., North Macedonia**
Robertsonian Translocation 45, XY,der(13;15)(q10;q10) in an Azoospermic Patient

PP-59. **Naser Durmishi, et al., North Macedonia**
Cryopreservation of Human embryos and Neurodevelopmental disorders

PP-60. **Mila Sleptsova, et al., Bulgaria**
Whole Exome Sequencing in Prenatal Diagnostics – Advantages and Disadvantages

PP-61. **Melda Erdoğdu, et al., Turkey**
Preliminary Study Results of Families' with Fetal Ultrasound Abnormalities Approaches to Invasive Diagnosis and Outcomes in Pregnancies

PP-62. **Sretenka Vidić, et al., Serbia**
A Case Report on Maternal Translocation t(X;21) (q13; p12) and Its Inheritance

PP-63. **Gorjan Milanovski, et al., North Macedonia**
Linking KIR and HLA Polymorphisms to Reproductive Challenges in Macedonian Couples

PP-64. **Gjorgji Bozhinovski, et al., North Macedonia**
Whole-Exome Sequencing on Products of Conception from Early Pregnancy Losses Reveals a High Frequency of Various Monogenic Disorders

October 07, 2023 (Saturday)

12:40 – 13:40 **Poster sessions 6. Personalized medicine/Pharmacogenomics/ Immunogenetics/Other topics (MONITOR 3)**
Moderator: Meri Kirijas, North Macedonia
Posters PP-65 to PP-76

PP-65. **Ivan Barbov, et al., North Macedonia**
Pregnancy Course and Delivery in Woman with Spinal Muscular Atrophy Type II: A Case Report

PP-66. **Milena Jankovic, et al., Serbia**
CYP2C9 Screening: Important Step in Siponimod Treatment of Secondary Progressive Multiple Sclerosis

PP-67. **Hristina Dicevska, et al., North Macedonia**
Possible association between 3p21.31 (rs11385942) and 9q34.2 (rs657152) and the severity of COVID-19 disease in patients from N. Macedonia

PP-68. **Megi Micevska, Maja Popova, North Macedonia**
Correlation Between the Most Prevalent HPV Types and Cytological Findings in Macedonian Women

PP-69. **Mirko Spiroski, et al., North Macedonia**
Killer Cell Immunoglobulin-Like Receptors in SFS – Marrow Donor Registry (MK-SFSMDR): Feasibility in Identifying Better Donors

PP-70. **Shqipe Spahiu-Konjusha, Kosovo**
Hyper IgM Syndrome- Case Report

PP-71. **Lada Živković, et al., Serbia**
Evaluation of Antioxidant Potention of Biochaga invitro

PP-72. **Ela Zaimi, et al., Albania**
A Case of Chimerism in a Paternity Study

PP-73. **Renata Jankova, et al., North Macedonia**
Use of Y Chromosome Demographic Characteristic in Tracing Balkan Population Origins

PP-74. **Mehmet Berkay Akcan, et al., Turkey**
Evaluation of Genetic Variants Related to Congenital Monosaccharide and Disaccharide Metabolism Disorders from Data Obtained by Whole Exome Sequencing, and Determination of Carrier Ratios in Çanakkale

PP-75. **Zimere Saiti Musliji, et al., North Macedonia**
Association of the FABP2 Ala54Thr Polymorphism with Obesity in Young North Macedonians

PP-76. **Kristina Stamatovska, et al., North Macedonia**
VDR Gene Polymorphisms – First Experience of Our Laboratory

WORKSHOPS/SYMPOSIA

October 05, 2023 (Thursday)

12:30 – 14:30 PharmGenHUB Pre-congress Workshop
Pharmacogenomics

Pharmacogenomics (PGX) aims to individualize therapy upon patients' unique DNA profiles. IMGGE is a PGX pioneer in the Western Balkans (WB). Through the PharmGenHUB project, IMGGE will become WB's central place for PGX diagnostics and R&I, education and training, and translation of PGX knowledge into clinically applicable digital solutions. The workshop will present high-throughput DNA sequencing methodology and bioinformatic analyses used in Project realization.

12:30 – 12:50 ***Population pharmacogenomics***
Branka Zukić, PhD, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia

12:50 – 13:00 ***PharmGenHUB in Western Balkan Project***
Branka Zukić, PhD, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

13:00 – 13:30 ***25 Years of Pharmacogenetics in N. Macedonia: from research to implementation***
Acad. Prof. Aleksandar Dimovski, MD, PhD, Research Center for Genetic Engineering and Biotechnology "Georgi D. Efremov"; Faculty of Pharmacy, University "SS Cyril and Methodius" in Skopje, North Macedonia

13:30 – 13:45 ***Next Generation Sequencing (NGS) Technology***
Branka Zukić, PhD, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

13:45 – 14:00 ***Bioinformatic preprocessing of NGS data: from raw data to genetic variants***
Nikola Kotur, PhD, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

14:00 – 14:15 ***Bioinformatics resources in pharmacogenomics research***
Nikola Kotur, PhD, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

14:15 – 14:30 ***Interpretation of NGS Results: analysis of pharmacogenomics variants***
Vladimir Gašić, PhD, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Serbia

October 05, 2023 (Thursday)

17:30 – 18:00 ELTA 90mm Satellite Symposium
"Introduction to VeriSeq NIPT v2 solution"

Detecting chromosome aberrations beyond trisomies 21, 18, and 13 using genome-wide NIPT – introduction to VeriSeq NIPT v2 solution
Agnieszka Grybos-Gajniak, Illumina

NGS based NIPT provides reliable screening results for fetal chromosomal aneuploidies as early as 10 weeks gestation—from a single tube of maternal blood. This talk will provide introduction to VeriSeq NIPT Solution v2 which takes advantage of powerful Illumina NGS technology to bring a whole-genome sequencing (WGS) approach to NIPT, expanding test menu options to include common aneuploidies (chromosomes 21, 18, and 13), rare autosomal aneuploidies (RAAs), select sex chromosome aneuploidies (SCAs), and partial duplications and deletions ≥ 7 Mb for all autosomes.

October 05, 2023 (Thursday)

19:20 – 19:50 Pfizer Satellite Symposium
"Genetic aspects of hereditary transthyretin amyloidosis"

Hereditary transthyretin amyloidosis (hATTR) is an adult-onset rare disorder characterized by the accumulation of misfolded amyloid fibrils. It most commonly affects the heart and/or the nerves, though other organs may also be affected. hATTR occurs due to pathogenic missense variants in the TTR gene. The prevalence and disease presentation varies in different regions in the world, with a high concentration of distinct variants in endemic regions. The tremendous advancement in therapeutic options in the last several years makes early and prompt diagnosis of hATTR more important than ever.

19:20 – 19:30 ***Introduction***
Dijana Plaseska-Karanfilska, Macedonian Academy of Sciences and Arts, Research Centre for Genetic Engineering and Biotechnology "Georgi D. Efremov", Skopje, North Macedonia

19:30 – 19:50 ***The genetics of hereditary transthyretin amyloidosis in Bulgaria***
Zornitsa Pavlova, IMDL Genome Center Bulgaria, GMDL Genica, Sofia, Bulgaria

October 06, 2023 (Friday)

10:00 – 10:30 CEGAT Satellite symposium
"Latest advancements in exome diagnostics"
Dr. Dirk Biskup, CeGaT GmbH, Germany

The talk concentrates on the different aspects to obtain the best medical results from exome sequencing and diagnostics. Dr. Dirk Biskup will discuss in depth laboratory aspects such as exome enrichment & sequencing, bioinformatical subtleties, data analysis and medical reporting. Only if all these aspects are optimized and go hand-in-hand, the best diagnostical yield can be obtained.

October 06, 2023 (Friday)

12:30 – 13:00 ELTA 90mm Satellite Symposium
"Advancing cancer care with Comprehensive Genomic Profiling"
Agnieszka Grybos-Gajniak, Illumina

Large-cohort studies show that Comprehensive Genomic Profiling maximizes the ability of pathology labs to identify relevant genetic alterations in cancer samples. A single, comprehensive assay to assess a wide range of biomarkers uses less samples and returns results more quickly compared to multiple, iterative tests. This presentation will discuss the importance of CGP and incorporating genomic signatures in clinical care to improve outcomes.

October 06, 2023 (Friday)

14:00 – 14:30 GENESYS BIOPHARMA Satellite Symposium
"Primary hyperoxaluria type 1: novel siRNA-based treatment options"
Moderator: Velibor Tasic

Pathophysiology and differential diagnosis of PH1
Prof. Velibor Tasic, North Macedonia

Treatment options of PH1 with siRNA gene silencing pathways
Dr. Dimitris Gkikas, Greece

October 06, 2023 (Friday)

16:00 – 16:45 AstraZeneca Satellite Symposium
"Rare genetic diseases - a meeting point between laboratory and clinics"

The symposium "Rare genetic diseases - a meeting point between laboratory and clinics" will provide a vital intersection for experts from both the laboratory and clinical fields to converge and discuss rare genetic diseases such as Neurofibromatosis type 1 (NF1), Lysosomal Acid Lipase Deficiency (LAL D), and Hypophosphatasia (HPP). This symposium will facilitate in-depth conversations on these conditions, emphasizing the crucial collaboration between laboratory diagnostics and clinical practices in understanding, diagnosing, and managing these complex genetic diseases. Attendees can anticipate gaining comprehensive insights into the genetic foundations of these disorders and the pivotal role of laboratory-clinical partnerships in improving patient care and treatment outcomes.

16:00 - 16:15 ***Hypophosphatasia: A Genetic Perspective on Alkaline Phosphatase Deficiency***
Professor Dr. Goran Cuturilo, Serbia

Attendees will explore the genetic causes behind this rare disorder, shedding light on the mutations responsible for diminished alkaline phosphatase activity. This informative session goes on to dissect the molecular consequences of these genetic aberrations, elucidating how they manifest in the clinical picture of HPP. Additionally, the lecture provides valuable insights into the diagnosis of this complex genetic disorder, offering a holistic understanding of its genetic, molecular, and clinical aspects.

16:15 - 16:30 ***Neurofibromatosis type 1: Clinical Manifestations and Therapeutic Approaches***
Professor Dr. Ivana Kavecan, Serbia

Attendees will gain a comprehensive understanding of this genetic disorder. The presentation will delve into the clinical manifestations of Neurofibromatosis Type 1, shedding light on its diverse array of symptoms and associated complications. Furthermore, the audience will be informed about the latest therapeutic approaches and strategies aimed at managing this complex condition, providing valuable insights into both the clinical challenges and potential treatment options for individuals affected by Neurofibromatosis Type 1.

16:30 - 16:45 ***Collaboration of Laboratory Diagnostics and Clinical Genetics in the Context of Pediatric Rare Metabolic Diseases***
Professor Dr. Ksenija Fumic, Croatia

Attendees will be immersed in the essential synergy between laboratory diagnostics and clinical genetics. This talk elucidates how these two critical domains intersect to address the unique challenges posed by rare metabolic diseases in pediatric patients. Participants will gain insight into the collaborative efforts required to effectively diagnose, ultimately highlighting the vital role played by this interdisciplinary collaboration in improving patient care and outcomes.

October 07, 2023 (Saturday)

12:10 – 12:40 BioMarin Symposium
"New treatments for non-metabolic bone dysplasia"
Professor Dr. Zoran Gucev, North Macedonia

The era of precision, personalized medicine, often based on novel molecular mechanisms resulted in novel treatments in several bone dysplasia. Indeed, the novel therapies of fibroplasia ossificans progressive, PIK3CA spectrum disorders and achondroplasia are based on the very foundations of those diseases.

Invited Lecturers
CVs and Abstracts

PL-01

Han Brunner
Radboud University Medical Center,
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Han Brunner is Head of the Institute of Human Genetics at Nijmegen and Maastricht Medical Centers, where he pioneers genomic technologies in medical genetics. Han believes that rapid implementation of genomic technologies in Medicine is advantageous for patients, and families, and can make the care for people with rare diseases more effective.

His scientific work has shown that new mutations are the main cause of intellectual disability, which led to the acceptance of exome sequencing as a first-tier test in neurodevelopmental disorders. Recently, his group established the landscape of autosomal recessive diseases in European populations.

Title / Abstract:
WHY WE HAVE THE DISORDERS WE HAVE

Most intellectual disability is due to new mutations. New mutations occur at any position in the genome and in any gene. However, large genes present a larger mutational target and this explains why ARID1B (Coffin-Siris) and ANKRD11 (KBG syndrome) are very common. The rate of mutation increases with the age of the father.

Some mutations are positively selected in the testis and for this reason occur more commonly than would be expected. This includes PTPN11 (Noonan syndrome) and FGFR3 (achondroplasia).

The landscape of recessive diseases is quite similar in the Dutch, British, and Estonians. However, the variants in these disease genes are largely different.

This suggests that we lose pathogenic variants because carriers are at a (very small) reproductive disadvantage.

This we found in a recent study that heterozygous carriers of an autosomal recessive variant are more likely to be childless, less likely to not have higher education, and more likely to have no education. Apparently, these people have slightly more difficulty finding a partner.

This means that sexual selection shapes the recessive disease landscape in our populations. The practical outcome is, that the rate of autosomal recessive intellectual disability is very low in coupes that are not consanguineous (2% of patients), but very high in offspring of first cousins (50% of ID patients).

PL-02

Detlef Bockenhauer
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Detlef Bockenhauer is a Professor of Paediatric Nephrology at the Katholic University Leuven and head of paediatric nephrology at the University Hospital Leuven. He previously was a Professor at the UCL Department of Renal Medicine and Honorary Consultant Nephrologist and Clinical lead for the Renal Unit at Great Ormond Street Hospital for Children NHS Foundation Trust. He has studied Medicine in Germany and trained in Paediatrics and Nephrology in Hamburg, Germany, as well as at New York University and Yale University, USA. He has a special interest in tubulopathies and other genetic renal diseases and has led or contributed to the identification of numerous Mendelian disorders and disease genes. He has studied typical clinical features, as well as long-term outcome data for rare inherited renal diseases. He currently leads the European registry for dRTA at the European Rare Kidney Disease Network (ERKnet)

Title / Abstract:
DIAGNOSIS OF UNCERTAIN SIGNIFICANCE:
THE CHALLENGE OF GENETIC VARIANT INTERPRETATION

Genetics is increasingly becoming part of routine clinical diagnostics. Yet, the interpretation of genetic testing results can be challenging and requires a solid understanding of variant interpretation and close collaboration between clinician and genetic scientist. In this lecture, I will present clinical cases, their genetic testing results and their interpretation in the clinical context.

PL-03

Borut Peterlin
Clinical Institute of Genomic Medicine,
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Borut Peterlin is a clinical geneticist and neurologist, head of the Clinical Institute of Genomic Medicine, University Medical Center Ljubljana. He is a professor of Human Genetics at the Medical faculty in Ljubljana and visiting professor at the Medical faculties in Beograd, Rijeka and Osijek. He is vice-president of the European Society of Human Genetics and Chair of the Professional Committee of the Slovenian Association for Medical Genetics. His research interests are discovering new genes and mechanisms of human disorders and implementing novel genomic technologies in rare diseases, public health and personalized medicine in health systems.

Title presentation:
FROM RARE DISEASES TO PUBLIC HEALTH GENOMICS:
A HEALTH SYSTEM PERSPECTIVE

IL-01

Svetlana Madjunkova
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Dr Svetlana Madjunkova MD, MSc, PhD is Senior Director and Head of Reproductive Genetics Department at CReATe Fertility Centre Toronto, Canada and adjunct faculty with the Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, at University of Toronto. Dr Madjunkova is a Board Director of the Canadian Fertility and Andrology Society and a Board Director of the Preimplantation Genetic Diagnosis International Society and Chief Operating Officer of Reprobiogen. She has established high complexity lab to provide advanced clinical preimplantation testing; fertility related genetic testing and translational research in reproductive biology aimed at improving embryo selection, preimplantation testing and further research in reproductive failure and improving outcomes in ART.

Title / Abstract:

THE ART OF ART: PREIMPLANTATION GENETIC TESTING AS A TREATMENT OF GENETIC CONDITIONS

Societal awareness of genetic testing, expanded use of carrier screening, genetic diagnostic tests, and higher utilization of in vitro fertilization (IVF) have increased demand for preimplantation genetic testing for monogenetic disorders (PGT-M). PGT-M is a therapeutic alternative to invasive prenatal tests; not only for common severe childhood disorders, but for serious and mild late onset disorders, including for cancer predisposition, *de novo* and variants of unknown significance (VUS), variants in multiple genes and HLA matching for siblings.

This brings to light ethical dilemmas and necessitates adjustment of generic genome wide approaches to complement or eventually replace targeted disease-specific PGT-M assays and add the preimplantation aneuploidy testing (PGT-A) as a first-tier test.

Utilizing non-targeted genome wide tests to obtain molecular karyotype and haplotype and personalized variant detection can offer actionable management of heritable disorders in couples at risk. Simultaneous PGT-A and PGT-M with optional direct variant testing provides optimal patient management that can optimize prioritization of embryos for transfer and significantly reduce the time to healthy pregnancy in couples at risk for inherited disorders.

The talk will summarize the current state of the art preimplantation genetic testing and will discuss the new and upcoming advanced diagnostic and treatment options for genetic disorders through PGT and assisted reproductive technologies.

IL-02

Syrrou Maria
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B.Sc. in Biology (Aristotle University of Thessaloniki) and PhD in Medical Genetics, National and Kapodistrian University of Athens, Greece.

Current position: Professor Gen. Biology/Medical Genetics, Lab. of General Biology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Greece.

My scientific and research interests are in the field of Medical Genetics (cytogenetics and molecular genetics, chromosomal abnormalities and genetic syndromes diagnosis, genetic variants associated with disease susceptibility). My current research focus on interactions of individual genetic and epigenetic profiles related to pathological phenotypes and especially on stress related endophenotypes.

Title / Abstract:

GENETIC AND EPIGENETIC SIGNATURES IN LOW BIRTH WEIGHT NEONATES AND FUTURE HEALTH RISKS

Christos-Orestis Tsiantis[1], Daniela Theodoridou[1], Aggeliki-Maria Vlaikou[2], Michaela.D. Filiou[3], **Maria Syrrou[1]**

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Background: Low birth weight (LBW) and prematurity are considered indicators of in utero adversities. Exposure to stressors during critical developmental stages can shape developmental programming and affect brain development, increasing the risk for short and long-term physical and mental health issues. Stressful life events during early gestation can activate HPA axis and mediate adult neuroendocrine responses. To correlate adverse birth outcomes, with genetic and epigenetic factors and to find reliable stress markers, we have studied variants of genes associated with stress response, immune response and prematurity, mitochondrial DNA copy number, and methylation status of 18 CpG sites in the promoter region of FKBP5.

Materials and methods: Participants: 53 preterm/LBW neonates and 30 full term neonates (control group). MBL2 and FKBP5 variants were genotyped. In selected samples, methylation levels were assessed. Blood mtDNAcn was evaluated.

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[3] Biomedical Research Institute, Foundation for Research and Technology-Hellas (FORTH) and Laboratory of Biochemistry, Department of Biological Applications and Technology, School of Health Sciences, University of Ioannina, Greece

Results: Variant rs1800451 (MBL2) was more frequent in preterm/LBW neonates, CpG3 and CpG8 (FKBP5) methylation levels were higher in preterm/LBW group and mtDNAcn was higher in preterm/LBW neonates compared to full term neonates.

Conclusions: Given that there is an association between birth weight and adult health, it is important to find stress-related reliable markers. This ongoing study indicates that the interactions of genetic and environmental (epigenetic) triggers might provide a marker system for risk assessment for LBW and preterm birth.

Acknowledgments: The project is co-financed by Greece and the European Union - European Regional Development Fund (ERDF) under the Operational Program "Competitiveness Entrepreneurship Innovation"; (EPAnEK), NSRF 2014-2020 (MIS 5047236)

Keywords: Low birth weight, prematurity critical developmental stages stress genetic epigenetic

Topic: Personalized medicine and Pharmacogenomics

IL-03

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Prof. Hadjidekova is Head of the Department of Medical Genetics at Medical University of Sofia. She is a genetic consultant and Head of the Genetics Laboratory at Nadezhda Hospital. Prof. Hadjidekova has over 100 original publications with more than 150 citations in the scientific databases Scopus and Web of Science. Her professional competences and skills are in the fields of medical genetic counselling, genetics of reproduction and infertility, oncogenetics, intellectual disability, congenital anomalies and in diagnostic analyses such as karyotyping, genomic analyses, prenatal diagnosis, preimplantation genetic tests, etc.

Title / Abstract:
IT'S TIME FOR EXTENSIVE REPRODUCTIVE CARRIER SCREENING

Genetic diseases individually are rare, but together they are a serious problem and affect 1-2 out of 100 individuals. All humans are known to carry at least 6-8 recessive pathogenic mutations and it has been found that about 5% of couples have mutations in identical gene. There are currently more than 10 000 known recessive diseases and only a few hundred have any treatment developed.

A highly successful strategy to prevent the birth of children with severe genetic diseases is the reproductive heterozygote screening for carriers of genetic diseases. It involves testing of the reproductive partners for autosomal recessive or X-linked genetic disease and identifying partners at risk of transmitting a monogenic disease to offspring. Subsequently, the couple is offered a prevention method (prenatal diagnosis, preimplantation test for the specific disease, etc.).

Several large studies have shown that extensive reproductive screening offered to all couples excels the previous ethnicity-based screening strategy and is much more effective in identifying at-risk couples.

The American College of Medical Genetics recently published a Practice Guide for Preconception and Prenatal Screening, distinguishing four levels of screening by recommending level 3 screening to be offered to all pregnant patients or those planning a pregnancy, regardless of their ethnicity. Level 3 screening covers a panel of 113 diseases.

Ensuring an equitable carrier screening programme that is accessible to all, as well as providing funding for additional reproductive interventions and support in the event of a positive outcome, is critical to successful implementation of effective prevention.

IL-04

Stättermayer Albert Friedrich

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since 04/2022	Responsible medical director of the molecular genetic laboratory of the Division of Gastroenterology and Hepatology
since 04/2021	Program director of the outpatient clinic for "autoimmune liver diseases" and "hereditary liver diseases" at the Medical University of Vienna
06/2017-06/2019	Sub-specialization in „Intensive Care Medicine"
06/2015-06/2017	Sub-specialization in „Gastroenterology and Hepatology"
17.06.2015	Board certification of the Austrian Medical Chamber (ÖÄK) in Internal Medicine
02/2009-06/2015	Training in Internal Medicine at the Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology
16.10.2008	Graduation in Medicine (MD), Medical University of Vienna

Title / Abstract:

SYNONYMOUS AND NON-CODING ADENOSINE TRIPHOSPHATASE COPPER-TRANSPORTING BETA (ATP7B) VARIANTS OF POTENTIAL DISEASE RELEVANCE IN PATIENTS WITH CLINICAL DIAGNOSIS OF WILSON DISEASE

Background: Wilson disease (WD) is an autosomal-recessive disorder of copper-metabolism resulting in copper accumulation in liver, the central nervous system and other tissues. Its underlying genetic defect resides on chromosome 13 in ATP7B, which encodes for adenosine triphosphatase copper-transporting beta, a copper-binding P-type ATPase that enables copper transport from the cytosol into the endoplasmic reticulum. Diagnosis is based on clinical, laboratory and histologic findings. Genetic testing confirms diagnosis but continues to present a number of difficulties; in large cohorts biallelic pathogenic variants are found in only 80-88%. There is growing evidence that synonymous and intronic variants may affect protein structure by alternative splicing. Aim of the study was to evaluate the presence of disease-causing variants by next generation sequencing (NGS) in WD patients with only one known pathogenic variant.

Methods: patients with established WD diagnosis and only one or no pathogenic variant in *ATP7B* from a large Austrian cohort were included. All patients were analysed by NGS.

Results: Thirty-two patients (f/m: 20/12, mean age at diagnosis: 24.4±11.7 years) were included in the study. NGS identified additional variants in 25 patients: 3 different synonymous (p.Leu709Leu, p.Tyr715Tyr, p.Phe764Phe), and 6 different intronic variants (c.1543+5G>A, c.1708-34G>A, c.1870-49A>G, c.2122-5T>G, c.2866-1521G>A, c.3700-3T>G) could be identified, of which 4 were not yet reported. Additionally, one large CNV was found in one patient.

Conclusion: Synonymous or intronic variants in ATP7B may cause WD by alternative splicing. Modern genetic testing approaches should be extended to patients with clinically established diagnosis of WD and their first-degree relatives.

IL-05

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Prof. Dr. Stojka Fushtikj is Head of department for Cystic Fibrosis (CF) and Medical director of the University Children's Hospital, Skopje. She is a Chair of Pediatric Cystic Fibrosis Group of the European Respiratory Society and national coordinator and member of Steering committee of European Cystic Fibrosis Society Patient Registry. CF is the area of her professional medical and scientific interest for more than 25 years with the sole purpose: to improve the quality and life expectancy of people with CF in North Macedonia and in the region. Her achievements include introducing the European standards of care for patients with CF, modern techniques of respiratory physiotherapy, introduction of neonatal screening for CF, introduction of the latest therapy with CFTR modulators in patients with CF in North Macedonia. Her working portfolio includes extensive volume of research work presented and published in the country and abroad.

Title / Abstract:
CYSTIC FIBROSIS IN THE ERA OF HIGHLY EFFECTIVE CFTR MODULATORS

Cystic fibrosis (CF) is the most common life-limiting inherited condition in Caucasians. It is a multisystem autosomal recessive disorder caused by pathogenic variants in each of the 2 CFTR genes on the long arm of chromosome 7 (locus 7q.31). CFTR protein is a cell-surface localized chloride channel and dysfunctional transport of chloride and other ions (such as sodium and bicarbonate) in CF leads to generation of thick, viscous mucus in the affected organs, including the lungs, pancreas, liver, intestine, sweat gland and reproductive tract. Respiratory disorder is the major cause of morbidity and premature death of CF individuals.

Since the identification of the gene for CF in 1989, more than 2100 CFTR gene variants have been reported to CF Mutation Database, being 719 confirmed as disease causing (https://cftr2.org/). However, one single mutation, the deletion of a phenylalanine at position 508 (F508del) located in NBD1, is found in about 70% of CF chromosomes and in at least one allele of 80–85% of individuals with CF worldwide. CFTR mutations have been grouped into functional classes, characterized by: (I) no production of full-length protein, (II) defective folding and trafficking, (III) defective gating, (IV) reduced anion conductance, (V) reduced protein production, (VI) reduced protein stability at the cell surface. This classification has been useful as mutations within the same group are expected to be treated by the same therapeutic strategy and the same drugs.

Treatment for CF have traditionally addressed to control of symptoms and slowing down the progression of the disease. Based on understanding of the functional effect of CFTR variants, two classes of CFTR modulators have been developed: "correctors" (lumacaftor, tezacaftor, elexacaftor) that facilitate processing and trafficking of the protein to the cell surface, and "potentiators" (ivacaftor) that increase the opening ability of the channel once at the apical membrane. For class III or IV variants, a potentiator alone might be enough to significantly improve ion channel function. But for class II variants such as F508del, a combination is required of a corrector(s), to facilitate trafficking of the misfolded protein to the cell membrane, and also a potentiator to

increase the amount of time that the CFTR channel is open, thus improving chloride transport. Four drugs of single or combined CFTR modulators are commercially available: Ivacaftor, Lumacaftor/Ivacaftor, Tezacaftor/Ivacaftor, Elexacaftor/Tezacaftor/Ivacaftor, with the latter triple combination being the most effective. The clinical benefits of these highly effective drugs are seen in improving lung function, nutritional status, health-related quality of life and survival.

IL-06

Ioana Streata
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Dr. Ioana Streata is an Associate Professor of Cell and Molecular Biology at University of Medicine and Pharmacy from Craiova, Romania, and my research is focused on molecular mechanisms involved in rare neurodevelopmental disorders.

She is also medical geneticist at the Regional Centre of Medical Genetics Dolj with main activities and responsibilities related to the evaluation, diagnosis, treatment and genetic counselling in genetic disorders. I am mainly involved in management of rare and complex medical conditions associated with congenital anomalies and intellectual deficiency. Since June 2016 I am part of Ro-NMCA-ID team (Network Multiple Congenital Abnormalities with Intellectual Disability), member of the European Reference Network ITHACA.

Title / Abstract:

ROMANIAN ACTIVITIES WITHIN EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES

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Over 6000 rare diseases (RD) affect at least 4% of each country's population in the EU. Patients with RD are often spread across regions, making it challenging to gather knowledge and expertise. Expertise in RD is limited and fragmented. To address this, the EU established the European Reference Networks (ERN) model, forming networks of specialized healthcare providers across Europe. These networks focus on specific medical domains, especially for complex diseases with low prevalence. The ERNs aim to enhance patient access to high-quality care, ensure equitable treatment, offer virtual expert consultations, facilitate knowledge generation, provide training, and support research. Romania is active involved through its national Expertise Centers in ERNs activities. Currently, our country has Expertise Centers members in 12 of the 24 ERNs.

Ro-NMCA-ID (Romanian Network Multiple Congenital Abnormalities with Intellectual Disability) is member of ERN for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders

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(ERN ITHACA). As ERN ITHACA member, RoNMCA-ID team is actively involved in ILIAD, CPMS, Neurodevelopmental disorders, Clinical guidelines and expert consensus statements and Research workgroups. Ro-NMCA-ID team members are also involved in IRDiRC (International Rare Diseases Research Consortium) Task Force - Framework to assess impacts associated with diagnosis, treatment, support, and community integration.

RO–NMCA ID through CRGM Dolj was designated in 2022 by the Romanian Ministry of Health to represent Romania in Joint Action projects call: EU4HealthProgramme - EU4H –2022 – JA – 05: support ERNs integration to the national healthcare systems of Member States.

IL-07

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Maja Stojiljkovic is a full research professor and head of Rare Disease Research and Therapeutics Development group at the Institute of Molecular Genetics and Genetic Engineering, University of Belgrade in Serbia. Her research is focused on genomics of rare diseases, functional characterization of novel genetic variants and discovery of novel molecular therapeutics for rare diseases. Dr Stojiljkovic is coordinator of ORPHANET-Serbia, secretary of ICORD and member of Expert Committee of National Organization for RDs of Serbia. Dr Stojiljkovic is actively involved in genetic testing of rare diseases in Serbia, bringing new technologies and experimental solutions to routine use.

Title / Abstract:

THE IMPACT OF NEXT-GENERATION SEQUENCING ON DIAGNOSIS AND TREATMENT OF RARE DISEASES

***Maja Stojiljkovic**, Milena Ugrin, Kristel Klaassen, Anita Skakic, Marina Andjelkovic, Jovana Komazec, Vesna Spasovski, Sonja Pavlovic*

Introduction: Rare diseases are heterogeneous group of diseases, with one common characteristics, a prevalence less than 1 in 2000 people. Vast majority of them are monogenic and finding pathogenic genetic variants is needed to set the correct diagnosis, enable adequate treatment and provide genetic counselling to members of affected family. This study is an overview of genomic studies of rare diseases in Serbia.

Methods: More than 1200 patients suspected to have a rare disease have been analyzed using sanger sequencing, clinical-exome sequencing, whole-exome sequencing or whole-genome sequencing in order to find disease-causing or disease-modifying variants. Novel variants were characterized using in silico modelling or in in vitro eukaryotic assays (standard or CRISPR/Cas9 developed).

Results: Disease-causing variants were found in more than 150 different genes associated with a rare disease. The most frequent were thalassemia syndromes (214 patients), followed by phenylketonuria (109 patients), congenital adrenal hyperplasia (>90 patients) and glycogen storage disease Ib (30 patients), while majority of diseases is seen only in a single patient. More than 40 new genetic variants were comprehensively characterized in silico or in vitro. For the first time, candidate modifiers (SHANK gene family) were identified in a group of phenylketonuria patients with an unusual phenotype.

Conclusion: In the genomics era, next-generation sequencing significantly shortens time to diagnosis and allows studying genetic modifiers of monogenic diseases and genotype-phenotype correlation. Furthermore, characterization of novel genetic targets boosts development of precision medicine.

Key words: rare diseases, next-generation sequencing, genomics, precision medicine

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IL-08

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Dr Alexandros Onoufriadis is Associate Professor of Medical Genetics at Aristotle University of Thessaloniki. Previously, he has worked at British academic institutions (King's College London and University College London) for 15 years whereby he gained extensive expertise in gene identification strategies and next-generation sequencing technologies. Following the identification of the major gene for Pustular Psoriasis, he embarked on a successful gene hunting endeavour for various rare diseases including Primary Ciliary Dyskinesia, for which he identified a plethora of new genes. He is also investigating the transcriptome of complex diseases to identify key pathways that may provide new treatment options for patients. For his overall contribution to dermatological research, he received the 2021 Early Career Investigator Award by the British Society for Investigative Dermatology.

Title / Abstract:
DELINEATING RARE DISEASES USING NGS TECHNOLOGIES

Discovering the genetic basis of rare diseases is fundamental to improving diagnostic accuracy and genetic counselling. Over the last 15 years the advent of next-generation sequencing (NGS) technologies has accelerated diagnostic discovery and precision. This presentation examines the application of NGS technologies in combination with various gene identification strategies that have led to the discovery of novel mutations in rare diseases. Moreover, the technology has also allowed for interrogation of clinically challenging cases in which more than one inherited disorder might be present. These genetic data improve diagnostic precision and make feasible accurate prenatal testing and better-targeted translational research.

IL-9

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Aleš Maver, MD, PhD; The principal focus of my work is the field of rare and complex human disease genetics. Principally, I have been involved in the application of high-throughput sequencing approaches for clinical diagnostics and research.

Currently, my work is focused on diagnostics based on exome, genome and RNA sequencing. I am particularly enthusiastic about implementing novel approaches to improve genome-level clinical variant interpretation, create resources of national variation and to increase use of data sharing to facilitate the diagnosis of rare genetic disorders.

Title / Abstract:
THE CHALLENGING PATH TO DIAGNOSIS IN HUMAN MONOGENIC DISORDERS - LESSONS FROM EXOME AND GENOME SEQUENCING IN OVER 10,000 INDIVIDUALS

Diagnostic next-generation sequencing (NGS) has revolutionised the diagnostic evaluation of patients with rare genetic disorders. Although exome and genome sequencing provide a near-complete characterisation of genes involved in monogenic disorders, a notable proportion of patients nevertheless remains undiagnosed after comprehensive genomic testing.

At the Clinical Institute of Genomic Medicine, we introduced exome and genome sequencing in 2013 as the primary diagnostic approach for patients with suspected rare genetic disorders. Since the introduction, our focus has been to maximise the diagnostic reach of NGS-based approaches.

Firstly, we show that the routine use of extended bioinformatic approaches, including copy number detection, mitochondrial variant analysis and homozygosity mapping considerably improves diagnostic rates. We have also introduced repeat expansion analysis, structural variant analysis and retrotransposon detection in our pipelines, which resulted in further diagnostic resolution in several undiagnosed patients. Secondly, we perform consistent reanalysis and re-interpretation of exome sequencing data in undiagnosed patients and systematically participate in match-making efforts to identify novel Mendelian disease genes. We also demonstrate how the development of the national database of pathogenic and population variation in the Slovenian population further streamlined the diagnostic process in patients with suspected monogenic disorders. Finally, we have also introduced whole genome sequencing and RNA sequencing as additional diagnostic modalities for diagnostic resolution in patients without a molecular diagnosis.

Our experience in the past ten years demonstrates the impact of a comprehensive approach to implementation of NGS that includes expanded bioinformatic analysis, data sharing and the introduction of novel technologies in the diagnostic assessment of patients with suspected monogenic disorders.

IL-10

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Mehmet Ali Ergun, MD, PhD, received his Doctor of Medicine degree from Gazi University Faculty of Medicine in 1995. Then, he completed his Medical Genetics Specialization in 1999 and completed his Doctorate in Medical Biology and Genetics in 2005. He has been working at Gazi University Faculty of Medicine since 2000 and has been working as a Professor in the Department of Medical Genetics since 2012. As a routine; he works in the fields of cytogenetics and molecular genetics, as well as research in the field of Bioinformatics. Apart from the Faculty of Medicine, he teaches graduate courses at Gazi University Informatics Institute, Department of Health Informatics. He has been on the board of directors of the Medical Genetics Association since 2017.

Title /Abstract:
THE ROLE OF NEXT GENERATION SEQUENCING ANALYSIS (NGS) TESTS IN BREAST CANCER

Although Sanger sequencing method is considered to be the gold standard, if there are many genes or panels to be analyzed, it becomes very costly and time consuming. So, Next generation sequencing (NGS), provides information about a larger DNA region in a shorter time with respect to Sanger sequence analysis. However, variants in non-coding regions in DNA, large deletions, duplications, rearrangements, nucleotide repeats or epigenetic changes cannot be identified with this method. By using NGS, Homologous Recombination repair genes can be easily analyzed such as: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, MSH2, MLH1, MSH6, PMS2, EPCAM, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53* genes. The results have to be based on ACMG criteria whereas, variant reclassification is advised.

IL-11

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Professor Ljiljana Šerman, MD, PhD, integrative psychotherapist, is a Vice-President of the Clinical Genetic Society of Croatia and the Head of the Department of Medical Biology at the University of Zagreb School of Medicine. She published 57 scientific papers, 35 professional papers and was a co-author of Croatian guidelines for genetic counselling and testing for hereditary breast and ovarian cancer. Her scientific focus is the genetics and epigenetics of the Wnt and Hedgehog signalling pathways in serous ovarian carcinoma. Since 2014 she has been participating as an integrative psychotherapist in psychotherapy, psychological and genetic counselling in the non-governmental medical support organization "Everything for Her" and since 2021 she has been leading the Genetic Corner for oncology patients.

Title / Abstract:
CANCER GENETIC COUNSELLING - A PSYCHOTHERAPIST'S APPROACH

Background: The demand of genetic counselling is to be a responsible process of high quality, that is also comparable, to a certain degree, to psychotherapy. It is clear that every person who needs genetic counselling is not in the psychotherapeutic process, but appreciating the significance and impact of emotions on cognitive processes would contribute to the effectiveness of genetic counselling.

Methods: Using the psychotherapeutic approach, we will describe how it can be of help in: 1. Making a decision whether to get genetic test or not? 2. Making a decision about what to do when we get a positive result of a pathogenic variation (PV)/mutation associated with hereditary cancer.

Results: The results will be presented through a series of case presentations, and these are just some examples for each of the topics:

1. A 35-year-old patient decided to undergo genetic testing after discussion with the surgeon at a hospital; however, two days before the appointment she was not sure whether she should be tested or not. The psychotherapeutic approach allowed her to make a decision with which she was satisfied.

2. A 27 -year-old woman with triple-negative breast cancer was informed by an oncologist during chemotherapy that she was a carrier of the BRCA1 gene mutation. Although the oncologist gave her thorough information, she was not sure whether to undergo a bilateral mastectomy immediately or to first operate the affected breast and then remove the healthy one. After psychotherapy, she decided to undergo bilateral mastectomy, and was satisfied with her decision both before and after the procedure.

Conclusion: Although genetic counselling is not psychotherapy, experience has shown us that knowing the skills common to both genetic counselling and psychotherapy can help patients and their family members to make the best decision for themselves, allowing for the whole process to take place in an emotionally supportive setting.

IL-12

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She founded the Centre for Medical Genetics and Immunology at the Clinical Centre of Montenegro, which she has been leading since 2000. Prof. dr Olivera Miljanović is a member of the Committee for Medical Research of Montenegro Academy of Science and art since 1998, the UNESCO International Bioethics Teachers' Forum (ITF) since 2014, the Committee for Bioethics of the Council of Europe (CDBIO) since 2013 and the President of the Committee for Medical Ethics and Bioethics at the Medical Faculty of the University of Montenegro since 2017. Her research and publications are in the fields of human genomics, pediatrics and bioethics.

Title / Abstract:
MATERNAL FOLATE METABOLISM GENE POLYMORPHISMS AND RISK OF ANEUPLOIDY

Backgorund: Recent research on chromosomal non-disjunction opens a new perception of aneuploidy as a metabolic disorder caused by DNA hypomethylation. Maternal folate metabolism gene polymorphisms can lead to DNA hypomethylation, which epigenetically increases the risk of improper oocyte maturation, DNA breakage and meiotic chromosome malsegregation. Two maternal methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms (677C>T and 1298A>C) have been shown to reduce the activity of this pivotal enzyme in folate metabolism, suggesting a direct correlation between pericentromeric DNA hypomethylation and these polymorphisms and that MTHFR is one of the few known human genes with the ability to modulate chromosomal aneuploidy rates. Research on this topic become of increasing interest worldwide, but the presented results are conflicting and with large variations among populations. The results of the first study on this topic in Montenegrin population, and one of several in the Mediterranean region are presented.

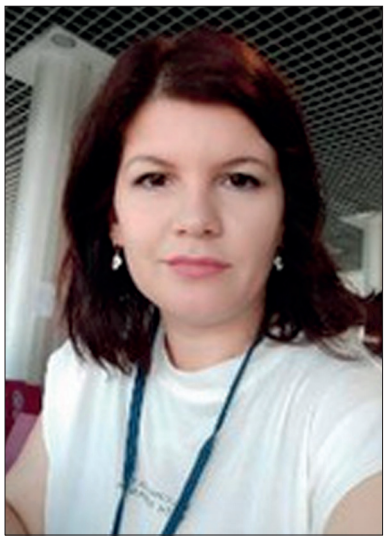
Materials and methods: The presence of MTHFR gene polymorphisms 677C>T and 1298A>C was investigated in total of 318 women: 163 women with offspring aneuploidy and 155 women with healthy children. Five genetic models were used to assess risk of offspring aneuploidy.

Results: An increased risk of aneuploidy was demonstrated in the presence of maternal MTHFR 677C>T polymorphism under a recessive (OR 3.499), homozygote (OR 3.456) and allele contrast model (OR 1.574). The more prominent association was found with sex chromosome aneuploidies and trisomy 13/18, and also in women ≤35 years at conception. No association was observed between 1298A>C polymorphism and risk of offspring aneuploidy, although synergistic effect of two polymorphisms increase the risk of aneuploidy, primarily amplifying the 677T allele effects.

Conclusions: Maternal MTHFR 677C>T gene polymorphism, alone or in combination with another 1298A>C polymorphism, appears to be a substantial risk factor for offspring aneuploidy in Montenegro population, especially for sex chromosome aneuploidies and trisomy 13/18, and among younger women.

Key words: folate metabolism, MTHFR gene polymorphisms, DNK hypomethylation, aneuploidies

IL-13



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Dr. Merita Xhetani is Associate Professor, member of Department of Biology, and Head of the Center of Molecular Diagnostics and Genetic Research, University Hospital Obstetrics and Gynecology "Queen Geraldine", in Tirana, Albania.

Her lab's research is primarily the study of hematopoietic disorders, with a focus on the regulation of erythropoiesis, on disease model development and in particular on gene therapy of β-thalassemia. Recently Merita's work is focused on applying genome editing tools for genetic engineering of blood cells and contributions to the field involve applying precise gene editing to monogenic blood disorders. She attended many training courses in molecular genetics in different European countries and recently completed her postdoctoral studies in Functional Genomics at LFKRI, Research Institute, New York Blood Center, NY, USA, supported by the Fulbright research program. She is also chair of the Albanian Society of Human Molecular Genetics.

Title / Abstract:

GENETIC TESTING OF MISCARRIAGES USING A QF-PCR AND MLPA STRATEGY: 2 YEARS EXPERIENCE FROM ALBANIA

Merita Xhetani[1], Eliona Demaliaj[2]

Background: Genetic analysis of product of conceptions (POC) has the benefit providing the patient with a reason for the pregnancy loss and may help to determine whether further investigations or treatments are required. This may be of interest in the evaluation of patients with recurrent pregnancy loss (RPL). Since the standard karyotyping tests need cell culture of the spontaneous aborted fetus material, we have implemented molecular techniques using a QF-PCR and MLPA tests to avoid the need for cell culture as a long and controversial technique for the accuracy of the diagnosis.

Methods: In this study, 34 patients with pregnancy loss more than 2 times were included, and the genome of the embryonic/fetal tissue was analysed. Depending on the week of spontaneous abort, the protocol was designed, and the QF-PCR assay for chromosomes 13, 15, 16, 18, 21, 22, X and Y and MLPA hybridization probes (P095 and P036) were combined.

Results: In QF-PCR reactions, chromosomal abnormalities were found in 52.9% of cases; respectively trisomies with 38.2%, X-monosomies 11.7%, and triploidies—2.9%. In the MLPA tests, a total of 61.1%

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samples were found with a chromosomal abnormalities, respectively with trisomies, X-monosomies and deletions/duplication in subtelomeric regions in genomic DNA isolated from POC. Maternal cell contamination remains a problematic issue.

Conclusions: Combining molecular methods QF-PCR and MLPA has revealed most genetic factors in recurrent pregnancy loss. Only couples with identified structural chromosomal abnormalities in POC have been recommended for paternal karyotype. Those techniques are robust and relatively fast, but still expensive while determining the genetic cause of pregnancy loss is a consolation for the couple and a psychological relief.

Keywords: miscarriages, karyotype, chromosome analysis, MLPA, QF-PCR.

IL-14

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Dr Slavica Trajkova MD, PhD, is a postdoctoral researcher at the Department of Medical Genetics at University of Turin, Italy. In 2019 she started the NeuroWES-Macedonia project together with Prof. Peltichkovski and Prof. Shukarova-Angelovska, an international multi-center study where it was performed trio-WES on many NDD patients in collaboration with the Autism Sequencing Consortium (Icahn School of Medicine at Mount Sinai). A large part of her research is functional characterization of VUS and description of novel disease-associated genes through implementation of various genetic and epigenetic techniques. For her work she received the Nicola Migone Award by the Italian Society of Human Genetics.

Title / Abstract:
GENE DISCOVERY AND PRECISION MEDICINE IN NEURODEVELOPMENTAL DISORDERS USING "EPISIGNATURES"

DNA methylation (DNAm) patterns, known as "episignatures", are associated with specific genes/pathways in NDD. We analyzed DNAm profiles in 164 NDD cases: i) 71 cases with LP/P variants; ii) 13 cases with VoUS; iii) 24 unsolved cases; iv) 56 to identify novel episignatures.

In the first group, we found the expected episignature in 65/71. Exceptions included proteins of the BAF complex. We found the SMARCA2:M856V variant in the Nicolaides-Baraitser-associated domain, that unexpectedly showed a DNAm profile for Blepharophimosis-impaired intellectual development syndrome. In SMARCB1, we found R37H matching the ARID1A/B:c.6200 sub-signature. We noted that the clinics of ARID1A/B:c.6200 cases corresponds to SMARCB1-R37H cases, once more suggesting functional overlap. By 3D protein analysis, we found that all above variants are close and likely interact in the BAF complex. In a patient with Rubinstein Taybi syndrome 2, we found a GNAS DNAm pattern suggestive of Pseudohypoparathyroidism 1B, as secondary finding. Eight/13 VoUS were reclassified as likely benign because they did not match the expected DNAm. Among these, one is likely a Cornelia de Lange (CdL) having the specific episignature, consistent with the clinics. In a second case, a CTCF-DNAm helped pinpointing the causative gene and excluding the role of PTPN11:E69K, subsequently found at mosaic state. Among unsolved cases, we found a second CdL-DNAm case. TRIP12-episignature disentangled the genetic diagnosis in a family with two brothers and similar phenotype caused by two independent de novo changes in TRIP12 and FBN.

Episignature analysis improved variant classification and unraveled novel protein interactions in the BAF complex.

Key words: BAF-opathy, Episignature, Epigenetics; Intellectual and developmental disability; Exome sequencing; Precision medicine

IL-15

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Sena Karachanak-Yankova has graduated molecular biology at Biological faculty, Sofia University "St. Kliment Ohridski" in 2004 and has acquired master degree in genetics in 2006. In 2013 she completed PhD on population genetics topic at the Department of Medical genetics, Medical University-Sofia.

Sena Karachanak-Yankova became assistant professor at the Department of Medical genetics, Medical University-Sofia in 2007 and was improved to senior assistant professor in 2015. Since 2018 she is also associated professor at the Department of Genetics, Biological faculty, Sofia University "St. Kliment Ohridski". Her publication activity is mainly in the field of population genetics/genomics and complex disorder analyses.

Title / Abstract:

GENETIC PROFILE OF ALZHEIMER'S DISEASE, FRONTOTEMPORAL AND UNSPECIFIED DEMENTIA BASED ON POOLED WHOLE EXOME AND WHOLE GENOME DATA

Sena Karachanak-Yankova[1,2], Dimitar Serbezov[1], Dragomira Nikolova[1], Marta Mihaylova[1], Olga Antonova[1], Lubomir Balabanski[3], Mikaela Stancheva[2], Diana Belejanska[4], Mariya Petrova[4], Shima Mehrabian[4], Latchezar Traykov[4], Savina Hadjidekova[1], Draga Toncheva[1,5]

Background: We have screened genetic variants in Alzheimer's disease (AD), frontotemporal dementia (FTD) and unspecified dementia (UD) by the cost and time effective pooled whole exome (WES) and whole genome (WGS) sequencing.

Materials and methods: WES was performed with 250 X coverage on: one AD, two FTD and one UD pooled sample (of 66, 70, 70 and 92 patients, respectively). WGS at 100 x coverage was undertaken on: one early-onset AD (49 patients), two FTD (50 patients each) and one UD pooled sample (50 patients).

Results: WES data contained > 300 000 SNPs in each pool. Rare pathogenic variants with statistically significant difference in frequency between obtained and gnomAD control data are as follows: (i) rs28936380, *PSEN2* and rs104894002, *TREM2* in AD patients, ascertained to be AD associated; (ii) rs181263868, rs761423892, SQSTM1; rs774128685, GRN; rs63751287, rs63751316, *PSEN1* in FTD patients, which are

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AD, FTD and amyotrophic lateral sclerosis related; (iii) ciliopathy related rs373478202, B9D1 and citrullinemia type 1 causing rs148918985, ASS1 variants in UD patients. WGS data yielded > 5 million SNPs in each pool. Rare variants were found in genes involved in neurological and psychiatric disorders. The frequency of the rs429359, *APOE* polymorphism, a well-established AD risk factor; shows statistically significant difference in AD and UD, but not in FTD patients compared to controls.

Conclusion: The performed WES and WGS validate the role of the aforementioned variants and genes in the genetic profile of AD, FTD and UD.

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IL-16

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Dr Danijela Radivojevic is the Head of Section of Molecular Genetics in the Laboratory of Medical Genetics, Mother and Child Healthcare Institute of Serbia "*Dr Vukan Cupic*" in Belgrade, Serbia. She is experienced molecular biologist and physiologist, with more than 20 years demonstrated history of working in the medical practice. Highly motivated research professional with a PhD focused in Human/ Medical Genetics. Skilled in molecular biology, cell culture, cytogenetic and molecular genetics techniques, population studies, clinical research, genetic testing and counselling. Contributed to the improvement of promoting of science regarding the use of genetic testing in modern medicine, from the scientific and practical point of view. Recognized lecturer with mentoring skills. She is a member of several national and international professional societies, through which she achieves active cooperation with colleagues with the same professional interests. She is author/coauthor of number of papers, abstracts and communications as a result of participation in more than 50 national and international symposia.

Title / Abstract:
THE ROLE AND SIGNIFICANCE OF THE LABORATORY OF MEDICAL GENETICS WITHIN HOSPITAL - SERBIAN EXPERIENCE

Medical genetics is an ever-evolving field, largely due to innovations in technology in recent years/ decades. Modern progress has led to an increasing number of techniques that allow the application of simpler, cheaper tests to obtain safe and accurate results in a short time.

To better solve the challenges that genetic testing brings, cooperation with doctors of different specialties is crucial. This idea was recognized almost 60 years ago by researchers who were pioneers of medical genetics in Serbia, who with great enthusiasm approached the establishment of genetic laboratories within the country's health institutions to enable the performance of analyses covered by the national health insurance fund. One of them was the founder of the Laboratory of Medical Genetics at the Institute for Mother and Child Health Care of Serbia "Dr Vukan Čupić" in 1982.

Today Laboratory of Medical Genetics exists as an organizational unit of the Institute's Pediatric Clinic. It is a team of molecular biologists, biologists and laboratory technicians. It consists of three formal units: Section of Cytogenetics, Section of Molecular Genetics, and Cabinet for genetics of hemato-oncological diseases. Analyses are strictly carried out after confirmation of medical indications by pediatrician, gynecologist or the Genetic Counseling team. Samples and methods used are various, depending on the indications, from karyotype through different methods of molecular biology.

The aim of this lecture is to show through this example how the work of the genetic laboratories within clinics in Serbia is organized.

IL-17

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Luca Lovrecic is an Associate Professor of Human Genetics at the Faculty of Medicine, University of Ljubljana. She studied medicine and biology and devoted her professional life to clinical evaluation, diagnostics, and research in the field of rare diseases. Due to her interests, she gained both clinical genetics and laboratory medical genetics training and works at the Clinical Institute of Genomic Medicine, UMC Ljubljana, where she is the Head of diagnostic laboratories, the most significant diagnostic unit in Slovenia. She is a member of several national and international advisory boards and the current president of the Slovene Association of Medical Genetics.

Title / Abstract:
INNOVATIVE APPROACH TOWARDS THE NATIONAL RARE DISEASE MANAGEMENT – SLOVENIAN NATIONAL PLAN

The care of people and families with rare disease (RD) started to develop more intensively as a policy issue in Europe after 1990. These activities have resulted in the Regulation of the European Parliament and of the Council on orphan medicinal products, the Council Recommendation on European action in the field of rare diseases and the Directive on the enforcement of patients' rights in cross-border healthcare. In 2012, Slovenia adopted its first 10-year national plan on rare diseases, taking into account the EUROPLAN project results, which provided uniform recommendations at EU level for the development of national plans on RD.

European experience has shown that having a plan in place does not necessarily mean successful implementation, and that Member States have different needs depending on their specificities. This is particularly true for small EU countries such as Slovenia; while international integration is necessary, it is crucial to organize certain activities at a national level to ensure patient access to health services and economic sustainability.

Thus, in 2021, we have entered a new ten-year period with a national plan that provides innovative solutions for optimal standards for RD patients and can be a model for other EU countries. In this context, the new programme foresees the provision of state-of-the-art health services by incorporating personalized medicine concepts, the integration of patients and their families in the creation of health and social policies, and the development of innovative, original solutions to address the needs in the field of RD in an integrated way.

IL-18

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Professor Florin Burada is Head of the Department of Medical Genetics at University of Medicine and Pharmacy of Craiova and Coordinator of Regional Centre for Medical Genetics Dolj (RCGM Dolj), Romania. In 2022, Dr. Florin Burada was elected as Vice President of the Romanian Society of Medical Genetics (RSMG). He has significant experience in cytogenetic and molecular genetic testing: conventional karyotyping, real-time PCR, QF-PCR, MLPA, array CGH, sequencing. His main areas of interest are prenatal screening and diagnosis, genetics of infertility, chromosomal disorders and congenital anomalies.

Title / Abstract:

THE RESEARCH AND DIAGNOSTIC ACTIVITIES OF THE ROMANIAN NETWORK OF MEDICAL GENETICS – FOCUS ON RCMG DOLJ

Florin Burada[1,2], Ioana Streata[1,2], Anca - Lelia Riza[1,2], Mihai Cucu[1,2], Razvan Plesea[1,2], Amelia Dobrescu[1,2], Claudia Jurca[3], Cristina Rusu[4], Vasilica Plaiasu[5], Camelia Alkhzouz[6], Claudia Banescu[7], Maria Puiu[8]

Regional Center for Medical Genetics (RCMG) Dolj is one of the six centers that constitute the Romanian Medical Genetics Network as was established by Ministry of Health in 2014. The other centers are located in Timisoara, Iasi, Bucharest, Cluj-Napoca and Oradea.

According to this order, each center has several counties assigned to and should include a clinical office, a genetic laboratory and a clinical compartment. RCMG Dolj is organised in the structure of the Clinical Emergency County Hospital Craiova, which is one of the most important regional and national health institution. Our team includes medical geneticists, medical doctors in training, laboratory medicine specialists, biologists, nurses, laboratory assistants and technicians.

We focus on prenatal and postnatal diagnosis and management of congenital malformations, intellectual disability, genetic cardiomyopathies, and hereditary cancer syndromes. We provide clinical consultation and genetic counselling in the outpatient clinical office, both covered by National Health Insurance House.

The Genetic Laboratory covers a wide spectrum of genetic analyses: conventional karyotyping, fragment analysis techniques, Sanger and next generation sequencing (gene panels, whole exome sequencing, and NIPT). Most of genetic tests are covered by National Health Care Programs or by National Health Insurance House.

RCMG Dolj is an expertise center for rare diseases and is a member of Romanian Network of Multiple Congenital Anomalies with Intellectual Disability part of European Reference Network ITHACA.

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IL-19

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Katarina Davalieva is a senior researcher and since 2015, Head of the Proteomics Department at the RCGEB "Georgi D. Efremov", MASA, Skopje, Macedonia. She has received her trainings at the several top institutions in Europe and USA such as Institute Cochin, Paris, France, Vienna University of Technology, Columbia University, NY, USA, Waters MS Technologies Centre, UK, ICGEB, Trieste, Italy, etc. Her research is focused on elucidation of the disease mechanisms through whole proteome comparison of diseased and healthy samples and search for non-invasive diagnostic biomarkers. Significant part of the proteomics work has been related to protein expression profiling of complex diseases/conditions such as cancer, infertility, neuropsychiatric disorders. She has published over 35 articles in peer-reviewed journals and has participated with more than 50 presentations on different scientific events.

Title / Abstract:
FUNCTIONAL PROTEOMICS INVESTIGATION OF BIOMARKERS AND MOLECULAR PATHWAYS OF INFERTILITY

Infertility represents one of the major societal issues today, affecting 10% to 15% of couples at reproductive age, and its prevalence marks a steady growth in the last decades. With the development of high-throughput technologies, studies have focused on the genomics, transcriptomics, proteomics and metabolomics aspects of infertility, providing an opportunity to identify the molecular mechanisms and biological pathways involved in it, as well as discovering new biomarkers.

Here we demonstrate our comparative shogun proteomics approach in the analysis of azoospermia, as the most severe form of male infertility and recurrent pregnancy loss (RPL), as a frequently occurring human infertility-related disease.

By using in-solution digestion method with two detergents (SDS and RapiGest) for sample preparation and label-free data-independent LC-MS/MS acquisition coupled with ion mobility we were able to confidently identify and quantify more than 2000 proteins in each of the studies, independently of sample type (fresh frozen or formalin-fixed, paraffin-embedded (FFPE) tissues).

Within the azoospermia study, we have identified 61 proteins that could quantitatively discriminate obstructive (OA) from non-obstructive (NOA) azoospermia and 30 to quantitatively discriminate NOA subtypes. Several pathways associated with azoospermia and a number of testis-specific and germ cell-specific proteins that have the potential to pinpoint the type of spermatogenesis failure were also identified. Furthermore, comparison with transcriptomics datasets based on genome-wide gene expression analyses identified proteins that could discriminate between OA and NOA subtypes on both protein and mRNA levels. Proteomics analysis of the decidua and chorionic villus tissue from individuals with RPL resulted in identification of 90 and 523 proteins with differential abundance, respectively.

Bioinformatics analyses of the differentially abundant proteins reflect the biological pathways involved in RPL, laying a foundation for further research.

Oral presentations

OP-01

PHENYLBUTYRIC ACID REDUCES MOLECULAR MARKERS OF ER STRESS-INDUCED APOPTOSIS IN GLYCOGEN STORAGE DISEASE TYPE IB *IN VITRO* MODEL SYSTEM

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Background: The current therapy for glycogen storage disease Ib (GSD Ib) fails to prevent the development of renal dysfunction, and hepatocellular/renal carcinoma in many patients. Therefore, new therapies for the treatment of life-threatening complications of GSD Ib are of great interest. Recent studies revealed that chronic endoplasmic reticulum (ER) stress and increased apoptosis are involved in pathogenesis of GSD Ib, whereas small molecule phenylbutyrate (4-PBA) showed the capability of reducing ER stress-induced apoptosis.

Methods: To analyze the function of 4-PBA as ER stress inhibitor, we created a G6PT-deficient FlpInHEK293 cell line using the CRISPR/Cas9 knockout method and tested if 4-PBA could decrease chronic metabolic stress and prevent cell death. We analyzed molecular markers of unfolded protein response (ATF4, DDIT3, HSPA5, XBP1s), and apoptosis (*BCL2/BAX, CASP3*, *CASP7*) in G6PT-deficient cells before and upon the treatment using RT-qPCR method.

Results: Treatment with the most effective dose of 1 mM 4-PBA reduced the expression of executioner caspases (*CASP3, CASP7*) and increased the *BCL2/BAX* ratio, indicating a reduced apoptosis level. Additionally, 4-PBA decreased UPR marker expression in G6PT-deficient cells. Our results proved the concept that 4-PBA could alleviate markers of ER stress detected in the GSD Ib in vitro model system and prevent cell death.

Conclusion: We demonstrated, for the first time, the potential of 4-PBA to be repurposed for patients with GSD Ib and open perspectives for translational research that could contribute to a knowledge of GSD Ib treatments and other genetic diseases where chronic ER stress-induced apoptosis contribute to the disease pathology.

Keywords: *GSD Ib in vitro model system, CRISPR/Cas9, 4-PBA treatment, ER stress, apoptosis*

Topic: *Rare diseases*

OP-02

OUTCOME OF A SERBIAN PILOT INITIATIVE: SPINAL MUSCULAR ATROPHY NEWBORN SCREENING OVER A 16-MONTH PERIOD

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Background: Spinal muscular atrophy (SMA) is the prevalent genetic cause of childhood mortality. Pioneering treatments yield utmost advantages only within the presymptomatic phase, underlining the significance of newborn screening.

Materials and methods: In 2022, the Centre for Human Molecular Genetics initiated a pilot study of the newborn screening for SMA, working closely alongside the University Children's Hospital Tirsova and Association SMA Serbia. The aim was to lay the foundation for the implementation of statewide newborn screening for SMA in Serbia by conducting screening for ~8000 infants from the Obstetrics and Gynaecology Clinic Narodni Front over the course of a year.

Results: In the initial year, 6950 newborns underwent testing, revealing SMA in two unrelated infants and in an asymptomatic 16-month old sibling of the first newborn. All three children received therapeutic interventions in <1 month from birth. To date, they have exhibited no signs of SMA, and there have been no false-negative outcomes among the newborns who tested negative during the screening.

As frontrunners in this field in Serbia, we orchestrated harmonized efforts across various tiers of healthcare, established screening and diagnostic algorithms and follow-up protocols. In the second year, we included a maternity hospital beyond Belgrade, introducing sample shipping via mail and extending screening accessibility to a greater number of infants. This resulted in 9800 infants undergoing testing within 16 months. Currently, we are actively preparing for the official incorporation of newborn screening for SMA into the national screening program.

Conclusions: Timely detection and treatment can transform SMA into a manageable condition.

Keywords: *Newborn screening, Spinal muscular atrophy, Pre-symptomatic diagnosis, SMA prevention, SMN1*

Topic: *Rare diseases*

OP-03

MTDNA NGS RESULTS IN MITOCHONDRIAL DISORDERS OF TRAKYA UNIVERSITY

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Background: Mitochondria are responsible for the regulation of various cellular processes such as oxidative phosphorylation, intracellular signaling mechanism and apoptosis. mtDNA is a circular and double stranded which is 16,569 bp long, contains 37 genes. Mitochondrial disorders are very heterogeneous group of diseases that occur as a result of respiratory chain dysfunction and are observed at a rate 1 /5000 births. NGS has improved the efficiency of mitochondrial mutation discovery, heteroplasmy levels and mtDNA depletion facilitated the molecular routine diagnosis.

Methods: The whole mtDNA genome was performed with the NGS method. Samples were run with the NextSeq550 system. MITOMAP and mtDB databases were used in the bioinformatics analysis. In addition, platforms such as Qiagen Clinical Interpret (QCI), Franklin, and Varsome were used for in silico evaluation.

Results: 88 patients with different phenotypes related to mtDNA diseases were studied. Homoplasmic pathogenic m.11778G>A variation was detected in 4 of the patients with a preliminary clinical diagnosis of LHON. In one patient, pathogenic m.6698delA and m.9537delC variations were observed as compound. Also a pathogenic m.6698delA and m.7445 G>A variations were found in 2 patient. VOUS variations m.11467 A>G, m.3394T>C and m.2755A>G were detected as homoplasmic in 3 patients. In 18 patients, m.12425delA variation, which was pathogenic in ClinVar, was detected as heteroplasmic. In 60 patients, heteroplasmic and non-pathogenic variations were detected according to bioinformatic analysis.

Conclusion: mtDNA sequencing performed with NGS overcomes the challenges and enables comprehensive analysis of variants associated with mitochondrial disease.

Keywords: *Mitochondria, mtDNA, Next generation sequencing, Bioinformatics Variation*

Topic: *Metabolic and mitochondrial disorders*

OP-04

DIAGNOSTIC UTILITY OF NEXT-GENERATION SEQUENCING GENE PANEL IN THE DIAGNOSIS OF SYSTEMIC AUTOINFLAMMATORY DISEASES

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Introduction: Autoinflammatory syndromes (AIS) are a heterogenous group of disorders characterized by recurrent episodes of inflammation and fever in the absence of autoantibody response and microbial infection. The aim of our study is to evaluate the diagnostic yield of NGS gene panel testing for AIS.

Materials and methods: Seventy pediatric and adult patients with clinical suspicion of AIS were referred for genetic testing at the Institute of Immunobiology and Human Genetics. Their DNA samples were sequenced on an Ion Torrent platform, using an AmpliSeq AIS gene panel, which included 34 genes (*ASAH1, CARD14, DDX58, ELANE, IFIH1, IL10RA, IL10RB, IL1RN, IL36RN, LPIN2, MEFV, NLRC4, NLRP12, NLRP3, NOD2, MVK, PLCG2, PSMB8, SAMHD1, RBCK1, SLC29A3, RNASEH2B, ADAR, RNASEH2A, RNASEH2C, TNFAIP3, TNFRSF11A, TNFRSF1A, NLRP1, OTULIN, TMEM173, HAX1, PSTPIP1, TREX1*). Variant calling and interpretation of pathogenicity was performed using the IonReporter v.5.14 and Qiagen Clinical Insight variant analysis software and the ACMG criteria.

Results: The diagnostic yield of our gene panel was 10%. Seven out of seventy (7/70) patients had a likely pathogenic or pathogenic variant, in four different genes: *MEFV* (c.2084A>G, c.2282G>A and 2080A>G) *IFIH1* (2465G>A), *TREX1* (341G>A) and *MVK* (1129G>A, 564G>A). "Significant" VUS variants were detected in additional 7 patients.

Conclusion: Our findings are comparable with those from the literature and support the use of this type of genetic testing in AIS, as it yields the diagnosis of these difficult and rare conditions. However, additional evaluation by a clinical geneticist might increase the diagnostic utility of the genetic testing.

Keywords: *Autoinflammatory syndrome, NGS panel, MEFV*

Topic: *Rare diseases*

OP-05

EVALUATION OF MITOCHONDRIAL MONONUCLEOTIDE REPEAT (D310) IN THE D-LOOP REGION IN BOSNIA AND HERZEGOVINA COLORECTAL CANCER AND POLYPOSIS PATIENTS

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Background: Recent studies have confirmed the presence of somatic mitochondrial DNA (mtDNA) alterations in a variety of malignancies. A non-coding section of the mitochondrial genome called the D-loop contains critical transcription and replication components and changes in that region may impact both of these processes. The D-loop has a poly-C tract (PCT) designated as D310, located between nucleotide positions 303 and 315, and has been identified as a frequent hot spot mutation site in primary cancers.

Materials and methods: In the present study, the D-loop of mitochondrial DNA was sequenced using the Sanger method in 30 pairs of colorectal cancer tissue (CRC) and colorectal polyposis tissue with matched normal controls.

Results: We evaluated the prevalence of mitochondrial microsatellite instability (mtMSI) in polyposis and tumor-bearing tissue and its relationship with the emergence of colorectal cancer. Both statistically and clinically significant mutations in D310 were reported in 19 of 30 (63%) colorectal cancer samples and in 11 of 30 (36%) polyposis tissue samples using a home-developed program named "Mitowizz".

Conclusions: This is the first study from Bosnia and Herzegovina on colorectal tumor and polyposis patients, indicating a relatively high frequency of D310 mtDNA mutations and suggesting that mtDNA instability at D310 might be a typical feature of colorectal cancer development. Taking into consideration the fact that changes were discovered in polyposis tissue, this may be a more significant change for the early development of the disease than its clinical onset.

Keywords: *D-loop mitochondrial DNA, mtMSI, colorectal cancer, D310*

Topic: *Metabolic and mitochondrial disorders*

OP-06

PGT IN SLOVENIA: A 20-YEAR EXPERIENCE IN A NATIONAL HEALTH SYSTEM

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Background: Preimplantation genetic testing (PGT) is the earliest form of prenatal diagnosis that has become an established procedure for couples at risk of passing a severe genetic disease to their offspring. At UMC Ljubljana, we conducted a retrospective register-based study to present PGT service within the public healthcare system in Slovenia.

Materials and methods: Data on the PGT cycles from 2004 to 2022 were collected, and clinical outcomes for chromosomal and monogenic diseases using different embryo biopsy and testing approaches were compared. In addition, the extent to which PGT has become the preferred option compared to classic prenatal diagnostics was assessed.

Results: We treated 269 couples, 147 with single gene disorder, 108 with structural chromosome rearrangement and 14 for numerical chromosome aberration. There were 445 PGT cycles with oocyte retrieval, while embryo transfer was possible in 325 cases, resulting in 120 pregnancies. Altogether, the clinical pregnancy rate per embryo transfer was 31% in 2004-2016 (blastomere biopsy) and 42% in 2017-21 (blastocyst biopsy), respectively. We assessed that approximately a third of couples would opt for PGT, while the rest preferred natural conception with prenatal diagnosis.

Conclusions: Our results show that providing a PGT service within the public healthcare system has become a considerable option in pregnancy planning for couples at risk of transmitting a severe genetic disease to their offspring. In Slovenia, approximately a third of couples would opt for PGT. Although the number of cycles is small, our clinical results are comparable to larger centres.

Keywords: *Chromosome aberration, Embryo biopsy, IVF, Monogenic disease, PGT*

Topic: *Reproductive and prenatal genetics*

OP-07

THE VALUE OF PRENATAL EXOME SEQUENCING IN CASES WITH ABNORMAL FETAL ULTRASONOGRAPHIC FINDINGS: A REPORT OF 25 CASES

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Backgorund: We investigated the diagnostic and clinical utiliy of exome sequencing in fetuses with sonographic abnormalities with normal karyotype and microarray. Here we report our laboratory's exome sequencing data of prenatal samples and describe phenotype-genotype correlations.

Materials and methods: Whole Exome Sequencing was performed on DNA from 25 fetuses with abnorml ultrasonographic findings. Fetuses with two or more ultrasonographic anomalies and ore hydrops fetalis were included. Interpretation was done according to the ACMG guidelines and pathogenic, likely pathogenic and clinically relevant VUS variants were reported.

Results: In 20 (80%) of 25 fetuses, exome sequencing provided a diagnosis or possible diagnosis with identification of variants in the following genes: *PKP2, VANGL2, PIEZO1, CHRNG, ROR2, FAT4, MKKS, CFHR5, YR1 , THOC6, DYNC1H1, CHD7, PEX1, FGFR3, FBLN5,ARSE , NSD1 , GALNS, CRB2, NEK1, NOTCH1, PKD1*. 5 of them pathogenic variants, 11 had likely pathogenic and 8 had VUS variants relevant with fetal ultrasonograhic findings. The most defined ultrasonographic findings in cases with pathogenic variants were skeletal anomalies, hidrops fetalis and brain anomalies.

Conclusions: Exome sequencing had diagnostic utility in fetuses with fetal structural anomalies diagnosed by ultrasonographic evaluation. Screening the monogenic diseases increases the power of prenatal diagnosis in highly suspected cases.

Keywords*: Exome sequencing, Prenatal diagnosis, Skeletal anomalies*

Topic*: Reproductive and prenatal genetics*

OP-08

THE ROLE OF THE COMPLEX *CPLANE1*C.1819DELT;7817T>A ALLELE IN EARLY PREGNANCY LOSS

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Background: High frequency of Joubert syndrome (JS) with *CPLANE1:*c.1819delT;7817T>A homozygosity was detected among early pregnancy losses (EPLs) in our previous studies. Up to date, no homozygous patient with the *CPLANE1:*c.1819delT;7817T>A allele has been reported. Here, we further investigated the impact of this allele on EPLs.

Materials and methods: Using allele-specific PCR, a total of 650 women with EPLs and 646 controls with a live birth and no EPL, matched by ethnic origin were screened. Twelve EPLs and 11 control fetuses of *CPLANE1:*c.1819delT;7817T>A carrier-women were also studied.

Results: We observed higher frequency of the *CPLANE1:*c.1819delT;7817T>A complex variant among the women with EPLs (AF=1.4%), compared to the controls (AF=0.8%), however without statistical significance (p=0.2). This variant was significantly more frequent (p=0.003) among the Albanian population compared to the Macedonian (AF=1.03% and 0.38%, respectively). Genetic diagnosis of JS was confirmed in five of the 12 (41.7%) EPL-fetuses (three homozygotes and two compound heterozygotes with a novel splicing variant), and in only one of the 11 (9.1%) control-fetuses (compound heterozygote with c.8263dup, genotype previously found in three of our JS patients), showing difference with borderline statistical significance of p=0.07.

Conclusions: Our findings show that fetuses homozygous for *CPLANE1:* c.1819delT;7817T>A allele or compound heterozygous with other severe *CPLANE1* variant are affected with a severe JS and are eliminated early in the pregnancy. Preconception screening for *CPLANE1*:c.1819delT;7817T>A allele could identify couples at risk of pregnancies with JS and could enable genetic counselling of the carriers.

Keywords: *Joubert Syndrome, Early pregnancy loss, homozygosity*

Topic: *Reproductive and prenatal genetics*

OP-09

CLINICAL SIGNIFICANCE OF X CHROMOSOME COPY NUMBER VARIATIONS

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Background: The X-chromosome (chrX) comprises ~5 % of the human genome but contains numerous genes crucial for human development, fertility, and cognitive function, with sex-dependent dose compensation as a unique feature. Copy number variations (CNVs), readily detected by microarray technologies, identified a multitude of clinically significant CNVs, bringing attention to submicroscopic genomic aberrations.

We aim to analyze all non-polymorphic chrX CNVs detected by chromosomal microarray in patients with different medical conditions and assess their clinical significance.

Materials and methods: From the original sample of 1300 patients analyzed by the chromosomal microarray, those with chrX CNVs were singled out. Agilent 8x60K or 4x180K+SNP microarrays were applied. Clinical data were collected from medical records. Pathogenic and likely pathogenic variants were considered clinically significant (csCNVs).

Results: Non-polymorphic chrX CNVs were detected in 34/1300 probands (2,6%). Six additional family cases were detected. In 29/40 (72,5%) cases CNVs were considered clinically significant. Their size ranged from 267 kb to 166 Mb, with deletions in 12 (41,4%) and duplications in 17 cases (58,6%). 10/12 cases with deletion were females, in contrast to 5/17 for duplications (p=0.007). Intellectual disability (ID) had all but one male, while almost half of females (7/15) did not have ID (p=0.03). The most common CNVs were: Xp22.31 del (5): Turner syndrome variants (4), MECP2 or Xq28 dupl (5), Xp11.23–p11.22 dupl (3), Xq24 del (2), others were rare non-recurrent CNVs.

Conclusion: ChrX CNVs have great clinical significance with specific sex differences. Deletions are significantly more common in females and ID in males

Keywords: *Copy number variations, Chromosome X, Chromosomal microarray*

Topic: *Neurogenetics and intellectual disability*

OP-10

GENETIC LANDSCAPE IN EPILEPSY RELATED DISORDERS

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Background: Epilepsy and neurodevelopmental disorders (NDD) that include epilepsy as a defining feature are one of the most common brain disorders that affect people of all ages, mostly children. Worldwide, ~0.8% of the population is affected with epilepsy and 3-5% of children suffer from NDD. The introduction of NGS has led to redefining the genetic landscape of epilepsy related disorders and increased the discovery of underlying genetic cause to ~ 40% in individuals suffering from those conditions.

Material and methods: In our study, we analyzed 79 patients with epilepsy and epilepsy related disorders using clinical exome sequencing (CES) in 24 patients and whole exome sequencing (WES) in 55 patients.

Results: Thirty-two patients had pathogenic/likely pathogenic (P/LP) variants fully explaining their phenotypes, giving an overall diagnostic yield of 40.5% (32/79). The discovery rate in patients with epilepsy was 14.8%; (4/27), while in epilepsy related disorders was 53.8% (28/52), with particularly high positive rate for epileptic encephalopathy (73.9%;17/23). Twenty-eight different sequence based changes were identified in 22 genes and 4 patients had pathogenic CNVs (all deletions), involving multiple genes. *SCN1A* was the most frequently altered gene (4 patients), followed by *KCNQ2* and *NEXMIF* in three and two, respectively, representing 32.1% (9/28) of all cases. The remaining 18 genes were mutated only in one patient each. Twenty two of the 28 positive cases (78.6%) had a P/LP variant in a gene associated with an autosomal dominant, 14.3% (4/28) with X-linked, one with recessive disorder and one patient had mitochondrial DNA variant. Most of the causative variants occurred *de novo* (74.1%) and 51.7% were novel.

Conclusion: In conclusion, the genetic landscape of epilepsy related disorders is very heterogeneous and NGS is useful diagnostic tool particularly for severe epileptic encephalopathy.

Keywords: *epilepsy, NGS, genetic landscape*

Topic: *Neurogenetics and intellectual disability*

OP-11

THE KEY ROLE OF CLINICAL DESCRIPTION IN DETERMINING THE SYSTEM APPROACH FOR GENETIC TESTING

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The first breakthrough in sequencing technology was the invention of the Sanger sequencing method, 24 years after the structure of DNA was discovered. Fast forward to 2022, the remaining 8 percent of the human genome are sequenced, which is made possible by the development of the latest Oxford Nanopore and Pacific Biosciences sequencers. With the improvement of these technologies and the implementation of personalized medicine, the need for development of a system approach, based on a detailed and accurate clinical picture, comes to the forefront. Here we report cases from our clinical practice where the determination of approach for genetic testing depends on examination of the clinical picture of patients.

Genomic DNA was isolated and samples were either sequenced by NGS (next-generation sequencing: whole exome sequencing or whole genome sequencing), Sanger sequencing or MLPA analysis (Multiplex ligation-dependent probe amplification).

Our results show the key role of clinical characersitics in choosing an accurate genetic testing approach: clinical diagnosis in Rett, Prader-Willi, Angelman and Fragile X syndromes, diagnostic imaging (Pelizaeus-Merzbacher syndrome and gastrointestinal encephalopathy), neurophysiological examinations (spinal muscular atrophy), metabolic screening (Pompe disease and fumarase deficiency), proteomic biomarkers (ataxias), characteristics of the patients' population (pontocerebellar hypoplasia and pyruvate dehydrogenase deficiency), time for analysis (antithrombin III deficiency and Alport syndrome) and various complex phenotypes.

Choosing an appropriate genetic testing approach is key, in order to clarify patients' diagnosis accurately and in a timely matter, and strongly depends on the initial clinical picture.

Keywords*: Whole Exome Seqencing, Sanger sequencing, Segregation analysis, Biomarkers, Genome data*

Topic: *Genetic Technologies*

OP-12

COMPREHENSIVE GENETIC EVALUATION OF ATAXIA: EXPERIENCE OF A SLOVENIAN TERTIARY CENTRE

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Background: Hereditary ataxias (HA) commonly represent a diagnostic challenge that requires comprehensive approach targeting diverse mutational mechanisms. Rapid advances in genetic technologies and the detection of new genes associated with ataxia, lead to continuous improvements of algorithms to guide the diagnosis and management of HA. Our aim was to present the experience of an evidence based comprehensive diagnostic approach to patients with HA, referred at the Clinical Institute of Genomic Medicine, University Medical Center Ljubljana, Slovenia.

Methods: Genetic testing was performed on patients with high risk for early or late onset HA, which were selected based history of the disease, family history, clinical presentation, and diagnostic workup. Our comprehensive genetic testing targeted the spectrum of different genomic variation associated with HA, including the DNA repeat expansions, copy number variations and pathogenic/likely pathogenic variants in genes associated with HA.

Results: The study comprised 123 patients, including 50 (41%) with early onset HA. We successfully detected a genetic cause in 41% of referred patients. Among those, the largest group represented HA due to pathogenic repeat expansions, including Friedreich's ataxia, CANVAS and spinocerebellar ataxia-8.

Conclusion: Addressing both clinical and genetic heterogeneity, we sought to assess the diagnostic yield and clinical utility of our evidence based comprehensive approach in patients who were consecutively referred to our centre with progressive ataxia symptoms. Our results showed that our approach facilitates diagnosis of HA, and also provide some new insights on the prevalence of different genetic causes for HA.

Keywords: *Cerebellar ataxia, Repeat expansion, Next-Generation Sequencing, Diagnostic yield*

Topic: *Rare diseases*

OP-13

VALUE OF OPTICAL GENOME MAPPING FOR DIAGNOSTICS OF RARE DISEASES

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Optical genome mapping (OGM) represents the current state-of-the art in the field of structural variant detection. The method is based on the laser image acquisition of single, labelled, high-molecular weight DNA molecules in order to detect structural genomic variants such as translocations, insertions, deletions, and complex structural rearrangements in size ranges not possible by other methods. Since 2021 we have used OGM at the Clinical Institute of Genomic Medicine, UMC Ljubljana, Slovenia for the testing of facioscapulohumeral muscular dystrophy 1 (FSHD1), characterization and resolution of variants identified by other technologies, and testing of rare-disease patients.

Regarding characterization of variants of interest, OGM was able to fully resolve most variants detected by other technologies such as karyotyping and microarrays. The additional information on the location (in case of translocations) or the orientation of the variant (tandem vs. inverted duplications) provided by OGM in most cases provided the basis for their classification to either likely pathogenic or benign.

Finally, by OGM testing of patients with rare-disease, we were able to identify both some likely pathogenic and some variants of interest, that we plan to confirm using functional assessment. In our experience, currently a major limitation of the method remains the difficulty of interpretation due to its novelty and the lack of healthy control population variants, that will hopefully be resolved and increase the diagnostic yield of this method in the future.

Keywords: *optical genome mapping, rare-disease diagnostics, structural variants, FSHD1*

Topic*: Genetic Technologies*

OP/CR-01

SETBP1 C.2608G>A (G870S) VARIANT IN A SYRIAN PATIENT WITH SCHINZEL-GIEDION SYNDROME: AN ILLUSTRATIVE CASE

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Background: Schinzel-Giedion syndrome (SGS) is a very rare identifiable malformation syndrome, characterized by a distinctive facial dysmorphism, severe growth failure, profound developmental delay, typical skeletal malformations, hydronephrosis, genital and cardiac anomalies, as well as an increased pediatric cancer risk. SGS is caused by de novo mutations in the *SETBP1* gene.

Case: A girl newborn was evaluated for dysmorphic appearance, antenatal hydronephrosis, ambiguous genitalia, and rocker bottom feet. She was born to a healthy 34-year-old G8P7 mother. Her parents are relatives. No similar patient in family history. On examination; opisthotonus, high, protruding forehead, shallow orbits, depressed nasal root, short nose, large ears, micrognathia, ambiguous genitalia, camptodactyly, rocker bottom feet, and hypertrichosis were seen. She was hospitalized recurrently with a combination of respiratory distress, poor feeding, hydronephrosis, seizure, etc. Imaging systems showed patent foramen ovale, severe bilateral hydronephrosis, presence of uterus and ovaries, non-functional right kidney, and hypofunctional left kidney, characteristic skeletal malformation such as bowed long bones, wide distal metaphysis of femur, and broad ribs, epileptic activity, and ventriculomegaly, cerebral atrophy, thin corpus callosum at follow-up.

Results: The diagnosis was made mainly based on clinical findings, and confirmed by Sanger Sequencing analysis. c.2608G>A(G870S) heterozygous variant was detected at *SETBP1* gene.

Conclusions: SGS is a rare disease that can be suspected by clinical findings in patients with multiple anomalies. This rare case has been brought to the literature with its clinical, laboratory and genetic results.

Keywords: *Schinzel-Giedion syndrome, Sanger sequencing, SETBP1 gene*

Topic: *Rare diseases*

OP/CR-02

A NOVEL *TIMM8A* MUTATION IN A TURKISH PATIENT WITH ULTRA RARE MOHR-TRANEBJAERG SYNDROME

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Backgorund: Mohr-Tranebjaerg Syndrome (MTS) is a rare X-linked recessive syndrome characterized by postlingual progressive auditory neuropathy followed by dystonia, cortical blindness, dementia and behavioral abnormalities. Hemizygous mutations on *TIMM8A* gene causes the clinical manifestations. *TIMM8A* encodes a small translocase of inner mitochondrial membrane which acts as a chaperone like protein that protects the hydrophobic molecules from aggregation and conduct them through the mitochondrial intermembrane space. Even though the whole function of TIMM8A protein is still unknown, the previous studies show that *TIMM8A* is important for neural development.

Materials and Methods: DNA was isolated from peripheral blood of the patient. Clinical Exome Sequencing (CES) was performed. The identified variant was studied with Sanger Sequencing from the mother.

Results: A two year old boy was referred to our clinic because of bilateral progressive sensorineural deafness. He had retractile testes. Other system evaluation was normal. He was born via uneventful normal delivery from non-consanguineous healthy parents. His birth percentiles were in normal range. He passed his newborn hearing test. His motor development was normal for his age but he didn't speak at time. After one year old he stopped responding when he was called and failed the hearing test that performed upon. Hemizygous c.65_66delinsAA (p.Phe22*) mutation in *TIMM8A* gene was detected in CES

Conclusion: MTS is an ultra-rare disease that causes progressive multisystemic symptoms throughout life. Early diagnosis is important for appropriate genetic counseling and preventive approach. To our knowledge, this is the first Turkish MTS patient that is documented.

Keywords: *sensorineural deafness; rare disease; TIMM8A, X-linked disease*

Topic: *Rare diseases*

OP/CR-03

FABRY DISEASE "*AD ASTRA PER ASPERA*"

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Introduction: Fabry disease (FA) is a rare X-linked disorder of Glycosphingolipid (fat) metabolism that was firstly recognized in early 1960s. This process generally leads to accumulation of globotriaosylceramide (Gl-3) in the vascular endothelium of the skin, kidneys, nervous system, and heart, thereby triggering inflammation and fibrosis.

Case presentation: We presented the first geneticly confirmed family with FD for North Macedonia ever. The nephrologists set the diagnosis a 46 year old male with end stage chronic kidney disease on hemodialysis. He was not able to control neuropathic pain from childhood, had intermittent abdominal cramps, anhidrosis and hypertension. The constellation of clinical signs accompanied with similar symptoms in the close family urged us to perform testing for FD. The enzymatic testing for α-galactosidase and Lyso Gl-3 were positive. Also, the performed Genitc testing confirmed FD with known missense mutation that was reported by Ashton-Prolla at al. In addition, family studies identified several other affected males and carrier female relatives with this X-linked recessive disorder.

Our further effort will be to possibly provide adequate treatment with modern enzyme replacement therapy with regular medical check-ups of all affected systems.

Achieving higher awareness for FD requires continuous medical education, research, and support from the government, private sector, nongovernmental and professional organizations.

Conslusion: In this review, we reported the first case of FD in North Macedonia. Although it is a rare disease, it is still around us requiring specific knowledge about the disease to diagnose.

Keywords: *Fabry Disease, Chronic Kidney Disease, Hemodialysis, α-galactosidase, X-linked disorder*

Topic: *Rare diseases*

OP/CR-04

A CASE REPORT OF DONNAI BARROW SYNDROME: FIRST GROSS DELETION MUTATION IN *LRP2* GENE

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Donnai-Barrow Syndrome (DBS)/ Facioculoacousticorenal (FOAR) Syndrome is a multiple congenital malformation syndrome characterized by typical facial dysmorphism, ocular findings, hearing loss, agenesis of the corpus callosum, low-molecular-weight proteinuria and variable intellectual disability. DBS is an autosomal recessive disorder caused by loss of function variants in the *LRP2* (low-density lipoprotein receptor-related protein 2) gene (2q31.1) encoding the protein megalin, an endocytic transmembrane glycoprotein.

We present a case with a deletion in exons 17-19 of the *LRP2* gene with optic disc hypoplasia, pigmentary retinopathy, corpus callosum hypoplasia, developmental delay, growth retardation, hypothroidism, bilateral hypoplastic kidney and proteinuria in addition to dysmorphic findings compatible with DBS. We performed whole exome sequencing (WES), karyotype and microarray analysis for diagnosis and validated the exon 17-19 deletion with PCR. Karyotype and microarray analysis from peripheral blood were normal. No reads were observed between exons 17 and 19 of the *LRP2* gene in WES analysis. These exons could not be amplified with PCR. Then, we amplified exon 16-20 with long PCR from cDNA samples of the patients and the parents for validation. We observed deletion in exon 17-19 region in patient's sample when loaded into the gel electrophoresis.

Small deletions or insertions causing frameshifts, as well as conserved splice site, nonsense and missense mutations of *LRP2* gene in DBS/FOAR families were reported before. We report the first case of gross deletion in *LRP2* in a patient clinically diagnosed with DBS.

Keywords*: Donnai Barrow Syndrome, LRP2 gene, Gross deletion, Whole exome sequencing, Gel electrophoresis*

Topic*: Rare diseases*

OP/CR-05

FOLLOW-UP OF A BOY WITH A *CBL*-RELATED DISORDER AND GROWTH HORMONE DEFICIENCY

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Background: Noonan syndrome-like is a developmental disorder with a heterogenic phenotype (macrocephaly, dysmorphic facial features, congenital heart disease, motor delay, short stature in 31% of cases etc.). Most patients carry heterozygous mutations in the *CBL* gene, with an increased risk of malignancies, particularly juvenile myelomonocytic leukemia.

Case report: A 4-year-old boy born in term with intrauterine growth retardation (IUGR) (birth weight, –5.18 SDS and birth length, -0.38 SDS), microcephaly (-3.46 SDS), other clinical features typical for Noonan-like syndrome, has been followed up since the age of 1 year. The diagnosis has been confirmed with the targeted resequencing analysis and revealed a heterozygous (nonsense) pathogenic variant, c.1675C>T, p. (Arg559Ter) in exon 11 of the *CBL* gene. Unfortunately, our patient is an orphan living with foster carers and the evaluation of his ancestors was unavailable.

At the age of 2-and-a-half years, due to short stature (height, -2.3 SDS and weight, -2.7 SDS) and persistent microcephaly (-2.23 SDS) the evaluation has shown low IGF1 (29.7 ng/ml) and IGF BP3 (2.79 μg/ml) serum concentrations, as well as two tests of pituitary reserve (peak 6.9 ng/ml). The commencement of the growth hormone therapy was reasonably doubted and was delayed due to molecular findings.

Now, at the age of 4 years, his height (-2.5 SDS), weight (-2.05 SDS) and head circumference (- 1.94 SDS) are below the average for his age and sex. There are no signs of hematologic malignancy. His motor development is significantly improved, but delayed, he does not walk on his own, yet.

Conclusions: The aim of our study is to present an IUGR-born child with microcephaly and a very rare Noonan syndrome-like disorder without malignancy, associated with growth hormone deficiency. Initiation of growth hormone replacement therapy remains questionable given its genetic burden and cancer predisposition. The timely mannered and adequate monitoring of patients with CBL-related disorders is not only necessary but also lifesaving.

Keywords: *Noonan syndrome-like disorder, growth hormone deficiency, motor development delay, CBL gene mutation*

Topic: *Rare diseases*

OP/CR-06

TERF1: A NOVEL CANDIDATE GENE FOR DYSKERATOSIS CONGENITA

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Background: Dyskeratosis congenita (DKC) is a rare genetic disease characterized by nail dystrophy, skin pigmentation and bone marrow failure. The genes constituting telomerase and shelterin complexes have been shown to cause DKC. However, in nearly half of DKC patients, there is no known causative gene. Here we present *TERF1*, a component of shelterin complex, as a novel candidate gene for DKC.

Materials and methods: A male newborn referred to our clinic due to lymphopenia and generalized erythroderma. He was fifth child of a non-consanguineous couple who are from the same village. Two of his siblings died due to immunodeficiency at the age of 6th and 18th months. Neither of his siblings had a definitive genetic diagnosis. Physical examination showed generalized erythroderma and nail dystrophy. Laboratory examination revealed lymphopenia and decreased CD19 and CD56 levels in flow cytometry analysis. Whole Exome Sequencing (WES) conducted to the patient and the parents.

Results: WES showed no known pathogenic variations explaining the patient's phenotype. Further analysis focused on all protein coding genes revealed *TERF1*:c.265G>T variant in homozygous state in the patient and heterozygous in both parents. *TERF1*, contributes the formation of shelterin complex. Although *TINF2*, another component of shelterin complex, is shown to cause DKC, *TERF1* is not associated with any phenotype in the literature.

Conclusions: *TERF1* gene was not associated with any phenotype to date. This publication is a first stating *TERF1* as a candidate gene for DKC.

Keywords: *Dyskeratosis congenita, TERF1, Shelterin, Telomere Immunodeficiency*

Topic*: Rare diseases*

OP/CR-07

TWIN MONOZYGOTIC EARLY NORMAL AND COMPLETE MOLAR PREGNANCY

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Introduction. Concomitant normal and complete molar pregnancy is a rare event described in the scientific literature. Complete molar pregnancy is caused by abnormal zygote formation that leads to complete loss of maternal DNA, and therefore loss of positivity for p57 marker on immunohistochemistry. The complete hydatidiform mole is clinically important due to the increased risk of development of gestational trophoblastic neoplasia in these the patients.

Case presentation. We present a case of a 37 years old female patient presenting with uterine bleeding and elevated serum HCG suspicious for molar pregnancy. Dilatation and curettage was performed and the material obtained was sent for histopathological analysis.

The microscopic examination revealed presence of two types of chorionic villi. In some areas thi vili had normal contours and were covered by two layers of trophoblastic cells. In other areas the villi were enlarged, with irregular villous contours, also showing exuberant circumferential proliferation of the trophoblastic cells. The immunohistochemical analysis showed complete od partial loss of expression of p57 in cytotrophoblasts and villous stromal cells.

Additional molecular analysis was performed on both types of chorionic villi. The QF PCR analysis confirmed loss of maternal DNA in the abnormal villi. The paternal DNA showed homozygosity for all STR markers analysed. These findings suggest monozygous normal and complete molar pregnancy.

Conclusion: Monozygous twin molar pregnancy is extremely rare. Additional research is needed to clarify the exact mechanisms of its occurrence. Careful monitoring for possible occurrence of gestational trophoblastic neoplasia is important.

Keywords*: Molar pregnancy, Twin pregnancy*
Topic: *Reproductive and prenatal genetics*

Poster presentations

PP-01

STRENGTHENING THE NEXT-GENERATION SEQUENCING AND BIOINFORMATICS CAPACITIES IN THE REPUBLIC OF SERBIA

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In 2021, the Center for Genome Sequencing and Bioinformatics was established at the IMGGE in collaboration with the Beijing Genomics Institute (BGI) and with the support of the Government of the Republic of Serbia. The Center was founded with the aim of accelerating the implementation of 4P medicine (Preventive, Predictive, Personalized, and Participatory), in our country by using the cutting-edge tools of molecular biology and information technology. As such, the center is unique in Serbia and the South East Europe region.

The state-of-the-art equipment existing at the Center (DNBSEQ-G400 (BGI), NextSeq 550Dx, 2000 and MiSeq (Illumina) Sequencing Systems; MinION (OxfordNanopore); MGISP-9600 High-throughput Automated Sample Preparation System) offered a wide range of application: the whole genome and whole exome sequencing, targeted sequencing, transcriptome sequencing and more. The analysis of data was facilitated by the access to the National Platform for Artificial Intelligence providing space for secure data storage, and to a supercomputer (Nvidia), critical for processing and analyzing Big Data.

Since its establishment more than 2000 SARS-CoV2 genomes were sequenced, 300 patient samples undervent diagnostic work-up. Pilot project for NIFTYPro screening was finished encompasing 58 pregnant women. First transcriptomes and metagenomes were analyzed.

Further implementation of NGS methodology in research and for diagnostics, and intensive development of bioinformatics, by strengthening the hardware and software capacities and the education of the bioinformatics team, will lead us in becoming driving force of the development of biomedicine and biotechnology in Serbia, extending collaboration beyond our borders.

Keywords: *NGS, 4P medicine, molecular diagnostics, NIPT, bioinformatics*

Topic*: Genetic Technologies*

PP-02

USING EXOME DATA FROM CLINICAL GENETIC TESTING TO INFORM FOR POPULATION CARRIER STATUS OF PATHOGENIC VARIANTS IN RECESSIVE MONOGENIC DISEASES: A SINGLE CENTER REPORT

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Background: Recessive monogenic diseases (RMDs) represent a significant burden on the healthcare system. Detecting at-risk couples for RMDs represents a major health goal since it may allow for different reproductive choices to prevent the birth of affected children. Here we aimed to identify the landscape of the recessive pathogenic variants among our population.

Materials and Methods: We have used clinical exome/whole exome sequencing data from 680 patients referred to our institution for clinical genetic testing. Only pathogenic variants in a panel of 1283 genes associated with childhood-onset life-limiting or disabling recessive conditions (panelapp.agha.umccr.org/panels/3139), reported as germline in ClinVar, were included in the analysis. Pathogenic alleles responsible for patients' clinical phenotypes were excluded from the study. Different filtering strategies were used, combining variant quality, automated ACMG classification and ClinVar review status.

Results: We have identified a total of 1220 alleles consisting of 622 different pathogenic variants in 364 genes. Approximately one third of the alleles (n=412) were included in 21 genes, each with more than 10 pathogenic alleles. Nine of the 21 genes were associated with metabolic diseases. Of the 116 distinct variants in the 21 genes group, 61 showed significantly different allele frequency compared to gnomAD exomes global frequency (19 after Bonferroni correction), suggesting a population-specific distribution of these variants.

Conclusion: In conclusion, our results provide insights into the population genetics of RMDs in our country and contribute to wider rare diseases knowledge base. They could also guide the national public health policies, such as design of preconception carrier screening and counselling.

Keywords: *recessive monogenic disease (RMD), carrier frequency, population level genetics, ClinVar pathogenic variants*

Topic: *Rare diseases*

PP-03

MOLECULAR DIAGNOSES IN THE GENETICS LABORATORY SERVICE WITH THE SEQSTUDIO GENETIC ANALYZER

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Abstract Text:

Background: The aim is the application of molecular diagnostic techniques for a rapid and accurate diagnosis for the most frequent diseases in the Albanian population such as β-thalassemia, Cystic Fibrosis (CF), Muscular Dystrophy Duchene/Becker and microdeletion syndromes.

Materials and methods: We performed Snapshot reaction for identification of 8 mutations of β-Thalassemia and 11 mutations of Cystic Fibrosis. MLPA technique was performed for the determination of deletions in DMD/DMB and microdeletions in 31 chromosomal syndromes. DNA fragments were analyzed through automated capillary electrophoresis and interpretation was performed with GeneMapper software.

Results: Among the 28 patients analyzed for β-thalassemia mutations, the most frequent mutations are IVS-I-110 (G->A), Codon 39 (C->T) and IVS-I-6 (T ->C).

Also with the same technique, 42 patients were analyzed for the CF mutations, where the most frequent mutation is F508del.

Among the 10 patients analyzed for DMD, one of them resulted with a deletion of codon 17 and 5 patients resulted with deletions between 45-53 codons. MLPA technique was performed also for molecular diagnosis of 9 patients suspected for genomics disease where one patient resulted with 15q11 deletion, the other one resulted with 4p16 deletion and one patient with 22q11 deletion.

Conclusion: SNaPshot and MLPA techniques are reliable, fast and cost-effective results are achieved for the molecular diagnosis of diseases with the most frequency in the Albanian population.

Keywords*: Molecular diagnosis, SNapShot, MLPA, Rare diseases*

Topic: *Rare diseases*

PP-04

ADVANCEMENTS IN PARALLEL CLINICAL EXOME SEQUENCING: A COMPREHENSIVE ANALYSIS OF ITS ROLE IN RARE DISEASES DIAGNOSTICS OVER A 24-MONTH PERIOD

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Background: Rare diseases, affect 5,9 percent of the population, pose unique challenges for patients, families, and healthcare providers due to their conflicting etiology. Diagnosis of the rare disease can be challenging, as the symptoms may be similar to more common illnesses, and there could be a lack of awareness among medical professionals. As a result, patients may experience delayed or incorrect diagnoses, leading to delayed treatment and more adverse consequences.

Materials and Methods: DNA extraction was performed on blood and amniotic fluid samples, followed by DNA quantification, and library preparation using TruSight One sequencing panel from Illumina. Sequencing was performed on the MiSeq Illumina platform and comprehensive bioinformatic data analysis using Varsome clinical software. Based on the detected variants, in-house primers for Sanger sequencing were designed for confirmation and availability of familial testing.

Results: Since it is a comprehensive approach to rare disease diagnostics, the findings will be presented in the form of patient case reports, categorizing variants as pathogenic, likely pathogenic, and variants of uncertain significance, which are associated with rare genetic disorders.

Conclusion: Overall, the ability to perform molecular diagnostics of rare diseases is essential for improving patient care, and addressing public health challenges associated with rare diseases. Clinical exome testing on amniotic fluid is a powerful tool for early diagnostics of rare genetic diseases in a developing fetus, providing parents with valuable information to prepare for potential medical or developmental needs.

Keywords: *Clinical exome sequencing, diagnostics rare diseases, next generation sequencing*

Topic: *Rare diseases*

PP-05

FREQUENCIES OF LIKELY PATHOGENIC AND PATHOGENIC VARIANTS IN THE THRACE REGION: A SINGLE CENTER EXPERIENCE

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Backgorund: Genetic evaluation is required for different diseases, such as cancer and hereditary diseases. Detected variants are essential for patients and important in determining diagnosis and treatment strategies. Identification of likely pathogenic/pathogenic variant (LP/P) frequencies is genetically necessary for the population.

Materials and Methods: This study included genetic analysis results of 1431 patients who applied to the Trakya University, Genetic Diseases and Evulation Center, an outpatient clinic with cancer findings (1062) and signs of hereditary disease (369) between March 2015 and 2023. Cancer patient samples were analyzed with the NextSeq-550-Illumina system using the Targeted DNA Panel (Illumina/Qiagen). A whole exome sequencing (WES) study was performed for patients with more than one hereditary clinical findings. Variants were classified according to ACMG-2015 guidelines.

Results: Of the 35 LP/P variants detected in cancer patients, four are above five. Regarding LP/P variant frequency, the most common variant is NM_007294.4(BRCA1):c.5266dupC (p.Gln1756ProfsTer74), with a frequency of 1.12%. Forty of the LP/P variants detected in patients with WES study were found to be more than five, and the most common variant was NM_000410.3(HFE):c.187C>G (p.His63Asp), and its frequency was 21.4%.

Conclusions: The variant we detected in the BRCA1 gene is the pathogenic variation defined as the founder mutation in the Ashkenazi Jewish population, and it is the most common pathogenic variation among patients in our region. The GnomAD_exome frequency of the pathogenic variant we detected in the HFE gene is G=0.109240. In terms of our current population, the percentage of finding this variant is relative

Keywords: *Whole exome sequencing, Next generation sequencing, Variant frequency, Cancer Hereditary disease*

Topic: *Other*

PP-06

POTENTIAL NEW GENES INVOLVED IN CYSTIC FIBROSIS PHENOTYPE

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Background: Cystic fibrosis (CF) is autosomal recessive disorder characterized by chronic respiratory problems and poor growth. CF is caused by defect in transmembrane conductance regulator (CFTR) protein. CF is diagnosed by sweat chloride analysis (>60 mmol/L) with the identification of two CF-causing variants of *CFTR* gene. With a longstanding history of *CFTR* gene analysis, our laboratory identified several patients with elevated sweat chloride and clinical manifestations of CF in whom no CF-causing mutations were detected after sequencing of whole coding region and testing for large insertion/deletion of *CFTR* gene. In order to elucidate genetic background of conditions that mimic CF we performed whole exome sequencing (WES) in two such patients.

Methods: Library preparation was done using DNA nanoball technology. Produced fastq files were mapped to hg38. VCF files were generated using GATK and annotated with InterVar and AnnoVar tools. Variants filtering for disease relevance was done using the following criteria: QC, GnomAD Allele Frequency, Functional consequences and phenotype-genotype relationship.

Results: *CACNA1H* and *MUC5B* genes were found to be impaired in both patients. Similar number of variants predicted to impair protein function were detected (27 and 25) in each patient. Loss of function variants were found in 7 and 11 genes, respectively.

Conclusion: Further assessment of selected variants will clarify their functional effect and relevance for the patient's clinical phenotype. WES analysis will help identify genetic aspects of disease and assist in optimal patient management in about 0.01% of patients with elevated sweat chloride and high clinical suspicion of CF that do not carry any CF-causing variants.

Keywords: *cystic fibrosis, WES, variant assessment, patient management*

Topic*: Rare diseases*

PP-07

BARDET-BIEDL SYNDROME – A RARE CASE WITH HEARING LOSS

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Background: Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive disorder caused by primary cilia- dysfunction and it is characterized by a wide spectrum of clinical manifestations. Pigmentary retinopathy, polydactyly, obesity, learning disabilities, various degrees of intellectual disability, hypogonadism in males, renal abnormalities, nystagmus, speech disorders, developmental delay, polyuria/polydipsia, ataxia, are all common symptoms of this condition. It affects males and females equally. Beside clinical manifestation, genetic testing may assist in diagnosing the disorder in selected cases. This syndrome has been related to twenty-two different loci (BBS1-BBS22).

Case presentation: We report the case of a 26-year-old male individual with delayed diagnosis who is presented with multi-system manifestations: truncal obesity, polydactyl- bilateral postaxial polydactyly of the toes, severe visual impairment, cognitive deficit, chronic kidney disease grade 3A and conductive hearing loss which is unusual and not a typical symptom in BBS. The patient's kidney function is monitored regularly and treated to slow down its progression. Genetic testing showed mutations in *BBS7* gene. Genetic testing showed a homozygous frameschift variant in the *BBS7* gene (c.712_715del; p.Arg238fs).

Conclusion: As there is no specific treatment for BBS, multidisciplinary care is required to prevent avoidable morbidity and mortality.

Keywords: Bardet-Biedl syndrome; Retinitis pigmentosa; Polydactyl Renal failure

Topic: Rare diseases

PP-08

RETROSPECTIVE EVALUATION OF GENES RELATED TO FATTY ACID OXIDATION DEFECTS FROM WHOLE-EXOME SEQUENCING (WES) ANALYSIS WITH CURRENT DATA

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Fatty acids are released from adipose tissue and undergo mitochondrial β-oxidation to meet energy needs during prolonged starvation and disease. Defects lead to inadequate energy production. Our objective is to retrospectively evaluate specific genes encoding fatty acid oxidation proteins via WES analysis, determine cohort carrier frequency, and correlate genotype-phenotype in patients with mutations.

We formed a panel of fatty acid oxidation genes (*ACADM, ACADS, ACADVL, CPT1A, CPT2, ECHS1, HADH, HADHA, HADHB, SLC25A20*). We retrospectively analyzed 485 patients' clinical data and mutations.

Cohort had 2.06% pathogenic/likely pathogenic mutation carriers and 8.24% Variants of Uncertain Significance (VUS). Cohort had 10.3% (50/485) with pathogenic, likely pathogenic, or VUS mutations in fatty acid oxidation genes. 12 of 43 individuals with mutations showed fatty acid oxidation defect-associated phenotype.

Autosomal recessive inheritance doesn't exclude clinical signs in heterozygous carriers. 27.9% with heterozygous mutations displayed fatty acid oxidation defect phenotype. Heterozygous state could contribute to clinical findings due to fatty acid oxidation defects affecting multiple systems.

Keywords: *Carrier frequency, Energy production, Next generation sequencing, Phenotype-genotype correlation, Population genetics*

Topic: *Metabolic and mitochondrial disorders*

PP-09

EVALUATION OF NEONATAL SCREENING FOR PHENYLKETONURIA IN NORTH MACEDONIA – PILOT STUDY

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Phenylketonuria (PKU) is autosomal recessive disorder due to phenylalanine hydroxylase deficiency causing blood phenylalanine (Phe) elevation and accumulation in all parts of the body, including brain. The pilot study for PKU in Macedonia started in June 2022 and it is still running. The phenylalanine was measured from dry blood spots collected 48-72 hours after birth on filter paper using fluorescent ninhydrin method. Presumptive positive value for phenylalanine was >182 μmol/L while equivocal zone was between the range 127-182 μmol/L. Second dry blood sample was analyzed in cases above 127 μmol/L. Final diagnosis is done by molecular testing on PAH (phenylalanine hydroxylase) gene.

In the period June 2022 – August 2023, 11438 newborns were screened. During this period, 6 newborns were called for second PKU test with recall rate of 0.052. Two of them had positive second screening test, one newborn with 742.5 μmol/L for Phe diagnosed as PKU and the other one with 185.7 μmol/L observed as hyperphenylalaninemia (H-PHE). Estimated incidence was 1/11438 for both diagnoses. Molecular diagnosis was performed by PAH gene analysis. In the newborn with classic PKU was found c.143T>C p.(Leu48Ser) pathogenic variant in PAH gene inherited from both parents. The newborn with H-PHE were detected two pathogenic variants c.898G>T p.(Ala300Ser) inherited from father and c.1208C>T p.(Ala403Val) from mother, and he is having normal values for phenylalanine still without diet.

Our results support the importance of PKU newborn screening for early testing and treatment with Phe-restricted diet therapy which prevents development of any intellectual disabilities and mental retardation.

Keywords: *Phenylalanine, Newborn screening, PAH gene*

Topic: *Metabolic and mitochondrial disorders*

PP-10

COMPOUND HETEROZYGOUS *DCHR24* GENE VARIANTS IN DESMOSTEROLOSIS: A CASE REPORT WITH DEVELOPMENTAL DELAY AND CORPUS CALLOSUM AGENESIS

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Background: Desmosterolosis is a rare autosomal recessive disease characterized by neurological problems, such as brain abnormalities and developmental delay caused by the pathogenic mutations in the *DHRC4* gene. Herein, we present a 3-year-old female patient with biallelic compound heterozygous variants in the *DCHR24* gene.

Materials and Methods: Our patient, a 3-year-old girl, was referred to our outpatient clinic due to development delay, failure to thrive, corpus callosum agenesis, strabismus, hypotonia, and abnormal hepatic enzymes. Since no pathogenic/likely pathogenic variant that could explain the clinical features was detected in chromosome and microarray analyses, we performed clinical exome sequencing (CES) analysis.

Results: CES analysis of the patient revealed the presence of two likely pathogenic variants in the *DCHR24* gene (*DCHR24* c.1412A>G;p.Y471C and *DCHR24* c.275C>T;p.T92M). In segregation analysis revealed that these variants are located in trans position.

Conclusions: Desmosterolosis is an extremely rare genetic disease due to DCHR24 gene variants. Our case contributes to the current literature by emphasizing the importance of advanced genetic testing methods such CES and parental analysis in the diagnosis of rare diseases.

Keyword: *Desmosterolosis, DCHR24 gene, CES*

Topic: *Rare diseases*

PP-11

A CASE REPORT OF A PATIENT WITH NEURODEVELOPMENTAL DISORDER WITH IMPAIRED SPEECH AND HYPERKINETIC MOVEMENTS: A NOVEL BIALLELIC VARIANT IN *ZNF142* GENE

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Background: *ZNF142* gene is associated with neurodevelopmental disorder with impaired speech and hyperkinetic movements-NEDISHM, which is characterized by developmental delay, intellectual disability, speech delay, and movement disorders. Here we present a case with a homozygous pathogenic novel variant in *ZNF142*.

Material and methods: An 8-year-old male patient with consanguineous parents was brought to our clinic because of developmental and speech delays, seizures, gait disturbance, intellectual disability. There were no abnormalities in his natal history. there was delay in gait, speaking, growth, and developmental milestones, microcephaly, hypertelorism, and loss of muscle strength. He had a seizure at 4 months old. He has attention deficit, hyperactivity, hyperkinetic movements in his extremities. His brain MRI showed immature myelinisation of posterior periventriküler white matter.

Result: His chromosomal and microarray analyses were normal. A biallelic c.3528_3529delTG; p.C1176fs*5 (NM_001105537.4) variant in *ZNF142* found by WES analysis.

Conclusion: NEDISHM was first described by Kahn et al.(2019) and has been reported 38 patients in total to date. We aimed to report this novel variant and show genotype phenotype correlation.

Keywords: *ZNF142, neurodevelopmental delay, speech delay, NEDISHM*

Topic: *Rare diseases*

PP-12

A FAMILIAL RETT SYNDROME CASE WITH DELETION AND INSERTION IN *MECP2* GENE

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Background: Rett syndrome is a progressive neuro develop mental disorder caused by mutations in *MECP2* gene.The spectrum of MECP2-related phenotypes in females ranges from classic Rett syndrome to variant Rett syndrome with a broader clinical phenotype. It affects approximately 1 in 10,000 live female births. Although inherited in X-linked dominant, pathogenic *MECP2* variants in patients with Rett Syndrome are mostly de novo. Were port here a rare familial case with a new variant.

Case: A 4-years-old girl wase valuated for develop mental delay and seizure. She was born to 30-year-old mentally handicapped G2P2 mother. Her parents were non-consanguineous. Maternal uncle and aunt had suffered seizures. On examination; she was making eye contact. She could sitting unassisted, crawl, but no independent walking. She could say a few simple words but not make sentences. Repetitive, stereotypic and movements were seen. She had no spasticity. Brain MRI was normal. EEG showed generalized epileptic activity.

Results: The *MECP2* gene sanger sequencing study showed a large deletion (128bp) and two different insertion in exon 4:1155_1282 in the case, and a larger deletion (236bp) in the mother and the same 21 bp insertion as her daughter: c.1155_1390. It was predicted to generate a premature termination codon. The heterozygous deletions were confirmed by the MLPA analysis.

Conclusions: Familial cases of RETT syndrome are rare. Here, a familial case with a novel large deletion, insertion, and clinical heterogeneity is presented as a contribution to the literature.

Keywords: *Familial RETT syndrome, MECP2, deletion, insertion*

Topic: *Rare diseases*

PP-13

A CASE WITH SPINOCEREBELLAR ATAXIA TYPE 10

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Background: Autosomal recessive spinocerebellar ataxia type10(SCAR10; MIM#613728) is associated with *ANO10*, encoding the transmembrane protein anoctamin10. Presently, disease has been identified more than 40 spinocerebellar ataxia (SCA) cases, with an estimated prevalence of %0.4-5 among hereditary ataxias. This study presents a SCA case with a novel *ANO10* gene variant. Methods: The patient with ataxia was referred to genetic clinic underwent a comprehensive evaluation, pedigree analysis, and cranial imaging studies. Whole exome sequencing (WES) was performed, followed by Sanger sequencing for segregation.

Results: The case was a 34-year-old male presenting with hereditary ataxia. Though the absence of consanguinity, the patient had similarly affected three other siblings. His symptoms began at 25 years of age, marked by unsteadiness, ataxic gait, and dysarthria. Cranial MRI revealed cerebellar hemisphere atrophy and significant changes in cerebellar folia. His earlier genetic tests ruled out the repeat expansion anomalies. WES uncovered two different heterozygous alterations in the *ANO10* gene (NM_018075.5), a known nonsense and a novel missense, both classified as pathogenic. Family segregation confirmed their compound heterozygosity; (c.[206T>A];[1628G>C]/p.[Leu69Ter];[Arg543Pro]).

Conclusions: Our study contributed a novel missense variant responsible for SCAR10. Moreover, the identification of two rare variants in compound heterozygous form in four affected individuals from the same family enhances the significance of this study. In conclusion, this case underscores the presence of a novel mutation and emphasizes the necessity for advanced molecular analyses to facilitate diagnosis and future treatment strategies for SCA.

Keywords: *SCA, SCAR10, Spinocerebellar ataxia, ANO10, Hereditary ataxia*

Topic*: Rare diseases*

PP-14

NEW APPROACH IN QUANTITATIVE ESTIMATION OF X CHROMOSOME CENTROMERE INSTABILITY IN ALZHEIMER DISEASE

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Background: Chromosome instability (CIN) in Alzheimer's disease has been found in peripheral blood lymphocytes, and also in neurons of affected individuals. CIN is a result of errors in chromosome segregation during mitosis leading to numerical and structural chromosomal abnormalities.

Material and Methods: Fluorescent In Situ Hybridization. (FISH) has been a method of choice for the evaluation of CIN in various diseases. We have studied a specific type of X chromosome instability, or premature centromere division (PCD) in interphase nuclei of the hippocampus brain tissue neurons from sporadic AD females. PCD was studied by using a new approach to FISH.

Results: Namely, we have established a methodology that allows quantitative analysis of centromere fluorescence intensity, i.e. the size of individual FISH spots, thus giving a more focused view of the centromere region of interest. By using the micro image system, our results show that quantitative FISH can distinguish PCD positive signals vs. PCD negative signals in cells of brain tissue.

Conclusion: This could be a specific biomarker in affected cells in order to verify CIN, thus supporting the established qualitative analysis of FISH spots in the study of centromere and chromosomal alterations in interphase nuclei of patients affected by AD.

Keywords: *Chromosome instrability, Alzheimer disease, X chromosome, premature centromere division biomarker*

Topic: *Neurogenetics and intellectual disability*

PP-15

TREM2 R47H AS A RISK FACTOR FOR ALZHEIMER'S DISEASE IN SERBIAN PATIENTS

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Background: Alzheimer's disease (AD) is a chronic neurodegenerative disease, which clinically manifests by the development of dementia. Studies of genetic susceptibility to AD indicate a whole range of genes and their variants that can potentially influence an individual's susceptibility to develop the disease. AD17 represents the form of Alzheimer's disease associated with mutation(s) in the TREM2 gene, encoding triggering receptor expressed on myeloid cells 2.

The aim of this study was to determine the frequency of R47H variant of the TREM2 gene in the cohort of AD patients, to compare the frequency of the variant in the population of AD patients and the control group, and to determine the possible association of a certain genotype with the susceptibility to develop the disease. Study comprised 168 consecutive patients with AD and 190 healthy controls. The clinical inerview, neurologic examination, and neuropsychological set of cognitive assesment was performed by neurologists and neuropsychologists in expertise with neurodegenerative deseases.

In the group of AD patients the frequency of C allele was 98.8%, while the T allele was present in 1.2% of patients. The frequency of the T allele was statistically significantly higher among AD patients than among the control group ($p<0.05$). The frequency of homozygotes without mutation (CC genotype) was 98%, while the frequency of heterozygotes for the mutation (CT genotype) was 2% among patients with AD, and the frequency of homozygotes without mutation (CC genotype) was 100% among healty controls.

Our study indicated a possible association of the heterozygous form of the R47H variant of TREM2 gene with the susceptibility to AD in Serbian patients.

Keywords*: Alzheimer's disease, polymorphism prevalence, TREM2, R47H*

Topic*: Neurogenetics and intellectual disability*

PP-16

ARTHROGRYPOSIS AS A RARE PRESENTATION OF NOONAN SYNDROME TYPE 2? THE CHALLENGES OF GENETIC VARIANTS OF UNCERTAIN SIGNIFICANCE IN CLINICAL PRACTICE

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Background: Arthrogryposis is the term used for multiple congenital contractures that affect two or more different areas of the body.

Next generation sequencing techniques rapidly expand our knowledge about it's genetic etiology, but the identification of the number of variants of unknown significance (VOUS) brings challenges in clinical practice. Recently, arthrogryposis was associated with biallelic mutation in LZTR1 gene, as a part of Noonan sindrome type 2 (NS2). Among 30 patients with NS2 reported so far, two had arthrogryposis.

Materials and methods: Here we present a patient with arthrogryposis with inconclusive LZTR1 gene findings. Patient's exomes were sequenced using NextSeq (Illumina) and the results were verified by Sanger sequencing.

Results: The patient is a 7-year-old girl with arthrogryposis and some NS2 features, including a broad neck and a history of atrial septal defect and polyhydramnios. Two rare heterozygous variants in trans position in LZTR1 gene were identified, pathogenic c.120C>G and c.2131G>A which is classified as VOUS in the absence of functional studies. Variant c.2131G>A is observed at an extremely low frequency of 0.009% in the gnomAD database and most prediction bioinformatics tools assign a deleterious effect of this variant on structure/function of protein. Also, analyses failed to identify pathogenic variants in other genes associated with arthrogryposis. These results led to NS2 being considered as a potential diagnosis, but further studies are needed to determine the role of c.2131G>Avariant.

Conclusions: This paper shows the challenges faced by clinicians in the era of genomics and possibly increases the knowledge of genetic findings in arthrogryposis.

Keywords: *arthrogryposis, Noonan syndrome type 2, LZTR1 c.2131G>A*

Topic: *Rare diseases*

PP-17

INVESTIGATION OF *SHOX* GENE MUTATIONS

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Introduction: Short stature (SS) is a definition in which the mean height of the same population is below -2 standard deviation (SSD). SS's genetic etiology includes chromosomal abnormalities and single gene disorders, and one of the most important is the *SHOX* (Short Stature HOmeoboX) gene. The *SHOX* gene, located in the PAR1 region of the sex chromosomes, controls the formation of many organs and the growth of bones in the lower and upper extremities during early embryonic development. It has been shown that *SHOX* gene mutation causes idiopathic short stature (ISS), Leri-Weill dyschondrosteosis (LWD), Langer mesomelic dysplasia (LMD), SS in Turner syndrome with additional skeletal findings.

Methods: This study was conducted in 120 patients who consulted to the Istanbul University, Istanbul Faculty of Medicine, Department of Medical Genetics with a pre-diagnosis of SS for genetic evaluation in the last three years. Karyotype analysis was performed on all cases, and possible microscopic chromosomal anomalies were excluded. Then, fluorescence in-situ hybridization (FISH) and a-CGH analysis were applied, respectively. A gene panel test prepared with genes associated with SS was performed in 10 cases without any anomaly detected in cytogenetic and molecular cytogenetic methods.

Results: Chromosomal anomaly in eight cases (6.6%), deletion in eight cases (6.6%) by FISH analysis and in three cases (2.5%) in a-CGH technique; anomalies associated with the *SHOX* gene were detected in a total of 13 cases (11%). This rate was observed to be consistent with studies in the literature.

Conclusion: In this study, cytogenetics, molecular cytogenetics and Next Generation Sequencing results of 120 SS cases will be discussed.

Keywords: *Short stature, SHOX gene, Chromosomal abnormalities*

Topic: *Rare diseases*

PP-18

APPLICATION OF ARRAY CGH IN DETECTION OF MARKER CHROMOSOME- A CASE REPORT

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Introduction: Recent studies confirm that a variation of copy number in the human genome are important cause of intellectual disability. There are a lot of novel syndromic cases described in the literature where microdeletion/duplication is the underlying cause of the disease. The origin of extra marker chromosomes often remain undetected with conventional cytogenetic methods (karyotype, fluorescent in situ hybridization).

Case report: We report on a patient with moderate intellectual deficiency. She is the third child in a family of healthy and unrelated patients with nonremarcable family history. Developmental milestones were detected early in life. At the admittance at the hospital, she had short stature, dysmorphic stigmata, IQ of 65, poor vocabulary and happy demeanor. Since pubertal signs were not present at the age of 12, karyotype was performed with the following result- 47,XX,+mar. The effort for detecting the origin of the small marker chromosome with several FISH probes for common marker chromosomes remain unsuccessful at that moment. Array CGH performed years after showed chromosomal alteration on both chromosomes occurred de novo: - arr 2q13q14.1(110,639,619-112,354,279) x3 (1,715 kb); arr 8p23.1(9,340,150-10,672,631) x3(1,332 kb).

Discussion: Although small, both microduplications that comprise the marker chromosome include many genes that are responsible for impaired mental development. Most of the phenotypic effects of microduplications are due to changes in a several dose-sensitive genes or, rarely, in a single gene. The etiology of microduplication lies upon the non-even crossing-over event on both chromosomes during meiosis.

Conclusion: Novel technologies such as array CGH are essential in detecting minor chromosomal changes.

Keywords: *intellectual disability microdeletion/duplication Array CGH*

Topic: *Neurogenetics and intellectual disability*

PP-19

CLINICAL SIGNIFICANCE OF MICRODELETIONS AND EPIGENETIC MODIFICATIONS ON CHROMOSOME *11P15.5* IN PRENATAL AND POSTNATAL DIAGNOSIS

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Background: Molecular characterization of imprinted gene clusters of genetic and epigenetic regulations on chromosome 11p15.5 region plays a vital role in growth and development. Beckwith-Wiedemann syndrome OMIM 130650 is relatively rare, a pediatric overgrowth disorder with an estimated prevalence of 1/13.700 manifesting equally in males and females. The chromosome 11p15.5 region has two distinct regulatory domains separated by a non-imprinted region. The domains are named IC1 and IC2, these centers are also called differentially methylated regions (DMR). The IC1 gene cluster is controlled by *IGF2/H19* domain and the IC2 is controlled by *CDKN1C/KCNQ1OT1/KCNQ1* domain.

Materials and methods: Our study included eighty-six cases who applied to Trakya University Health Research and Application Center, Genetic Diseases Evaluation Center, with pre-diagnosis of BWS between the years of 2015 January- 2023 June. DNA samples isolated from the peripheral venous blood of the patients were analyzed with the Multiplex ligation-dependent probe amplification method using probe ME030-C3.

Results: As a result of analysis related to the 11p15.5 region of the cases, we detected epigenetic modifications that are associated with BWS. Nine of eighty-six cases were diagnosed with BWS. Five of these nine cases were prenatal. One of the cases was diagnosed with Silver Russell syndrome.

Conclusions: Molecular characterization of this region has an important part in the diagnosis process. The methylation of these regions determines the clinical findings of patients. Herein in our study, the diagnostic rate is 10.4%. The aim of our study is to present the importance of this heterogeneous region in prenatal and postnatal cases.

Keywords: *Beckwith–Wiedemann syndrome, Chromosome 11p15.5, Epigenetic modifications, Prenatal diagnosis, Postnatal diagnosis*

Topic: *Rare diseases*

PP-20

LERI-WEILL DYSCHONDROSTEOSIS SYNDROME, PATIENT WITH 45,X,PSU DIC(X;15) (P22;P11.2) DN TRANSLOCATION CAUSES THE *SHOX* LOCUS HETEROZYGOSIS DELETION

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Background: Leri-Weill Dyschondrosteosis is a Pseudoautosomal dominant inherited disorder characterized by Short stature, Mesomelia, Madelung wrist deformity. This disorder caused by shox heterozygous deletion in X chromosome. *SHOX* homebox located in Xp22.33 region.

Methods: İn this case report, We present an individual has symptoms of Shox deletion who has 45,x,PSU DİC(x;15)(P22;P11.2)dn translocation . We performed Karyotype and *SHOX* FISH analysis on patient and also her parents.

Results: We present a 13 year-old female patient exhibiting the features of this syndrome such as 'Short stature,Madelung deformity, and Mesomelia'. Patient has regular menstrual cycles, normal brain MR results, normal echocardiogram signs and normal intellectual devolopment.Karyotype analysis detected, Patient is a carrier of with whole –arm reciprocal translocation which is -45,x,PSU DİC(x;15)(P22;P11.2)- Evantually, this unbalanced translocation causes to heterozygous deletion in *SHOX* region in X Chromosome. FİSH analysis demonstrated the deletion in SHOX homebox. As a result of the chromosome analysis performed on the patients mother and father, it was determined that this change was *de novo*.

Conclusion: This case report indicates the unbalanced translocations can cause deletion of some functional *SHOX* and OMIM morbid genes. Case shows the importance of structural and functional studies and emphasizes that evaluate this abnormal results with clinical correlation of patient

Keywords: *Short stature, Genetics, translocation, SHOX*

Topic: *Rare diseases*

PP-21

MOLECULAR CYTOGENETICS OF NON-SYNDROMIC POLYDACTYLY

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The most prevalent congenital limb malformations are syndactyly and polydactyly, which are characterized by fused and extra digits, respectively. Syndactyly is thought to affect 1 in every 2,000 to 3,000 live births, while polydactyly affects 1 in every 700 to 1,000 live births. The etiologies of syndactyly and polydactyly remain poorly known due to their wide phenotypic and genetic variation, despite their relatively frequent clinical appearance. There also doesn't seem to be a single comprehensive publication that summarizes all syndromic and nonsyndromic syndactyly and polydactyly presentations, and there is definitely no resource that maps all syndromic and nonsyndromic syndactylies and polydactylies to their genetic bases, despite the fact that concrete knowledge of genotypic links has been established for some variants of syndactyly and polydactyly.

We examined non-syndromic dactyls with array cgh in our group of 35 patients. Different sizes of genomic changes were detected in 12 patients.

There are nine unique kinds of nonsyndromic syndactyly, and at least 11 loci and eight related genes have been found. The diverse genetic basis and inheritance patterns of the dactylies reflect this phenotypic diversity. Numerous genes, such as the hedgehog pathways (SHH and IHH), WNTs, HOX genes (especially HOXD13), GJA1, LMBR1, FMN1, GREM1, LRP4, SHFM2, GLI3, and cartilage-derived morphogenetic proteins, have been linked to specific syndactyly types, but the genetic basis of nonsyndromic subtypes VI and IX is still unknown. The advantages of polydactyly and syndactyly genetic diagnosis extend beyond the affected person.

Keywords: *Molecular Cytogenetics, Non-Syndromic Polydactyly, array CGH*

Topic: *Genetic Technologies*

PP-22

EVALUATION OF THE ROLE OF VARIANTS IN *JAK1* AND *STAT1* GENES ASSOCIATED WITH MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL INFECTION IN NEUROINFLAMMATION-RELATED NEUROLOGICAL DISEASES

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Background: Mendelian Susceptibility to Mycobacterial Disease (MSMD) is an immunodeficiency disorder caused by defects in IL-12/IFN mediated immunity pathways including *JAK1, STAT1, IFNG, IKBKG, ZNFX1*, and *PDCD1* genes, linked to neurological findings and neuroinflammatory diseases. The study aims to identify and correlate variants in these six genes with neurological findings in patients referred for genetic diagnosis with MCA-MR indication.

Materials and Methods: This study examined variants in six MSMD-related genes in 56 patients and these variants assessed as pathogenic or unknown clinical significance were reviewed in-house WES data and searched using tools like MutationTaster, SIFT, and PolyPhen2.

Results: The study examined genetic variants in exonic and splice sites in six candidate genes in 56 cases. Only *STAT1* and *JAK1* genes were found in three out of 56 patients. A unique homozygous variant that has not been previously reported in *STAT1*; c.1341C>A was classified as disease-causing, benign, and tolerated by MutationTaster, PolyPhen2, and SIFT. Heterozygous *JAK1* variants; c.1541G>A and c.1594C>T were found in two different cases. The first variant was described as polymorphism and probably damaging, while the second variant was categorized as disease-causing and probably damaging by MutationTaster and PolyPhen2. There is no available information for either of these variants in the SIFT in silico database. None of these three variants were found in our in-house WES data.

Conlusion: This study examines MSMD genes involved in the JAK-STAT pathway associated with neuroinflammation, but further experimental studies are needed to demonstrate functional effects and their role in neurological findings.

Keywords: *MSMD, Neuroinflammation, Neurological disease JAK1, STAT1*

Topic*: Rare diseases*

PP-23

A *DE NOVO* LARGE 5Q35 DUPLICATION AS A RESULT OF TRANSLOCATION; REVERSED SOTOS SYNDROME WITH CRANIOSYNOSTOSIS

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The duplication of 5q35 region encompassing the critical *NSD1* gene, has been associated with a phenotype, clinically described as a reversed Sotos Syndrome (reversed sos). This phenotype commonly includes short stature, microcephaly, Developmental Delay/Intellectual Disability (DD/ID) and distinctive facial features. Clinical findings can vary depending on the size, location and genes contained within the duplicated region. We present a patient with a larger duplication of the 5q33.3–q35.3 region, including *NSD1* and *MSX2* genes, in order to contribute to the phenotypic spectrum and to state an opinion to the discussion of the term 'reversed sos'.

A standard karyotype analysis and Agilent technology-based array CGH analysis were conducted on a 3-month-old male patient who presented with symptoms of severe laryngomalacia, dysmorphic features, and craniosynostosis without microcephaly.

By karyotype analysis, a reciprocal translocation between chromosomes 1 and 5 was detected. In the array CGH analysis, a de novo duplication of ~20 MB in size at the 5q33.3q35.3 region, including the *NSD1* and *MSX2* genes along with over 200 other genes, was identified.

The craniosynostosis finding observed in the patient was considered to be associated with the *MSX2* gene within the duplicated region due to its previously reported gain-of-function mutations. The absence of short stature and microcephaly findings in the patient who harbors duplicated *NSD1* gene will provide new insights, along with the potential impact of other duplicated genes, to our understanding of this known duplication, since it does not encompass the specific features associated with 'reversed Sos'.

Keywords: *craniosynostosis, microcephaly, de novo translocation, array CGH duplication*

Topic*: Rare diseases*

PP-24

THE IMPORTANCE OF MULTIDISCIPLINARY APPROACH AND EARLY GENETIC TESTING IN A PATIENT WITH 7Q11.23 DUPLICATION SYNDROME. A CASE REPORT.

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Background: 7q11.23 duplication syndrome is defined as a heterozygous recurrent duplication of the Williams-Beuren syndrome critical region (WBSCR), a 1.5 to 1.8 Mb-long region, containing 26 genes. It is a rare disease, affecting 1:7500 to 20000 people.

Here we report a case of a 9-year-old boy who firstly presented with hypotonia, delayed development of speech and motor skills, followed by ADD, resulting in severe difficulties in daily activities and social behavior. Despite developmental delay, patients often have congenital heart defects, unilateral renal agenesis and other congenital anomalies.

Materials and methods: Physical examination and evaluation by clinical speech therapist. Ultrasound scanning of the heart and viscera. Genomic testing - array Comparative Genomic Hybridization (aCGH).

Results: The patient has a small fund of words, where the vocabulary does not correspond to the age. He has difficulties in understanding, structuring and expressing linguistic thought. Lack of concentration, attention and focus are also noted. The patient has severe difficulties in reading and writing. Cardiac examination, ultrasound of the heart and viscera did not reveal any abnormality. The aCGH testing revealed a pathogenic de novo duplication in the WBSCR, 1.6 Mb in size, in the proband's sample.

Conclusion: Multidisciplinary approach and early genomic testing is absolutely needed in these patients and it can have a great positive effect if integrated from the earliest age.

Keywords: *7q11.23 duplication syndrome, aCGH development delay*

Topic: *Rare diseases*

PP-25

THE IMPACT OF WHITE MATTER ALTERATIONS IN 16P11.2 DELETION AND DUPLICATION SYNDROME

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Background: Copy number variants (CNVs) in the chromosomal locus 16p11.2 predispose individuals to neurodevelopmental disorders like autism spectrum disorder, intellectual disability, epilepsy, dysmorphic features, congenital anomalies, macrocephaly, and microcephaly. Intracortical myelin is believed to play a significant role in neural circuit and functional network development, with consistent evidence of typical network connectivity in children with neurodevelopmental disorders. Emerging imaging studies indicate abnormal white matter microstructure, potentially explaining clinical phenotypes like cognitive decline and developmental delay. Our study investigates myelin-related changes in the corpus callosum using a mouse model with 16p11.2 alterations.

Materials and Methods: We investigated white matter alteration and oligodendrocyte maturity level in 16p11.2 deletion and duplication mouse models.

Results: Our findings indicate that compared to controls, the expression level of myelin is altered in both the 16p11.2 duplication and deletion mouse models. Importantly, these myelin changes do not improve with mouse aging. Furthermore, the level of mature and immature oligodendrocytes were comparable in 16p11.2 CNVs mouse model. However, we observed changes in myelin thickness in the area of the corpus callosum.

Conclusion: These findings suggest that alterations in myelin microstructure are associated with changes in the 16p11.2 locus, which may contribute to the neurodevelopmental disorders caused by 16p11.2 CNVs.

Keywords: *16p11.2, Copy number variants, myelin, oligodendrocytes*

Topic: *Neurogenetics and intellectual disability*

PP-26

A NOVEL SPLICE SITE VARIANT IN *FLNA* GENE IDENTIFIED IN THREE SIBLINGS AFFECTED WITH MULTIPLE CONGENITAL ANOMALIES

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Background: Multiple congenital anomalies (short stature, bilateral hearing loss, muscular thickening of lower extremities, distal hyper-extensibility, congenital heart disease) observed in similarly-affected three siblings of a family with consanguineous parents suggest a genetic cause for this disease phenotype. Since it is more efficient in finding of genetic changes underlying such clinically ambigious cases, we performed WES analysis in affected siblings with aiming to reach clinically significant variants.

Methods: We performed WES, and Sanger sequencing for segregation analysis.

Results: In the index and his affected sibling, we found hemizygous c.1829-1G>T splice-site variant in FLNA, while not in the healthy sibling. Segregation analysis has shown that a second affected sibling was also hemizygous for same variant, while mother heterozygous and father normal.

Conclusion: The X-located FLNA gene encodes a cytoskeleton component, filamin A that regulates cellular signaling pathways by binding to over 70 proteins to perform cellular adhesion, migration, and survival. Pathogenic FLNA variants are associated with a wide spectrum of clinical findings affecting connective tissues in skeletal and cardiovascular systems. Its gain-of-function variants cause various bone dysplasias, while loss-of-function variants are responsible mostly for X-linked cardiac valvular dysplasia with variable soft connective tissue involvement. We found a novel splice-site variant that may cause a multisystem-disorder. Overlapping clinical findings in three affected siblings suggest that muscular thickening of lower extremities can be distinctive for this variant, despite further studies are needed to support this genotype-phenotype correlation.

Keywords: *FLNA, whole exome sequencing, multiple congenital anomalies, rare diseases, consanguineous parents*

Topic: *Rare diseases*

PP-27

NEW ERA IN ONCOGENETICS: BULGARIAN EXPERIENCE IN BREAST AND OVARIAN CANCER

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The analysis with NGS panel for the most common genes associated with Breast and Ovarian cancer is important for adequate genetic counseling and future planning in Bulgaria. Different kind of genetic variants in *BRCA1* and *BRCA2* genes are associated with high risk for breast (female), prostate (male), pancreatic cancer and melanomas.

We use NGS panel which includes 26 most common genes and screened 100 Bulgarian woman for genetic variants connected with breast and ovarian cancer.

The most frequent mutation in Bulgarian patients is in *BRCA1* gene: c.5266dupC. We found this mutation ten times. Other mutations in the same gene are small deletions, duplications and point mutations. In *BRCA2* gene we found c.7913_7917delTTCCT and c.6914delC. Another commonly affected genes are *STK11* (two mutations), *ATM* (three mutations), *RAD50* (two mutations), *NF1, EPCAM* and *CHEK2* genes.

The genetic analysis with NGS panel for the most common genes associated with Breast and Ovarian cancer is important in cases: with clinical findings, in familial cases, in hormonal therapy and sometimes before surgical operation.

Keywords: *Breast Cancer, Ovarian Cancer, NGS Panel, Segregation*

Topic: *Cancer genetics*

PP-28

THE ASSOCIATION OF *ACSL1* RS8086 POLYMORPHISM WITH CLINICOPATHOLOGICAL CHARACTERISTICS OF COLORECTAL CANCER PATIENTS

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Background: Colorectal cancer cells rely upon fatty acids for proliferation, survival and metastasis, and utilize them for the production of energy and membrane maintenance. Both fatty acid biosynthesis and β-oxidation are found to increase in many cancers. Acyl-CoA synthetase long-chain family member 1 (ACSL1) supports fatty acid synthesis and β oxidation. Overexpression of ACSL1 has been observed in colon cancer and is associated with poor clinical outcomes. A functional polymorphism, rs8086, C>T is located in the 3'-UTR region of the *ACSL1* gene.

The aim was to investigate the association of rs8086 polymorphism with clinicopathological characteristics of colorectal cancer patients.

Materials and methods: The study included 194 patients with colorectal cancer, 116 men (59.8%) and 78 (40.2%) women, mean age 62.18±12.04 years, who underwent surgical treatment at Clinic for digestive surgery, Clinical Centre of Serbia. Genotypes were detected by Real-time PCR. Information about tumor location, histological differentiation, lymph node metastases, presence of distant metastases and stage of the disease was recorded.

Results: Our results have shown that patients carriers of T allele (CT or TT genotype) had colon cancer significantly more often than rectal cancer (p=0.006). It has also been observed that distant metastases were significantly more frequent in carriers of TT genotype in comparison to carriers of CC or CT genotype (p=0.046). There were no statistically significant associations with other analyzed clinicopathological characteristics.

Conclusions: *ACSL1* rs8086 polymorphism may be associated with tumor location and the occurrence of distant metastases in colorectal cancer patients.

Keywords: *Colorectal cancer, ACSL1 Polymorphism, Rs8086, Tumour metastasis*

Topic: *Cancer genetics*

PP-29

DROPLET DIGITAL PCR AS A MOLECULAR TOOL FOR THE DETECTION OF THE *EGFR* T790M MUTATION IN NSCLC PATIENTS WITH THE *EGFR* ACTIVATING MUTATIONS

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Background: Almost 50% of NSCLC patients who initially showed a successful response to tyrosine kinase inhibitors targeted therapy (TKI therapy) eventually develop acquired *EGFR* T790M mutation. The T790M secondary mutation can cause the resistance to the targeted therapy and disease relapse. Since this mutation can be present at very low frequencies in liquid biopsy samples, droplet digital PCR (ddPCR), due to its high sensitivity, has opened the possibility for minimally invasive monitoring of the disease during TKI targeted therapy.

Materials and methods: For this research, a total of 45 plasma samples from NSCLC patients with previously detected *EGFR*-activating mutations were analyzed. Extracted circulating free DNA was amplified and examined for the presence of T790M mutation using ddPCR technology. For the data analysis, QuantaSoft Software was used.

Results: Among 45 tested plasma samples, a total of 14 samples were identified as positive for the T790M mutation. Same samples evenutally showed the presence of T790M mutation in FFPE. Droplet digital PCR showed its great advantage in high sensitivity detection of rare allele variants. Our ddPCR assay detected T790M mutant allele in frequencies from 0,1%. Average number of droplets generated by ddPCR was 9571.

Conclusion: Monitoring of the T790M mutation has an important role in examination of the effects of the prescribed TKI therapy. Since monitoring of potential changes during TKI therapy requires repeated sampling, our results showed that ddPCR technology has made it possible to use the liquid biopsy as an adequate minimally invasive alternative for SNP detection.

Keywords: *Droplet digital PCR, T790M secondary mutation, liquid biopsy, NSCLC patients, TKI targeted therapy*

Topic: *Cancer genetics*

PP-30

EXOSOMAL MICRORNAS DERIVED FROM ORAL PREMALIGNANT (DOK) AND MALIGNANT (SCC-25) CELL LINES

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Small extracellular vesicles called exosomes play a significant role in intercellular communication and tumor progression. In this study, we examined exosomal microRNAs (miRNAs) from oral premalignant and malignant cells to uncover possible biomarkers for oral cancer development and progression.

Commercial cell lines, premalignant (DOK), and squamous carcinoma (SCC-25), were used. Cells were cultured in free-serum medium (20h). Exosomes were isolated from the medium by magnetic sorting (CD63 beads). Purity and identity were verified by flow cytometry, transmission electron microscopy, and nanoparticale tracking analysis. Total RNA from exosomes was isolated, and quantitative reverse transcription-polymerase chain reaction was used to measure the expression levels of two oncogenic (miR21, miR31) and one tumor-suppressor (miR133) miRNA.

Isolated exosomes were intact and round-shaped, or aggregated into groups. There were no statistically significant differences between exosomes mean diameters (107.3 nm vs. 106.9 nm), nor particle concentrations (1.80x1011 particles/ml vs. 1.93x1011 particle/ml) from DOK and SCC-25 samples, respectively. However, miR21 and miR31 were significantly upregulated in the exosomes derived from SCC-25 compared to those from DOK.

Findings suggest exosomal miRNAs might serve as biomarkers for oral cancer diagnosis and prognosis. Understanding how exosomal miRNAs affect oral cancer formation and progression might lead to non-invasive diagnostics and targeted therapies.

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Keywords: *Exosomes, microRNAs, oral cancer, premalignant cells, magnetic sorting*

Topic*: Cancer genetics*

PP-31

THE MOLECULAR CHANGES THAT LACK THE PRESENCE OF THE *FGFR3* OR *CDKN2A/2B* DEFECTS IN BLADDER CANCER PATIENTS FROM THE N. MACEDONIA USING WHOLE EXOME SEQUENCING

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Background: Bladder cancer (BCa) is one of the most common malignancies worldwide with more than 570,000 new cases annually. Literature data have implicated the involvement of *FGFR3* or *CDKN2A/2B* defects with BCa. We evaluated the molecular changes in BCa patients that lack the presence of those common driver mutations.

Materials and methods: We have analyzed a total of 34 tumor tissue samples using whole exome sequencing (WES). The average age of the tested group was 64.5 ± 11.1 years, of which 28 were males and 6 were females. Histopathological and clinical features were available for 26 patients, of which 17 had the early-stage disease (Ta-T1), while 9 had advanced disease (T2-T4).

Results: WES analysis detected 151.622 variants of which 83 were pathogenic/likely pathogenic variants. Ten of these mutations were present in 30/34 (88.0%) of patients and were distributed in genes previously associated with BCa, of which the most common was *TP53* gene (found in 9/34 patients, 26.5%), followed by *PIC3CA* gene (6/34, 17.6%), RB1 gene (5/34, 14.7%), *KRAS* gene (3/34, 8.8%), *BRCA2* gene (2/34, 5.8%) and *VHL, FGFR3, FBXW7, RXRA*, and *ERBB2* genes (1/34, 2.9% each).The *TP53* mutations were predominantly found in patients with more advanced tumors (stage T2-T4), whereas mutations in the *PIK3CA* and *RB1* genes were detected in patients with early stages (Ta-T1). Copy Number Variations (CNV) analysis showed 39 deletions and 1 duplication in tumor tissues of 21/34 patients (61.8%); most of these patients had ≥2, and 6 patients had >7 CNVs.

Conclusions: No common driver mutation was detected in a group of BCa patients that lack the common *FGFR3* or *CDKN2A/2B* driver mutations. The most common defect was the TP53 mutation that was associated with an advanced stage indicating its primary role in the progression of the disease.

Keywords: *Bladder cancer, tissue, whole exome sequencing (WES), pathogenic/likely pathogenic variants.*

Topic: *Cancer Genetics*

PP-32

THE ROLE OF FIRST-LINE *BRCA* SCREENING METHOD FOR POPULATION-SPECIFIC PATHOGENIC VARIANTS IN BREAST CANCER PATIENTS

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Background: *BRCA* genetic testing is recommended in breast cancer (BC) patients who meet specific criteria, most importantly positive family history and early age of onset (<40 years). However, many BC patients who carry *BRCA* PVs are not tested because they do not fulfil these criteria. We aimed to design a fast, accurate and cost-effective method for *BRCA* screening in unselected BC patients.

Materials and methods: Utilizing data on prevalent *BRCA1/2* pathogenic variants (PVs) in Europe and our initial findings on population-specific *BRCA* PVs, we designed a method based on single base extension, targeting 14 *BRCA* PVs. Using this method, we have analyzed 1870 unselected BC patients. In parallel, a total of 774 BC patients were analyzed with a panel of 94 cancer genes.

Results: A total of 58 BC patients were positive for one of the 14 PVs, giving a detection rate of 3.1% (58/1870). Seventeen of the *BRCA* positive BC patients did not report a positive family history, 30 were older than 40 years, while eight BC patients did not meet both of these criteria and most probably would not have been tested if *BRCA* testing criteria were followed. NGS cancer panel testing in 774 BC patients identified a total of 36 different *BRCA* PVs in 106 BC patients, among which one relatively common PV which will be included in the updated screening panel. This will increase the detection rate of the screening method from 54.7% to 59.4%.

Conclusion: A first-line *BRCA* screening tool allows for cost-effective *BRCA* testing in unselected BC patients and identification of *BRCA* carriers who do not meet the testing criteria. Identifying *BRCA* carriers not only enhances patient management but also offers opportunities for cancer prevention in their families.

Keywords: *BRCA1/2 genes, pathogenic variants, population-specific, screening*

Topic: *Cancer genetics*

PP-33

CONVENTIONAL AND EMERGING PROGNOSTIC MARKERS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: The occurrence of novel prognostic factors for risk stratification in childhood acute lymphoblastic leukemia (cALL) along with the conventional ones, necessitate a more profound evaluation of their combined and independent prognostic significance.

Material and methods: We analysed the clinical (age, WBC count), biological (immunophenotype), cytogenetic (gene fusions, copy number alterations-CNA) and molecular (MRD) characteristics of 50 cALL patients. Gene fusions and CNAs associated with ALL were identified by qRT-PCR and MLPA methods, respectively. MRD at the end of induction (EOI) was determined with NGS analysis using patient-specific IGH/TCRG gene rearrangements.

Results: During a median follow-up of 40 months, 6/50 patients relapsed presenting MRD>1E-3 in 5/6 of them. Hyperdiploidy was detected in 14/45 (31%) patients, (6 with MRD>1E-3 at EOI). All patients with ETV6-RUNX1 gene fusion (15%) had MRD clearance at EOI and three co-occurred with either *CDKN2A/2B, PAX5, BTG1* or *ETV6* deletions. One of each *CDKN2A/2B, IKZF1* or *RB1* deletions were found in TCF3-PBX1 patients (6,5%). *CDKN2A/2B* and *PAX5* deletion was found in both SIL-TAL1 and BCR-ABL1 patients, the latter with MRD>1E-3 (who eventually relapsed). *CDKN2A/2B* deletions (27%) occurred in 7 other patients, with different MRD levels. *IKZF1* deletions (13%) were associated with higher MRD levels, especially in one T-ALL patient with IKZF^{plus} subtype (combined *CDKN2A/2B* deletion; MRD>1E-1).

Conclusion: Our findings suggest that CNAs for genes associated with ALL should be incorporated in clinical strategies, and along with gene fusions, clinical and biological factors, to obtain more precise risk group stratification. MRD at EOI should remain the primary tool for making subsequent treatment decisions.

Keywords: *ALL, MRD, prognostic factors*
Topic: *Cancer genetics*

PP-34

PATHOGENIC MUTATIONS IN THE *FLCN* GENE IDENTIFIED IN A FAMILY WITH APC-NEGATIVE FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

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Introduction: Familial adenomatous polyposis (FAP) is a hereditary syndrome associated with increased susceptibility to colorectal cancer (CRC). Germline mutations in the APC and MUTYH gene are present in 70% and ~10% of the FAP patients, respectively. However, in a significant proportion of these patients (>20%), the genetic background of the disease development remains unexplained.

Material and methods: Peripheral blood DNA samples from 15 polyposis patients were analyzed for the presence of germline mutations in 109 CRC-associated genes using NGS on the Illumina platform.

Results: Mutations in the *APC* gene were detected in 13/15 (86.7%) patients. A known mutation (c.1285dupC; p.His429ProfsTer27) in the folliculin (*FLCN*) gene that affects FLCN protein stability and function was detected in one of the APC-negative patients. This patient had a family history of polyposis/CRC and synchronous CRC at 47y. *FLCN* is a known susceptibility gene for Birth-Hogg-Dubé syndrome (BHDS) that predisposes to noncancerous skin tumors and increased risk for kidney/lung cancer. The detected mutation is reported in multiple BHDS families and colorectal polyps were also observed in some of these families. No mutations in the analyzed genes were detected in the other APC-negative patient.

Conclusion: Our results support the evidence of the association between *FLCN* gene mutation and increased risk for CRC. Deep intronic variants/large rearrangements in the APC gene should also be excluded by further analysis, to clarify whether *FLCN* is a causative/modifying gene in CRC development in this family. However, the association between BHDS and CRC is still debated and larger studies are necessary to confirm these findings.

Keywords: *FAP, FLCN, Birth-Hogg-Dubé syndrome, CRC*

Topic:*Cancer genetics*

PP-35

FREQUENCY OF *RAS/RAF* MUTATIONS IN PATIENTS WITH METASTATIC COLORECTAL CANCER FROM NORTH MACEDONIA

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Introduction: Mutations in *RAS/RAF* lead to a constitutively activation of the MAPK signaling pathway leading to unregulated proliferation and differentiation of the cancer cells. Their role as negative predictive biomarkers for anti-EGFR targeted therapy in metastatic colorectal cancer (mCRC) is well established. Herein, we present the frequencies of the *RAS/RAF* mutations in mCRC patients from North Macedonia.

Material and methods: Genomic DNA was extracted from formalin-fixed paraffin-embedded tumor tissues from 684 mCRC patients. Mutations in exons 2, 3, and 4 of the *KRAS/NRAS* genes were analyzed using High Resolution Melt (HRM) analysis and subsequent bidirectional Sanger sequencing of the corresponding gene/exon in positive samples for validation. *BRAF* V600E/K mutation was tested in 600 of the patients using fluorescent allele-specific PCR and subsequent fragment analysis.

Results: Overall, *RAS* mutations were found in 393/684 (57,5%) patients. *KRAS* mutations were detected in 323 (47,2%) patients, among which 282 (87,3%), 18 (5,6%), and 23 (7,1%) in exons 2, 3, and 4, respectively. *NRAS* mutations were detected in 27/684 (4%), of which 16 (59,3%) and 11 (40,7%) in exons 2 and 3, respectively. *BRAF* V600E/K mutation was detected in 43/600 (7,2%) patients, of which 38/336 (11.3%) in *KRAS/NRAS* negative patients and 5/264 (1.9%) in patients positive for *KRAS* mutation.

Conclusion: Our results for the detected mutations correspond with previously published frequencies. The HRM analysis combined with Sanger sequencing is a compatible, sensitive, and cost-effective approach for detecting the most common RAS pathway mutations in CRC.

Keywords: *RAS, BRAF, CRC*
Topic: *Cancer genetics*

PP-36

PEDIGREE ANALYSIS IN PROBANDS WITH VARIANTS IN THE *CDH1* GENE

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The loss-of-function mutations in the *CDH1* gene are correlated with malignancies. We discuss the relationship between *CDH1* gene mutations and cancer cases diagnosed in them and in their family histories, of patients with for several indications whom we performed NGS analysis and detected mutations at *CDH1* gene.All exonic regions and exon-intron junctions of the *CDH1* gene were analyzed by NGS. 48 adult patients with variants were re-evaluated in terms of malignancies and their family histories were questioned and their pedigrees were updated.48 variants(22B,11LB,-15VUS) detected no LP/P variants were found. Among patients with VUS variants; 1 patient has endometrial ca,1 patient has CRC, 2 patients with LB variants has breast and renal ca.In the group of VUS variant patients 1st degree relatives had history of pancreatic, prostate, ovarian, lung ca, and lymphoma. The comprehensive family histories also encompass cases of brain, larynx, and liver ca. None of the patients with benign variant had malignancy; however, a majority of them had a family history of cancer.It is known that *CDH1* gene related to gastric ca, breast ca,CRC, ovarian cancer. Our cohort shows that probands with *CDH1* variants may also be at risk for other cancers.

Keywords: *CDH1, cancer, malignancy, pedigree,*

Topic: *Cancer genetics*

PP-37

PHARMACOGENETIC TESTING IN PATIENTS WITH LEUKEMIA AND COLORECTAL CANCERS

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Background: Several genetic variants affect dihydropyrimidine dehydrogenase (DPD) activity, involved in pyrimidine degradation, as well as the activity of UDP-glucuronosyltransferase (UGT), responsible for the glucuronidation of irinotecan. More than 30 genetic variants reduce the activity of the thiopurine-metabolizing enzyme thiopurine methyltransferase (TPMT). An individual approach based on genetic predispositions is enabled by determining the optimal drug dose to achieve the maximum therapeutic response for each patient.

Materials and methods: Real-time PCR or PCR with reverse hybridization was performed. *DPYD* variants c.1236G>A, c.1679T>G, c.1905+1G>A, and c.2846A>T were genotyped in colorectal cancer patients, before use of 5-fluorouracil. (TA)n repeat polymorphism of *UGT1A1* gene promoter was analyzed before irinotecan therapy in colorectal cancer and solid tumors, and the analysis of *TPMT* variants c.238G>C, c.460G>A, and c.719A>G was included before thiopurine treatment in acute lymphoblastic leukemia, and inflammatory bowel disease patients.

Results: Several months after the introduction of the methods, among twelve samples for DPD analysis, one had heterozygous c.1236G>A (HapB3). *UGT1A1* (TA)n promoter genotyping was conducted in 24 samples. Eight samples had genotype (TA)6/(TA)6, another 6 (TA)6/(TA)7, and ten (TA)7/(TA)7. *TPMT* testing in 22 samples showed *TPMT**1/*1, one *1/*2, and one *1/*3A or *3B/*3C genotype. One patient received modified 5-fluorouracil therapy. The modified therapy received 17 patients with colorectal cancer and 2 patients with acute lymphoblastic leukemia.

Conclusions: Based on these initial analyses, the side effects of therapy were reduced, as well as treatment costs, to a minimum.

Keywords: *TPMT, DPYD, UGT1A1*

Topic: *Personalized medicine and Pharmacogenomics*

PP-38

EXAMINING NON-INVASIVE PRENATAL TESTING (NIPT): OVERVIEW OF CHALLENGES, PERSPECTIVES, CASE REPORTS, AND DATA IN ONE YEAR PERIOD

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Background: Non-invasive prenatal testing (NIPT) is a screening technology that analyzes fetal DNA fragments found in the mother's plasma (cffDNA). For over a year, Alea Genetic Center has been using NIPT for genome-wide sequencing of fetal DNA. This study examines case reports of detected aneuploidies, their prevalence, and methods used for confirmation.

Materials and methods: Hamilton Microlab STAR was used for plasma isolation, cfDNA extraction, library preparation, and pooling. The Illumina NextSeq instrument was used for NGS sequencing. Amniocentesis and QF PCR were used as a CE-IVD method for confirmation of the detected anomalies.

Results: The NIPT results showed genetic anomalies in six patients in 422 samples, including two samples with trisomy 21, one trisomy of chromosome 18, one trisomy of chromosome 13, and rare autosomal aneuploidies (RAAs) of chromosomes 20. QF PCR method from amniotic fluid confirmed the results of trisomies 13, 18, and 21 while karyotyping confirmed trisomy of chromosome 20.

Conclusions: This report underlines the need for collaboration between molecular biologists and healthcare providers, as well as ongoing education and training to ensure the highest quality of non-invasive prenatal testing. The presented results serve as a reminder of the critical role played by the genetic laboratory in modern healthcare. Our report suggests that NIPT detects genome anomalies with high accuracy and should be used as a screening methodology for high-risk pregnancies.

Keywords: *Non-invasive prenatal testing, Prenatal screening, Fetal anomalies, Trisomies NGS sequencing*

Topic: *Reproductive and prenatal genetics*

PP-39

ANALYSIS OF IDENTIFIED HUMAN GENETIC VARIANTS IN COVID-19 PATIENTS AND THEIR CORRELATION WITH OTHER VIRAL INFECTIONS

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Background: It was accepted that environmental, demographic, and clinical factors have an impact on severity of COVID-19, but that the host genetics may also have a significant role in the severity, as well as susceptibility to SARS-CoV-2 infection at the first place.

Materials and methods: Blood samples were collected from RT-PCR-confirmed COVID-19 patients (n=60) in the General Hospital Tešanj from March to October 2021, and delivered to the testing laboratory. Based on the patients overall condition, samples were divided into mild, moderate and severe clinical symptoms group. Ion AmpliSeq Designer was used to create primers for 16 selected genes. Next generation sequencing was performed using Ion GeneStudio S5 System and data was analyzed using Torrent Browser Software.

Results: The results showed that different comorbidities were significantly more common in severe when compared to mild and moderate symptom groups. We have detected variants that might be predisposing the patients towards milder or more severe symptoms of COVID-19, based on significant differences in the frequency of appearance of the study variants between the defined clinical groups.

Conclusions: These variants are reported with recommendations for their future testing and analysis in order to fully understand their role, not only in COVID-19, but in other viral infections as well, in terms of both susceptibility and disease progression. Despite being limited by small sample size, this study also contributes to the present state of knowledge related to COVID-19, as it provides the unique look into the Western Balkans populations in relation to this infection.

Keywords: *COVID-19, next generation sequencing, human susceptibility, viral infections, confirmatory sequencing*

Topic: *Personalized medicine and Pharmacogenomics*

PP-40

CHARACTERIZATION OF 16 NOVEL GENETIC VARIANTS IN GENES RELATED TO CHILDHOOD EPILEPSIES

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Background: Childhood epilepsies are caused by heterogeneous underlying disorders where approximately 40% can be attributed to genetic factors. Application of next-generation sequencing (NGS) has revolutionized diagnostics and therefore has enabled the identification of disease-causing genes and variants in childhood epilepsies.

Materials and Methods: Patients who presented with epilepsy of unknown etiology in childhood, with suspicion of a genetic cause were included in this study. In total, 55 patients from unrelated non-consanguineous families were included and analyzed by NGS either using clinical-exome sequencing (MiSeq, Illumina) or whole-exome sequencing (DNBSEQ-G400, MGI). Variants were prioritized using Variant Interpreter and VarSome and classified according to the ACMG recommendations.

Results: Using CES we analyzed 38 patients, and for 22 of them a diagnosis was established. Using WES we analyzed 17 patients with childhood epilepsy, which led to the identification of disease-causing genes in 11 patients. The diagnostic success rate for CES was 55.3% (21/38) and the diagnostic rate for WES was 64.7% (11/17), with the overall diagnostic rate being 58.2% (32/55). For these patients, we detected pathogenic, likely pathogenic variants or VUS in 24 epilepsy genes that correlate well to the observed phenotype. Sixteen novel genetic variants were identified and characterized using various in silico algorithms.

Conclusion: This is the first study reporting the molecular-genetic basis of childhood epilepsy in Serbia. The prompt establishment of a specific diagnosis is essential in order to make available the prognosis, optimize therapy, and enable counseling on recurrence risk in future pregnancies.

Keywords: *Childhood epilepsy, CES, WES, novel variants*

Topic: *Rare diseases*

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MOLECULAR DIAGNOSIS OF EYE DISORDERS BY NEXT-GENERATION SEQUENCING

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Background: Eye disorders are characterized with a considerable phenotype and genotype heterogeneity. With more than 300 genes involved in visual process, molecular testing using Sanger sequencing is too expensive and time-consuming. Nowadays, a whole exome sequencing (WES) is a powerful tool for simultaneous analysis of numerous genes of interest, providing faster approach to molecular diagnosis.

Material and methods: WES was applied in 20 patients with different eye disorders: Stargardt disease, macular dystrophy, retinitis pigmentosa, aniridia, vitreoretinopathy, glaucoma, cataract, as well as syndromic forms of visual impairment.

Results: Genetic diagnosis was confirmed in 15 patients (75%). A total of 20 different causative pathogenic variants were determined in 13 genes with different mode of inheritance: nine autosomal recessive (AR) genes: *ABCA4, CDHR1, CYP1B1 FAM161A, ALMS1; RDH12; RP1, USH2A* and *TSPAN12*, three autosomal dominant (AD): *BEST1, SLC39A5* and *PAX6*, one X-linked *RPGR* gene. Six of the variants were novel (*PAX6:c.806_807+12del; ZNF469:c.2904del; RP1:c.4239delA; USH-2A:c.13137del; TSPAN12:c.468+2T>C, RP-GR:c.1060-2A>C*). With the exception of *ABCA4* gene, which was causative in three patients (2/homozygotes, 1/compound heterozygote), all other genes were implicated in only one patient. In two patients, a single pathogenic variant in AR gene (*ZNF469* and *PDE6B*) was determined, while in one a VUS variant in *RP1L1* gene was found.

Conclusion: Using WES the disease-causing variants were detected in 75% of the studied patients with eye disorders, allowing for more accurate prognosis, more appropriate therapeutic approach and more adequate genetic counselling.

Keywords: *Eye disorders, Retinopathies, WES, Genetics*

Topic: *Rare diseases*

PP-42

GENOMIC LANDSCAPE OF INHERITED RETINAL DEGENERATIONS IN A COHORT OF 103 BULGARIAN FAMILIES

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Background/Objectives: Inherited retinal degenerations (IRD) are a group of retinopathies with more than 300 genes associated and more than 20 different clinical phenotypes described. The aim of the present study was to identify the genetic diagnosis in a group of Bulgarian patients affected by IRDs.

Methods: A cohort of 103 cases diagnosed with different forms of IRDs was recruited. We performed targeted next-generation sequencing (NGS) of clinical exome (CES) in 80 patients and whole exome sequencing (WES) with deletion/duplication analysis in 23 probands. Variants were validated, classified according to ACMG guidelines, and subjected to segregation analysis if family members were available.

Results: Overall, 92% of our IRD cohort has been characterized with an increase of diagnosis rate of ~+2% from 2020. One hundred and eleven candidate variants (82 known and 29 novel) that could be responsible for the disease were found in 49 IRD genes were found in 95 out of 103 analyzed patients. Based on genetic analysis more than 15 clinical phenotypes were characterized in the studied patient group with predominance of macular degeneration caused by mutations in the common gene responsible for this disease, *ABCA4*.

Conclusion: Implementation of NGS (CES and WES) allowed detection of disease-causing mutations in 92% of our cases, a percentage which exceeds previously reported diagnostic yield of 60-70% for IRDs. However, genetic cause of the disease was not identified in 8%, possibly due to the presence of undiscovered variants/genes, or genomic rearrangements difficult to identify through this technology.

Keywords: *inherited retinal degeneration, next-generation sequencing*

Topic: *Rare diseases*

PP-43

FREQUENCY OF *CYP21A2* POINT MUTATIONS IN MACEDONIAN PATIENTS WITH 21-HYDROXYLASE DEFICIENCY

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Background: 21-hydroxylase deficiency is an autosomal recessive disorder of adrenal steroidogenesis with a broad spectrum of clinical presentations, ranging from the severe classical salt-wasting (SW) and simple-virilizing (SV) form, to the mild nonclassical form. Approximately 75% of the *CYP21A2* mutations belong to the group of nine pseudogene-derived point mutations, and 20% of alleles show large gene deletions and/or gene conversions resulting from unequal crossing during meiosis.

Materials and Methods: Molecular analysis of the nine most common mutations in *CYP21A2* gene - p.P30L, In2G (c.293-13A/C>G), Del 8ntG110, p.I172N, cluster 6 mutations, p.V281L, p.F306+T, p.Q318X and p.R356W, was performed in 91 Macedonian patients with clinical and biochemical diagnosis of 21-hydroxylase deficiency, using PCR/ACRS method, and subsequent restriction enzyme analyses. Molecular analysis allowed detection of the mutations as well as determination of the zygosity of the analyzed mutations.

Results: Seven different mutations were detected on 148/182 (81,3%) of the analyzed alleles. The most frequent mutation was In2G (c.293-13A/C>G) present on 34.1% of the analyzed alleles, followed by p.P30L (24.2%), p.Q318X (8.2%), p.I172N (7.7%) p.V281L (3.8%), Del 8ntG110 (2.7%) and p.R356W detected on the 1.6% of the alleles. Two multiple alleles were also observed, the first had three and the second allele had two different mutations.

Conclusions: In2G mutation was the most frequent mutation in the Macedonian patients with 21-hydroxylase deficiency. It is described as the most common mutation in patients with the classic form of the disease in many populations worldwide, and is considered as a hot spot mutation.

Keywords: *21-hydroxylase deficiency, CYP21A2 gene, point mutation*

Topic: *Metabolic and mitochondrial disorders*

PP-44

HFE GENOTYPE, FERRITIN AND *FE* LEVELS IN PATIENTS WITH SUSPECTED HEREDITARY HEMOCHROMATOSIS

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Background. Hereditary hemochromatosis is an autosome recessive disease that is characterized by increased iron absorption and iron overload due to variants in the iron-regulating HFE gene. Diagnostic criteria sufficient to diagnose haemochromatosis are C282Y homozygosity in HFE gene and iron overload based on serum iron parameters (transferrin saturation >45% and ferritin >300 μg/L). The aim of our study is to determine the association between the HFE genotype and biochemical findings, age and gender.

Material and methods. Thirty-four patients were referred to the Institute of immunobiology and human genetics, Skopje with increased iron or ferritin levels or a family history of hemochromatosis. The presence of 18 different variants in the HFE gene were analyzed with reverse line strip (RLS) kits from Vienna Lab, Vienna, Austria. Iron and ferritin levels were detected with Cobas 501 Roche and Integra 400 Roche, accordingly.

Results. We analyzed 11 female and 23 male patients, with age median of 47.9±11.2 and 40.7±13.5, respectfully. The results were very heterogenous regarding the association of ferritin levels and HFE gene variants. We observed 12 H63D heterozygotes, one S65C heterozygote, one C282Y/H63D compound heterozygote, 3 H63D homozygotes and one H63D and S65C compound homozygote. We didn't detect C282Y homozygotes in our group of patients. Elevated levels of ferritin (>300 μg/L) were observed in 11 patients. Only 5 (45.4%) had variants in the HFE gene.

Conclusion. The different gene penetration of the most common variant H63D makes the diagnosis of hereditary hemochromatosis more challenging. Additional tests like transferrin saturation and hepatic iron overload on MRI or liver biopsy, might be helpful in the diagnostic process.

Keywords: *Hereditary hemochromatosis, HFE gene, H63D*

Topic: *Rare diseases*

PP-45

THE SPECTRUM OF *ATP7B* PATHOGENIC VARIANTS AMONG PATIENTS WITH WILSON DISEASE IN NORTH MACEDONIA

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Introduction: Wilson's disease (WD) is an autosomal-recessive inherited disorder associated with copper accumulation in different organs (liver, brain, kidneys and corneas), caused by pathogenic variants in the *ATP7B* gene. The distribution of *ATP7B* pathogenic variants is population-specific. The aim of our study was to determine the spectrum of pathogenic variants among our WD patients and to design *rapid and inexpensive first-line genetic screening test.*

Material and methods: We have tested 116 patients suspected for Wilson's disease. All patients were screened with Multiplex Ligation Probe Amplification Analysis (MLPA) detecting deletions/duplications and four common pathogenic mutations in *ATP7B* gene. For 26 patients subsequent sequencing was performed using Sanger or next generation sequencing (NGS) panel testing.

Results: In total, the genetic diagnosis of WD was established in 20/116 patients (17.2%).The most common pathogenic variant was c.3207C>A, present in 40% of the *ATP7B* alleles. Six variants (c.3207C>A, c.2304dup, c.4022G>A, c.865C>T, c.2532delA, c.2732C>T) comprised 80% of the alleles. Based on these initial *ATP7B* genotyping data, we have designed a protocol, based on single base extension method, targeting the six most common variants.

Conclusion: The low detection rate in our study suggests that clinicians in our country use the *ATP7B* genetic testing mainly as a screening rather than a confirmatory diagnostic tool. Therefore, the first-line *ATP7B* genetic screening for the most common variants in our population is expected to be time and cost effective and to facilitate the genetic testing for WD in our country.

Keywords: *Wilson's disease, ATP7B gene, pathogenic variants, population-specific, screening*

Topic: *Rare diseases*

PP-46

PCYT1A FRAMESHIFT VARIANT IN AN ALBANIAN FEMALE PATIENT WITH SPONDYLO-METAPHYSEAL DYSPLASIA WITH CONE-ROD DYSTROPHY

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Background: Spondylometaphyseal dysplasia with cone-rod dystrophy (SMDCRD) is a rare autosomal recessive disorder characterized by severe short stature, lower limb bowing, flattened vertebral bodies, metaphyseal involvement, and visual impairment due to cone-rod dystrophy. It is caused by homozygous or compound heterozygous mutation in the *PCYT1A* gene on chromosome 3q29.

Material and Methods: We report a case of a 10 year old female Albanian patient, born of healthy, unrelated parents. She presented short stature, lower limb deformity with rhizomelic shortening of the long bones, prominent joints, mild thoracic scoliosis and vision impairment. A radiographic evaluation revealed platyspondyly, shortened long bones, generalized irregular metaphysis. Funduscopy showed bilateral macular atrophic lesions. Whole exome sequencing (WES) was performed on genomic DNA of the patient obtained from peripheral blood.

Results: WES identified a homozygous frameshift variant NM_001312673.2:c.968dup (p.Ser323ArgfsTer38) in the exon 9 of *PCYT1A* gene. It has been observed in homozygous state in individual (s) with SMDCRD and it has also been observed to segregate with disease in related individuals. Functional studies were however not able to prove a damaging effect. The observed variant has allele frequency at 0,0005% in gnomAD database. This variant has been submitted to the ClinVar database as Pathogenic/Uncertain Significance (VUS). However since this variant is present in the last exon, functional studies will be required to prove protein truncation. Hence the variant is classified as VUS.

Conclusion: Our case provide an other evidence on the pathogenicity of this variant and support the implication of this variant as a disease.

Keywords*: SMDCRD rare disease, PCYT1A gene, frameshift variant, Whole Exome Sequencing*

Topic: *Rare diseases*

PP-47

EXPLORING POTENTIAL ASSOCIATION BETWEEN AUTISM SPECTRUM DISORDER, GENETIC DELETIONS IN *GSTT1, GSTP1, GSTM1,* AND HEAVY METALS FOUND IN HAIR SAMPLES

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The aetiology of ASD is complex and likely involves a combination of genetic and environmental factors. The increasing prevalence of ASD has led to an increased interest in environmental factors and their potential influence. In this study, we investigated the association between genetic deletions of the *GSTT1, GSTP1*, and *GSTM1* genes analyzed by Array-CHG and levels of heavy metals in hair samples of children with ASD analyzed by inductively coupled plasma optical emission spectrometry. We analyzed a total of 50 children (aged 2-8) of which 25 had been diagnosed with ASD and had genetic deletions in one or more of the analyzed genes (*GSTT1, GSTP1,* and *GSTM1*), and 25 control samples from children from the same geographic area exposed to the similar environmental conditions but with no deletions in these genes. We found that children with deletions in these genes had significantly elevated hair levels of aluminium (Al) in 100% of the examined children, and in some cases in combination with, mercury (Hg) – 1 case, lead (Pb) – 2 cases, cadmium (Cd) – 1 case, barium (Ba) - 8 cases, and nickel (Ni) – 2 cases. In the control group of children, 23 out of 25 had normal levels of heavy metals in their hair, while one child had a borderline value of aluminium (Al) and another had an increased level of thallium (Tl). Our findings suggest that genetic deletions in detoxification and antioxidant enzymes like *GSTT1, GSTP1,* and *GSTM1* might be associated with increased levels of heavy metals thus leading to possible complex interactions between genetic and environmental factors, influencing the level of expression of symptoms and impairment in people with ASD.

Keywords: *Autism spectrum disorder (ASD), GSTT1, GSTP1, GSTM1, Heavy metals, Hair Samples, Aluminium*

Topic: *Neurogenetics and intellectual disability*

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CLINICAL EXOME SEQUENCING IDENTIFIES WOODHOUSE-SAKATI SYNDROME IN SIBLINGS BY DETECTING DE NOVO MUTATION

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Background: Woodhouse-Sakati Syndrome (WSS) is a rare autosomal recessive genetic disorder characterized by a range of multi-systemic symptoms, including hypogonadism, hypothyroidism, hearing loss, and diabetes mellitus. The diagnosis of WSS traditionally involves a combination of clinical assessment and genetic testing.

Methods: In this case report, we present two siblings, a brother and a sister, both have symptoms suggestive of WSS. Given their consanguineous background and shared phenotypic features, we performed CES on both siblings .

Results: Our CES analysis revealed homozygous frameshift variants (c.1382_1383del) in the *DCAF17* gene associated with WSS in both siblings. The genetic results confirmed their clinical manifestations.

Conclusion: This case report highlights the successful application of clinical exome sequencing in diagnosing Woodhouse-Sakati Syndrome in a sibling cohort. CES proves to be a valuable tool in rare genetic disorders and underscores the importance of considering genetic testing in consanguineous families with complex phenotypes.

Keywords: *Woodhouse-Sakati Syndrome, DCAF17, Clinical exome sequencing, Autosomal recessive, De Novo Mutations*

Topic: *Rare diseases*

PP-49

TWO SIBLINGS DIAGNOSED WITH SITOSTEROLEMIA RESPONDING WELL TO EZETIMIBE TREATMENT

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Background: Sitosterolemia is an inherited autosomal recessive metabolic disorder characterized by increased plant sterols in the blood. This disease is caused by loss-of-function mutations in the *ABCG5* and *ABCG8* genes which encode proteins that play essential roles in the selective excretion of plant sterols from the liver and intestine, leading to a failure to excrete plant sterols. Sitosterolemia clinical presentation includes hypercholesterolemia, tendon, and tuberous xanthomas, premature development of atherosclerosis, and abnormal hematologic and liver function test results.

Materials and methods: Herein we discussed a Turkish family with an index case of thrombocytopenia and abdominal pain. After evaluation of clinical findings of the index case and family histories, DNA was isolated from the peripheral blood of the patient and screened using a custom-designed thrombocytopenia panel via next-generation sequencing (NGS). Her parents and siblings were screened via the Sanger sequencing method.

Results: Molecular analysis revealed a homozygous *ABCG8* (NM:022437) c.1715T>C (p.Leu572Pro) variation. According to ACMG guidelines, this variant was evaluated as pathogenic(PVS1, PM2, and PP5). The segregation analysis revealed that the parents were carriers for the *ABCG8* pathogenic variation while the sister was homozygous.

Conclusions: The clinical presentation of patients with sitosterolemia is quite heterogeneous. Also, patients diagnosed with Sitosterolemia respond well to Ezetimibe treatment. Therefore, defining the molecular etiology of sitosterolemia is important in terms of treatment options, screening family members, and giving appropriate genetic counseling for preimplantation genetic diagnosis opportunities.

Keywords: *Sitosterolemia, Plant Sterols, ABCG8 gene, Ezetimibe, Thrombocytopenia*

Topic: *Rare diseases*

PP-50

A TURKISH FAMILY WITH ACRODYSOSTOSIS 2 (ACRDYS2): A NOVEL MUTATION

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Background: Acrodysostosis 2 is an autosomal dominant disease characterized by short stature, facial dysmorphism, skeletal abnormalities, blue eyes and red hair. It is caused by mutations in the *PDE4D* gene.

Materials and Methods: After a thorough anamnesis and physical examination, DNA was isolated from peripheral blood and coding gene regions were sequenced on NovaSeq Platform via SOPHIA CES V3 kit. Obtained data were analyzed using SophiaDDM data analysis platform.

Results: The index patient was a 46 year old male who was referred to our clinic because of skeletal pain and abnormalities. He was born to a non-consanguineous family. He had short stature (160cm, adult height), obesity (78kg) and relative macrocephaly (58cm). The patient had a dysmorphic face, brachydactyly on both hands and feet, dystrophic nails. He had moderate hearing loss on both ears, due to recurrent ear infections. The patient had 2 children, a female and a male who have similar phenotypes and learning disabilities. All patients had blue eyes and red hair. The father had a heterozygous novel missense variant in *PDE4D* gene (NM_001104631) c.568T>C (p.Ser190Pro). This variant is reported as likely pathogenic according to the ACMG criterias. In silico platforms report this variant as disease causing.

Conclusions: We detected a novel mutation in the *PDE4D* gene. Multi-gene panels should be chosen due to genetic heterogeneity of skeletal dysplasias. Lastly, further studies are needed to establish the genotype-phenotype correlations.

Keywords: *Skeletal dysplasia, Autosomal dominant, Acrodysostosis, Novel mutation, Rare diseases*

Topic*: Rare diseases*

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DARK URINE KEY TO EARLY DIAGNOSIS OF ALKAPTONURIA: A CASE REPORT

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Introduction: Alkaptonuria (AKU) is a rare monogenic autosomal-recessive disease. It is characterized by the accumulation of homogentisic acid, resulting in darkened urine, pigmentation of connective tissues (referred to as ochronosis), arthritis affecting the weight – bearing joints and the spine, and damage to cardiac valves. The cause of AKU lies in mutation of the HGD gene that encodes the enzyme homogentisate 1,2 dioxygenase (HGD), which plays a crucial role in converting homogentisic acid into maleylacetoacetic acid as a part of the tyrosine catabolic pathway.

Case report: We describe the case of a previously healthy 7-year-old boy admitted due to a history of darkened urine occurring shortly after urination over the past three years. Initial tests, including ultrasound and urine analysis, showed no abnormalities. There were no other related symptoms. However, the sodium hydroxide test of the urine yielded a positive result for Alkaptonuria. Sanger Sequencing was performed and a compound heterozygous condition, characterized by two known splice mutations within the *HGD* gene (genotype: c.16-1G>A;1007-2A>T) was determined as a cause of the disease, a screening test was also conducted for the other sibling, and it returned a negative result. Nitisinone is considered a promising therapy for these patients currently approved only in adulthood.

Conclusion: In summary, pigmented urine is a hallmark symptom of Alkaptonuria, emphasizing the significance of early detection and evaluation.

Keywords*: darkened urine, Homogentisate 1,2 – Dioxygenas, Alkaptonuria*

Topic*: Rare diseases*

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PRENATAL KIDNEY HYPERECHOGENICITY: A CLUE TO AN EARLY DIAGNOSIS OF BARDET-BIEDL SYNDROME

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Introduction: Bardet Biedl syndrome (BBS) is a multistem recessive genetic disease, which is characterized by intellectual disability, retinal dystrophy, truncal obesity, postaxial polydactyly, cardiopathy, renal abnormalities, hypogonadism, and others. Herein we report a baby with a very early established genetic diagnosis of *BBS12*.

Case presentation: An otherwise healthy newborn was referred to Children's Hospital due to prenatal hyperechogenicity of both kidneys. Physical examination revealed polydactyly of the toes of both feet. The family history was negative for kidney diseases. Standard biochemical tests and cardiological examination did not reveal any abnormality. Ultrasonographic examination of the urinary tract showed bilateral hyperechogenic kidneys, which had normal size and no dilatation of the pyelocalyceal system. Polydactyly and hyperechogenic kidneys raised clinical suspicion for BBS and the family consented to the genetic study. Molecular analysis revealed two pathogenic heterozygous variants in the *BBS12* gene c.865G>C (p.Ala289Pro) and c.1658T>C (p.Leu553Pro). Segregation analysis of the parents confirmed biallelic state (genotype:c.865G>C;1658T>C) in the infant. Genetic counseling was arranged. Two months later kidney ultrasound revealed a complete resolution of the hyperechogeneicity.

Conclusion: An early genetic diagnosis of BBS in a healthy newborn brings enormous psychological stress to the family, but on the other hand, it enables early recognition of other abnormalities in BBS and early treatment and prevention (e.g. preemptive kidney transplantation and avoidance of dialysis). Genetic counseling and a multidisciplinary approach are of great importance in the management of these patients.

Keywords*: Bardet-Biedl syndrome, early diagnosis, BBS12 gene, genetic counseling*

Topic*: Rare diseases*

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INVESTIGATION OF THE RELATIONSHIP OF *NLRP2, NLRP7* AND *KHDC3L* GENE VARIATIONS IN PATIENTS WITH RECURRENT PREGNANCY LOSS HISTORY

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Backgorund: Recurrent pregnancy loss (RPL) is an important problem in reproductive health. The cause of approximately 50% of RPL cases has not been explained. Understanding the genetic basis in the etiology of RPL is important for diagnosis and prognosis. Therefore, in our study, we aimed to investigate the relationship of *KHDC3L, NLRP2* and *NLRP7* genes with RPL, which have important functions in the female reproductive system.

Materials and methods: Ninety-six female patients who applied to the outpatient clinic of Trakya University Medical Faculty, Department of Medical Genetics, Genetic Diseases Diagnosis Center with a history of RPL were included in the study. *KHDC3L, NLRP2* and *NLRP7* genes were analyzed in terms of possible variations by NGS method.

Results: We detected rs73055288, rs1276342435 in the *NLRP7* gene, rs200815567, rs199475713, rs147585490, rs149897717, rs145361990 in the *NLRP2* gene and rs1032302298, rs553706174 in the *KHDC3L* gene. In our study, no "pathogenic, likely pathogenic variation" was found in open access databases and / or according to ACMG-2015 criteria. The global allele frequency of the eight variations we detected in our study was less than 0.004 (0.004-0.000004).

Conclusions: We anticipate that investigating these variations in women with normal fertility will contribute significantly to the literature.

Keywords: *KHDC3L, NLRP2, NLRP7, Recurrent Pregnancy Loss, NGS*

Topic: *Reproductive and prenatal genetics*

PP-54

PRENATAL DIAGNOSIS OF SKELETAL DYSPLASIA – REVIEW OF THE LITERATURE AND EXPERIENCES OF THE CLINICAL GENETICS SERVICE FROM BELGRADE

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Background: Skeletal dysplasia are heterogeneous group of over 460 distinct genetic disorders affecting skeletal development. Some of them can present in the prenatal period as demonstrated by obstetric ultrasonography. Fetuses with different skeletal dysplasia are increasingly being diagnosed prenatally with increased usage of NGS in prenatal testing.

Materials and methods: We conducted a retrospective analysis from our skeletal dysplasia database. In our series of 168 patients with different skeletal dysplasia we performed 20 analyses on the fetal DNA sample.

Results: In 17 cases, i.e. for 13 families prenatal testing was performed during ongoing pregnancy. Out of these 17 cases of prenatal testing, in four cases suspected skeletal disease was in a fetus with a negative family history and without previously set molecular diagnosis of skeletal dysplasia in family. The following diagnoses were made in these affected fetuses: Otopalatodigital syndrome type I, Osteogenesis imperfecta type II, Mandibulofacial dysostosis Guion-Almeida type and Joubert syndrome type 5. In the remaining 13 cases, targeted prenatal diagnostic testing was done for known familial causative variant previosly identified in older sister/brother. The remaining three tests on the fetal sample, were analysis initiated after the pregnancy had already been terminated with ethical approval, and fetal DNA was isolated from paraffin embedded tissue stored during fetal autopsy. The following diagnoses were made in fetuses from the terminated pregnancies: Thanatophoric dysplasia type I, Craniofrontonasal dysplasia and Genitopatellar syndrome.

Conclusions: Prenatal diagnosis of skeletal dysplasia can present a considerable diagnostic challenge.

Keywords: *skeletal dysplasia, prenatal diagnosis, fetal DNA analysis, next generation sequencing*

Topic: *Reproductive and prenatal genetics*

PP-55

CASE REPORT: MALE PATIENT WITH BALANCED RECIPROCAL TRANSLOCATION 46,XY,T(1;8)(P32~34;P21)

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Background: Balanced translocations, are translocations where, there is neither excess nor loss of genetic material and that usually have no phenotypic effect. Balanced reciprocal translocations occur in 1/500 individuals. According to previous research, the chromosome most often involved in reciprocal balanced translocations is chromosome 1 in men with infertility and spontaneous abortions. Chromosome 1 may have a critical domain whose integrity is crucial for male fertility.

Materials and methods: Two thymidine cultures were cultured on two different media for each patient. After technical preparation and appropriate staining, it was possible to analyze the chromosomes for the presence of structural abnormalities. Constitutive aberrations were detected using GTG methods. The microscope used for the karyotyping was Nikon Eclipse 80i with Lucia cytogenetics software and camera.

Results: We have analyzed karyotypes of 40 patients with infertility and spontaneous abortions, and a balanced reciprocal translocation was detected in one male patient. In all analyzed cells in the cultures of this patient, was detected a balanced reciprocal translocation between the short arms of the chromosomes 1 and 8, with breaking points at p32~34 in chromosome 1 and p21 in chromosome 8, 46,XY,t(1;8)(p32~34;p21).

Conclusion: In this case the breaking point on chromosome 1 was between 1p32 and 1p34, which according to previous studies indicates pregestational and gestational infertility. In our case the patient had oligozoospermia and his partner had few spontaneous abortions, that indicates gestational infertility. Genetic counseling and prenatal diagnosis were recommended.

Keywords: *chromosome 1 infertility chromosome 8 constitutive aberrations oligozoospermia*

Topic: *Reproductive and prenatal genetics*

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ROBERTSONIAN TRANSLOCATIONS AND INFERTILITY

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Background: It is well known that carriers of balanced Robertsonian translocations usually have a normal phenotype, but they have problems with infertility associated with severe oligozoospermia in males and recurrent pregnancy losses in females, offspring with aneuploidy and birth defects, mental retardation, and complications associated with uniparental disomy.

Materials and methods: For each patient we have cultured two different lymphocyte mediums with thymidine. After technical preparation and appropriate staining, it was possible to analyze the chromosomes for the presence of structural and numerical abnormalities. Constitutive aberrations were detected using GTG methods. The microscope used for the karyotyping was Nikon Eclipse 80i with Lucia cytogenetics software and camera.

Results: We have analyzed karyotypes of 40 patients with infertility and spontaneous abortions, and we have detected 3 patients with Robertsonian translocation, of which 2 were men with 45,XY,der(13;14)(q10;q10) and 45,XY,der(13;15)(q10;q10), and a woman with 45,XX,der(13;14)(q10;q10). Derivative chromosomes are obtained by fusion of chromosomes 13;14 and 13;15, whereby this fusion results in 13qter->13q10::14q10->14qter and 13qter->13q10::15q10->15qter derivative chromosomes respectively.

Conclusions: In the cases of our patients, the patient with karyotype 45,XY,der(13;14)(q10;q10) had oligozoospermia, the patient with karyotype 45,XY,der(13;15)(q10;q10), had azoospermia, and the female patient with karyotype 45,XX-,der(13;14)(q10;q10) had fetal anencephaly in a previous pregnancy, uterus unicornis and missing left kidney. Genetic counseling and prenatal diagnosis are recommended in all cases with Robertsonian translocations.

Keywords: *oligozoospermia birth defects anencephaly uterus unicornis derivative chromosomes*

Topic: *Reproductive and prenatal genetics*

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EXPANDING PHENOTYPIC SPECTRUM OF *MPDZ* GENE MUTATIONS

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MPDZ is a protein-coding gene that plays a role in protein-protein interactions and formation of intercellular tight junctions through its highly conserved PDZ domains. Several central nervous system anomalies are associated with MPDZ mutations, including congenital hydrocephalus type 2 with or without brain or eye anomalies (HYC2, MIM 615219), as well as cerebellar vermis hypoplasia. Additionally, cardiac malformations are noted, primarily atrial septal defects.

A 19-year-old gravida was referred to genetic counseling at 26th gestational weeks due to sonographic anomalies detected in the fetus: Dandy-Walker malformation and univentricular heart with transposition of great vessels. Amniocentesis was performed. After DNA isolation, three analysis were conducted: QF PCR for common aneuploidies (Aneufast kit), chromosomal microarray analysis (CMA) (Agilent SurePrint G3 Human CGH Bundle, 8×60K) and clinical exome sequencing (Illumina DNA Prep with Enrichment protocol, TruSight One panel). Variants were classified according to the ACMG/AMP classification system.

QF PCR and CMA analyses indicated a normal male DNA profile. Clinical exome sequencing revealed a novel homozygous pathogenic variant in MPDZ gene, c.4576G>T (NM_001378778.1), p.(Gly1526Ter), which activates a nonsense-mediated decay pathway, leading to loss of functional protein. The variant is located within the PDZ 9 region.

To date, this is the first reported case of the c.4576G>T variant in the MPDZ gene. Our case implies the existence of previously undescribed prenatal manifestations of mutations in the MPDZ gene, such as Dandy-Walker malformation and univentricular heart, and potentially expands the aforementioned spectrum of phenotypic characteristics.

Keywords: *MPDZ gene, Dandy-Walker malformation, Congenital heart anomalies, Prenatal diagnosis*

Topic: *Reproductive and prenatal genetics*

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ROBERTSONIAN TRANSLOCATION 45,XY,DER(13;15)(Q10;Q10) IN A AZOOSPERMIC PATIENT

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Background: Azoospermia (complete absence of spermatozoa in the ejaculate) is the most severe form of male infertility. Based on the etiology, azoospermias can be classified as obstructive (OA) and non-obstructive (NOA), the latter having worse surgical sperm retrieval rate. Among the many causes of NOA are chromosomal and sub-chromosomal aberrations.

Materials and methods: We have cultured two different lymphocyte mediums with thymidine. After technical preparation and appropriate staining, constitutive aberrations were detected using GTG methods. The microscope used for karyotyping was Nikon Eclipse80i with Lucia cytogenetics software.

Results: A 34-year-old male with azoospermia diagnosed based on 2 spermiograms (1 month apart). The pre-operative serum reproductive hormones were: FSH 17.3 mIU/mL, LH 13.8 mIU/mL, other hormones – unremarkable, normal T/E2 ratio (12.8). No other risk factors were noted. On scrotal ultrasound, both testicles had reduced volume (11 mL) and scarce vascularization, with few macrocalcifications. AFP, betaHCG, CEA, LDH – within normal ranges. The patient underwent bilateral excisional surgical sperm retrieval during which no sperm were obtained. Histopathology revealed bilateral late maturation arrest to the level of spermatids (Johnsen score 6) in 2% of the tubules and Sertoly cell only syndrome in 98% of the tubules. Karyotyping revealed 13qter->13q10::15q10->15qter derivative chromosomes in all cells analyzed.

Conclusion: Carriers of balanced Robertsonian translocations often have normal phenotype, but mostly severe oligozoospermia or azoospermia are present. To our knowledge this is the first case where karyotype 45,XY,der(13;15)(q10;q10) has been described in a azoospermic patient.

Keywords: *Male infertility, Non-obstructive azoospermia, Karyotyping Chromosomal rearrangements, Surgical sperm retrieval*

Topic: *Reproductive and prenatal genetics*

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CRYOPRESERVATION OF HUMAN EMBRYOS AND NEURODEVELOPMENTAL DISORDERS

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Introduction: Studies following the Neonatal Outcomes specially the medium and Long-Term Follow-Up of Children Born from Frozen Embryo are still few and with conflicting conclusions worldwide. There are even less studies of early neurodevelopmental evaluation and Follow-Up of such children.

Background: The aim of our study was to outline a case presentation of two twins pairs of 6 and 4 y. children borne from frozen embryos compared to their brothers/sisters born from fresh embryos obtained by the same ovarian cycle. Clinical laboratory assessment/measurements of psychomotor parameters and psychosocial development and functioning of motor, speech, social, emotional, focus and attention as well as cognitive characteristics/capacities were performed.

Results: Our neurodevelopmental evaluation showed a significant deviation in the neurodevelopmental parameters of children born from cryopreserved embryos in comparison with freshly used embryos from the same ovarian cycle, i.e. brothers/sisters obtained from fresh-unfrozen embryos from the same cycle had average psychosocial and psychomotor neurodevelopmental parameters.

Conclusion/recommendation: Given observed early neurodevelopmental deviations and the relatively recent large-scale implementation of such techniques, used also by ART labs in RNM, represents the need and possibility for such cases to be followed systematically and objectively and further studies to be provided for more conclusive evidence on outcomes and implications.

Keywords: *neurodevelopmental disorders, cryopreservation; twins, fresh embryo transfer; frozen embryo transfer*

Topic: *Reproductive and prenatal genetics*

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WHOLE EXOME SEQUENCING IN PRENATAL DIAGNOSTICS – ADVANTAGES AND DISADVANTAGES

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WES in prenatal diagnostics can be advantageous for family planning and medical assistance when accompanied by thorough analysis and consultation, but it can also result in genetic reports with inconclusive statements. Moreover, pregnancies require quick results, but due to the analysis being a very time-consuming process, a report cannot always be ready in the necessary timely manner. Here we report 9 cases where WES was used in order to determine the cause of various fetal clinical manifestations.

Whole Exome Sequencing was performed for all fetuses and a panel of genes was analyzed depending on the observed ultrasound pathogenic markers. Variants flagged through the analysis were confirmed and segregated in the fetuses' families via Sanger sequencing.

Out of 9 cases we successfully concluded 8 and had one sample with unknown genetic etiology. The cases were analyzed based on ultra-sound data including clubfoot, cerebellar hypoplasia, skeletal malformations, etc. The genetic variants, determined as causative, were found in the following genes: *COL3A1, DLL1, ARSL, PLOD2, COL1A1, CEP290, RAPSN* and *AIFM1*.

WES provides incomparable advantages when it comes to prenatal diagnostics. It allows for careful planning in current and future pregnancies, given that the patients are supported by appropriate consultation. However, it needs to be considered that analysis of WES data is a time-consuming process and the known clinical manifestations in a fetus are limited, therefore successful diagnosis might not be feasible.

Keywords: *Prenatal diagnostics, Challenges, Whole Exome Sequencing*

Topic: *Reproductive and prenatal genetics*

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PRELIMINARY STUDY RESULTS OF FAMILIES' WITH FETAL ULTRASOUND ABNORMALITIES APPROACHES TO INVASIVE DIAGNOSIS AND OUTCOMES IN PREGNANCIES

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Prenatal diagnosis provides the earliest, fastest, and most accurate identification of fetal health problems caused by genetic or non-genetic factors. The risk of having a child with a chromosomal abnormality in each pregnancy is 1:400 and, in some cases, exceeds the population risk. This preliminary study aimed to evaluate the rates of invasive prenatal diagnostic testing and the attitudes of families referred to the Genetic Counseling Unit of the Department of Medical Genetic, Istanbul Faculty of Medicine due to fetal ultrasonography (USG) abnormalities.

In this study, face-to-face interviews were conducted with 164 families referred to our unit because of anomalies detected by fetal USG. Of the 122 families who agreed to participate in the survey, 74 had at least one of the invasive prenatal diagnostic tests. Karyotype analysis, fluorescence in-situ hybridization (FISH), and array-CGH studies were performed.

A chromosomal abnormality was detected in 14 (18.9%) of 74 families who underwent invasive prenatal diagnostic testing. Eight (57.2%) of these cases had a numerical anomaly, and 6 (42.8%) had a structural chromosomal anomaly. Trisomy 21 (n=5, 35.7%) was the most common numerical anomaly, and microdeletion/duplication of unknown parental origin (n=3, 50%) was the most common structural anomaly. Seven families with numerical chromosomal abnormalities and five with structural abnormalities accepted the termination option with the results.

This study emphasizes the importance of cytogenetic analysis in the follow-up, management, and prognosis of risky pregnancies.

Keywords: *Genetic counseling, fetal ultrasonography, prenatal diagnosis, chromosomal abnormality*

Topic: *Genetic counseling*

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A CASE REPORT ON MATERNAL TRANSLOCATION T(X;21)(Q13;P12) AND ITS INHERITANCE

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Reciprocal balanced translocations represent the exchange of segments between 2 chromosomes and it is known that such abnormalities cause no phenotypic effect on the carrier, but can elevate the risk of producing unbalanced gametes, which may lead to pregnancy complications. We report a case of a woman with balanced translocation 46,X,t(X;21)(q13;p12) who had two terminated pregnancies because of medical indications.

We conducted cytogenetic chromosomal analysis of the woman using peripheral blood, while prenatal cytogenetic diagnostic was performed using amniotic fluid by flask method. Conventional G-banding analysis and banding analysis using silver nitrate (NOR) were carried out by Applied Spectral Imaging (ASI) software.

Karyotype analysis of woman revealed a rare balanced translocation between q arm of chromosome X and p arm of chromosome 21 which seemed very interesting because of the breakpoint on chromosome 21 occurring within the region containing stalks and satellites. A woman faced first pregnancy termination due to a positive non-invasive prenatal testing (NIPT) result indicating high risk for trisomy of chromosome X. The second pregnancy was terminated because the prenatal analysis of the fetus from the chorionic villus showed the presence of a derivate of chromosome 21. Lastly, in her third pregnancy she underwent prenatal cytogenetic diagnostic of amniotic fluid, revealing that the female fetus had inherited the same translocation carried by the mother and she continued the pregnancy.

For couples where it is known that one of them is carrier of reciprocal balanced translocation and with a history of targeted abortions, proper genetics counseling for prenatal diagnostics is of crucial importance.

Keywords: *Reciprocal translocation, Postanatal diagnostic, Prenatal diagnostic, Maternal inheritance*

Topic*: Reproductive and prenatal genetics*

PP-63

LINKING KIR AND HLA POLYMORPHISMS TO REPRODUCTIVE CHALLENGES IN MACEDONIAN COUPLES

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Background: Uterine natural killer cells (uNK) have unique membrane receptors (KIRs) that interact with HLA molecules on extravillous trophoblast cells (EVT). Understanding the effects of this complex KIR-HLA interaction on implantation and pregnancy outcomes has been a major research focus. This study aimed to identify whether certain alleles, haplotypes, and combinations of KIRs and HLAs are linked to a higher risk of complications during implantation and throughout pregnancy.

Materials and methods: A total of 122 couples with fertility and pregnancy issues participated in the study after obtaining written consent as of May 2023. Genetic analysis was conducted using SSP technology (Olerup SSP™). Groups were formed based on their reproductive pathology. The control group was comprised of 122 previously studied, KIR-genotyped healthy females who had experienced successful pregnancies without any prior reproductive complications. Additionally, 17 couples with two or more children were included as a separate control group for comparative analysis.

Results: Statistical significance was found in **KIR2DS1 ($p<0.01$).** However, no significant associations were observed between specific KIR alleles/haplotypes or KIR/HLA combinations and particular reproductive pathologies across the different groups.

Conclusion: Preliminary findings suggest that activating KIR2DS1 is less common in females with fertility and pregnancy challenges compared to the control group. The absence of KIR2DS1 might lead to insufficient activation of uNKs, potentially causing issues with embryo implantation and placental development. Larger-scale studies are needed to better comprehend the specific KIR-HLA interactions and their effects on placental vascular remodeling.

Keywords: *KIR, HLA, fertility, pregnancy*
Topic: *Reproductive and prenatal genetics*

PP-64

WHOLE-EXOME SEQUENCING ON PRODUCTS OF CONCEPTION FROM EARLY PREGNANCY LOSSES REVEALS A HIGH FREQUENCY OF VARIOUS MONOGENIC DISORDERS

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Background: One of the most common pathologies during pregnancy is the early pregnancy loss (EPL) and in about 50% the etiology is unknown. Isolated studies have reported different monogenic conditions as a cause of EPLs.

Material and methods: We have performed whole–exome sequencing (WES) in 55 euploid products of conception (POCs) from EPLs (< 12 gestational week), from 53 couples.

Results: Genetic diagnosis of monogenic condition was confirmed in 27,3% (15/55) of the euploid EPLs. Pathogenic/likely pathogenic variants in 4 different autosomal recessive (AR) genes: *CPLANE1, DHCR7, RBM8A, F5* and 8 autosomal dominant (AD) genes: *SLC6A1, TSC1, VWF, TNNT2, FLNB, NF1, DVL1, DSG2* were identified in 7 and 8 EPLs, respectively. These genes fall into 5 disease categories: developmental/multisystem disorders (4 EPLs), followed by cardiac, skeletal and blood disorders (2 EPLs each), and neurologic disorder (1 EPL). With exception of CPLANE1-related Joubert and Smith-Lemli-Opitz syndromes determined in three and two EPLs, respectively, all other conditions were present in a single EPL. In addition, double heterozygosity of a pathogenic and a variant of unknown significance (VUS) in 5 AR genes (PAH, GBA1, ACDAM, RPGRIP1L and PKHD1) was detected in 4 EPLs. VUS variants in 4 AD genes (PRDM6, TBX18, SCN5A and MYH3) were also detected in 4 EPLs.

Conclusion: Our study reveals a high frequency of various monogenic diseases with both childhood and late-onset manifestations in euploid EPLs, suggesting their potential detrimental role to the early fetal development or contribution to the occurrence of EPLs together with other factors. Besides extending the knowledge, our findings are important for proper counselling and better management of couples experiencing EPLs.

Keywords: *Early pregnancy loss, EPL, WES*
Topic: *Reproductive and prenatal genetics*

PP-65

PREGNANCY COURSE AND DELIVERY IN WOMAN WITH SPINAL MUSCULAR ATROPHY TYPE II: A CASE REPORT

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Background: Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by the degeneration of alpha motor neurons in the spinal cord. Limited data is available to help guide neurologists and obstetricians in counselling their SMA patients on issues related to pregnancy and childbirth.

Materials and methods: To increase the present limited knowledge on pregnancy and delivery in women with spinal muscular atrophy.

Results: The authors report the pregnancy course and delivery features of a 42-year-old female patient with a clinical and genetic diagnosis of SMA type II. The genetic testing revealed a deletion of exons 7 and 8 of the SMN1 gene and three copies of the SMN2 gene, which confirmed the clinical diagnosis. The only natural pregnancy this woman experienced was 7 years ago, which resulted in the live birth of a boy after years of sterility treatment. The pregnancy was without any complications. The delivery was by caesarean section. Concerning this, this SMA mother presented increased weakness during pregnancy that persisted for some weeks after delivery. Currently, this patient is not on therapy for spinal muscular atrophy. It is planned to start by the end of this year.

Conclusions: This information regarding pregnancy in women with genetically confirmed SMA will prove useful in guiding future research and in providing counselling to women with SMA. This will be even more important now that carrier screening and perinatal screening are possible.

Keywords: *spinal muscular atrophy SMA type II pregnancy course pregnancy outcome delivery*

Topic: *Other*

PP-66

CYP2C9 SCREENING: IMPORTANT STEP IN SIPONIMOD TREATMENT OF SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: The siponimod has been recently approved as a treatment for active, secondary progressive multiple sclerosis (SPMS) in Serbia. This drug is predominantly metabolized by cytochrome P4502C9 and two alleles (CYP2C9*2 and CYP2C9*3) were associated with decreased enzyme activity. Subsequently, reduced siponimod metabolism is leading to increased drug exposure, as well as, increased risks of adverse events. The CYP2C9*3/*3 genotype represents contraindication for drug administration while genotypes CYP2C9*1/*3 and CYP2C9*2/*3 may require dose reduction.

Materials and methods: To estimate CYP2C9 genotype frequencies in Serbian SPMS patients we preformed CYP2C9*2 (c.430C>T, p.R144C, rs1799853) and CYP2C9*3 (c.1075A>C, p.I359L, rs1057910) genotyping using TaqMan assays and real-time PCR methodology. SPMS patients were recruited from August 2021. to August 2023. and 364 patients were selected as potential candidates for siponimod treatment.

Results: The majority of patients (n=230, 63.19%) had wild-type genotype, CYP2C9*1/*1. The genotypes CYP2C9*1/*2 and CYP2C9*2/*2 were identified in 70 (19.23%) and 7 (1.92%) patients, respectively. The frequency of genotypes containing CYP2C9*3 allele was in total 15.66%. The most common was CYP2C9*1/*3 genotype, found in 47 patients (12.91%), while CYP2C9*2/*3 was present in 6 patients (1.65%). Four patients (1.1%) were not suitable candidates for siponimod treatment as they had CYP2C9*3/*3 genotype and non functional enzyme.

Conclusion: The CYP2C9*3/*3 frequency was higher in our patients with SPMS compared with other Caucasian populations, although without statistically significant difference, while frequencies of other genotypes were in accordance to the literature.

Keywords: *CYP2C9, siponimod multiple sclerosis, pharmacogenetics*

Topic: *Personalized medicine and Pharmacogenomics*

PP-67

POSSIBLE ASSOCIATION BETWEEN 3P21.31 (RS11385942) AND 9Q34.2 (RS657152) AND THE SEVERITY OF COVID-19 DISEASE IN PATIENTS FROM N. MACEDONIA

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Background: The COVID-19 pandemic has profoundly affected global health and researchers are working to understand the factors contributing to the severity of the disease. Although advanced age, gender, obesity and underlying comorbidities significantly influence the variation observed in the clinical symptoms of COVID-19, it has been suggested that genetic variants may also be involved in the disease severity.

This study aimed to investigate the possible association between 2 single nucleotide polymorphisms (SNP) 3p21.31 (rs11385942) and 9q34.2 (rs657152) which were associated with the severity of COVID-19 disease in numerous populations.

Materials and methods: Using TaqMan genotyping analysis a total of 661 SarSCoV -2 positive patients were tested of which 214 (32.4%) were patients with a medium/ asymptomatic form, 297(44.9%) patients with severe, 150 (22.7%) were patients with a critical form of the Covid_19 disease. The mean age of the analyzed patients was 59.9±8.2 years and the sex distribution was 386 females and 275 males.

Results: A statistically significant difference was obtained between the group of patients with a critical form of the COVID-19 disease and the risk -A allele for the 9q34.2 (rs657152) polymorphism (p=0.00037) (Table 1). No association was found

between 3p21.31 (rs11385942) SNP and the severity of the COVID-19 disease. Based on previous findings and in line with our findings age> 50, and male gender were also associated with COVID-19 severity with a significant difference of $p<0.001$.

Conclusions: Only the 9q34.2 (rs657152) variant was associated with the severity of the COVID-19 disease in the Macedonian population, whereas no such association was found for the 3p21.31 (rs11385942). These data indicate that the genetic factors linked to these two variants act in cooperation with other, population specific, clinical and/or genetic factors in the determination of the severity of the COVID 19 disease.

Keywords: *COVID-19, rs11385942, rs657152, critical form of the disease, TaqMan genotyping analysis.*

Topic: *Other*

PP-68

CORRELATION BETWEEN THE MOST PREVALENT HPV TYPES AND CYTOLOGICAL FINDINGS IN MACEDONIAN WOMEN

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Objectives: Based on epidemiological and laboratory studies, human papillomavirus (HPV) is considered a primary cause of uterine cervical cancers. There also have been several studies regarding the role of genital co-infections in the development of cervical intraepithelial lesions (CIN) and cervical cancer in HPV infected woman. The aim of this study was to examine the association between the HPV infection and genital co-infections with cervical intraepithelial neoplasia / cervical carcinoma.

Methods: 9579 patients with ASCUS, CIN I, CIN II , CIN III, CIS or cervical carcinoma were analyzed. Both positive and control group were tested for seven types of genital co-infections. Pathogen detection was performed by multiplex testing with the method of cyclic-CMTA (Cyclic-Catcher Melting Temperature Analysis).

Results: The overall rate of HPV infection was 27.6 %. HPV infection was most common in patients with CIS, cervical carcinoma and adenocarcinoma (94,4 %, 98,0 % and 100 % respectively). The most common genital co-infections were Ureaplasma parvum (UP) Ureaplasma urealyticum (UU) and Chlamidia trachomatis (CT) an there was statistically significant association between HPV infections with UP, MH and CT infections.

Conclusions: There is strong correlation between HPV infection and cervical carcinomas. Associations between HPV infection with Ureaplasma parvum, Mycoplasma hominis and Chlamydia trachomatis can in part be explained as a result of the co-infection, taking in consideration that they share the same route of transmission. Infection with sexually transmitted pathogens is associated with separate cytological diagnoses ASCUS, CIN I, CIN II, but not with CIN III, CIS, invasive cervical cancer.

Keywords: *Human papillomavirus, Cervical cancer, Sexually transmitted disease*

Topic: *Other*

PP-69

KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS IN SFS – MARROW DONOR REGISTRY (MK-SFSMDR): FEASIBILITY IN IDENTIFYING BETTER DONORS

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Background: Different Killer Ig-Like Receptor (KIR) genes are valid for each donor-recipient pair based on the degree of HLA matching and the type of leukemia. The inhibitory or non-inhibitory effects of haplotype B among unrelated or sibling transplants is a perfect example for inconsistent results. KIR B haplotype donors are associated with reduced relapse risks and improved disease-free survival after unrelated donor transplants for acute myeloid leukemia. The aim of this study was to analyze KIR gene polymorphism in Scientific Foundation SPIROSKI - Marrow Donor Registry (MK-SFSMDR).

Materials and methods: The studied sample consists of 516 healthy unrelated individuals, aged 18-55 years. All individuals are donors of the MK-SFSMDR which signed Marrow Donor Registration and took buccal swabs. KIR gene content typing was performed by HistoGenetics (Ossining, NY 10562, USA) on Illumina platform. The population genetics analysis package, Arlequin, was used for analysis of the data.

Results: We found that all 16 KIR genes were observed in the MK-SFSMDR donors and framework genes *KIR3DP1, KIR2DL4, KIR3DL2,* and *KIR3DL3* were present in all individuals. The observed frequencies of other KIR genes were: *KIR2DP1* (0.971), *KIR2DL1* (0.971), *KIR2DL2* (0.562), *KIR2DL3* (0.882), *KIR2DL5* (0.523), *KIR3DL1* (0.942), *KIR2DS1* (0.0401), *KIR2DS2* (0.564), *KIR2DS3* (0.312), *KIR2DS4* (0.942), *KIR2DS5* (0.308), and *KIR3DS1* (0.374). We defined 35 genotypes from which one was AA group (genotype ID 1 = 27.13%) and the rest were Bx groups (34 genotypes = 72.87%).

Conclusions: Inclusion of KIR genotypes in molecular screening of bone marrow donors may increase efficacy for stem cell transplantation.

Keywords: *KIR gene polymorphism, KIR genotyping Illumina, SFS-Marrow Donor, Registry Scientific Foundation SPIROSKI*

Topic: *Immunogenetics and haemopoietic system*

PP-70

HYPER IGM SYNDROME- CASE REPORT

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Background: Hyper IgM syndrome is a rare primary immune deficiency disorders characterized by low or absent levels of serum IgG, IgA, IgE and normal or increased levels of IgM. The most common form is inherited as an X-linked disease affecting boys. Most other forms of HIgM are inherited as autosomal recessive traits and affect boys and girls.

X-linked hyper IgM syndrome affects about 2 in every 1 million boys. The autosomal recessive forms of HIgM are extraordinarily rare, affecting fewer than 1 in 1 million people in the general population.

Most individuals with hyper IgM syndromes are susceptible to recurrent and severe infections, including opportunistic infections – which are infections caused by organisms that do not normally cause disease in healthy individuals.

Diagnosis: Specialized blood tests: the level of IgM and other immunoglobulin classes in the blood.

Molecular genetic testing: specific genes known to cause hyper IgM syndromes. Additional tests, including X-rays, blood and urine tests may be performed to guide early symptomatic treatment.

Treatment: Antibiotic, Immunoglobulin replacement therapy, bone marrow transplant.

Case report: K.Z, boy, 18 months. Clinical manifestations: frequent infections from the seventh month of life, mycotic infections of the mouth.

Lab: Le↑, CRP↑, SE↑, IgG↓, IgA↓, IgE↓, IgM is normal.Positive gene analysis: CD40LG mutant gene.

Treatment: antibiotics, antimycotics, immunoglobulins, Bone marrow transplant

Conclusions: Hyper IgM syndrome is necessary to be diagnosed as soon as possible and start with adequate treatment in order to have as little irreversible damage as possible.

Keywords: *Hyper IgM Syndrome CD40/ CD40 Primary immunodeficiency*

Topic: *Rare disease*

PP-71

EVALUATION OF THE ANTIOXIDANT POTENTIAL OF BIOCHAGA *IN VITRO*

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Background: Antioxidants and prooxidants have an impact on the intracellular oxidative equilibrium. Overproduction of prooxidants leads to oxidative stress caused by imbalances in oxidative reduction pathways. The body can be supplied with non-enzymatic, low molecular weight antioxidants through diet.The edible medicinal mushroom Chaga, Inonotus obliquus (Ach. ex Pers.) Pilat, has long been long used to treat or prevent various health conditions and disorders. The bioactive compounds of Chaga exhibit antitumor, anti-inflammatory, hypoglycemic, immunomodulatory, antioxidant, and antigenotoxic effects.

Material and Methods: DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activity, FRAP (ferric reducing antioxidant power) total antioxidant activity, and hydroxyl radical scavenging capacity were measured.

Results: Commercial Biochaga (B), a water extract of Biochaga mushroom, was obtained from Sibpribor Ooo, Irkutsk, Russia. B (IC =5.9 mg/mL) showed moderate reducing power compared in comparison to vitamin C and strong compared to BTH. B (IC =1.78 mg/mL) showed remarkable free radical scavenging and moderate hydroxyl scavenging activity (IC =8.473 mg/mL).

Conclusion: We can place Biochaga in the radical scavenging category because it efficiently eliminates hydroxyl radicals against which the body has insufficient antioxidant defenses.

Keywords: *Biochaga comet assay, Antioxidant DNA damage*

Topic: *Other*

PP-72

A CASE OF CHIMERISM IN A PATERNITY STUDY

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Background: Chimerism is a condition where an individual carries more than one complete genome. Chimerism can be acquired or congenital. Working in forensic genetics can sometimes bring in a specific situation where the result of a DNA analysis from a reference sample surprises you. This is a case, in the beginning a simple one, of a paternity test where the alleged father wanted to know if the little girl was his biological child.

Aim: The aim of this work was to solve the paternity study and to evaluate its consequence in forensic genetics.

Methods: The test was performed from five buccal swabs taken three from the alleged father, one from the mother and one from the baby. The PCR method used tested 16 STR autosomal loci and AMELO (sex determination). Capillary electrophoresis was performed in Genetic Analyzer 3500.HID.

Results and Conclusions: All the samples analyzed from the alleged father gave a mix DNA profile-three loci with three alleles (D16S539, D22S1045, D19S433), three loci with four alleles (D21S11, D12S391, SEE33) and ten loci with two alleles. The alleged father underwent through a bone marrow transplant 12 years ago and the donor was his brother - these facts explained the surprising results we had and identified this case as chimera. This is the first chimera case identified for DNA paternity testing purposes in Albania and the information for medical history of the alleged father was very useful.

Keywords: *Chimera, DNA paternity testing, Forensic genetics, STR profile*

Topic: *Other*

PP-73

USE OF Y CHROMOSOME DEMOGRAPHIC CHARACTERISTICS IN TRACING BALKAN POPULATION ORIGINS

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The Y chromosome haploid marker is one of the most informative genetic markers with application in forensics, medical genetics, genealogy, human migration studies and evolutionary population studies. Y chromosome binary polymorphisms specified to haplogroups are genetically diverse with subhaplogroups geographically distinct from one another, consistent with population fragmentation and expansion in different parts of the world. The Y chromosome subhaplogroups shows geographic regionalization connected to the origin, diffusion and differentiation of haplogroups. Haplogroups F and H are the most frequent in Asian continent whereas haplogroups I and J are quite restricted to Europe and Middle East respectively. Geographical position of Balkan Peninsula, serving as a corridor between Europe and Asia Minor allowed population migration and cultural movements of people, to and from Europe into Anatolia and Middle East. The most frequent haplogroups in population of Balkan countries are haplogroups I2, R1a and E1b1b descending from Europe, west Asia and Africa respectively.

In our study we have analyzed population in the Republic of North Macedonia representing three major ethnic groups (Macedonians, Albanians and Turks) in the country. Individuals were analyzed for Y-STRs and Y-SNPs using minisequencing and fragment analysis. The most frequent haplogroups in these three ethnic groups differ between each group, but correspond to the overall genetic milieu of the Balkan population.

Keywords: *Y chromosom, population genetics, Balkan countries*

Topic: *Other*

PP-74

EVALUATION OF GENETIC VARIANTS RELATED TO CONGENITAL MONOSACCHARIDE AND DISACCHARIDE METABOLISM DISORDERS FROM DATA OBTAINED BY WHOLE EXOME SEQUENCING, AND DETERMINATION OF CARRIER RATIOS IN ÇANAKKALE

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Background: Adverse food reactions, often underestimated, encompass congenital monosaccharide-disaccharide metabolism disorders, yielding diverse outcomes such as abdominal pain, diarrhea, bleeding disorders, and even death. This study retrospectively scrutinized genetic variants linked to these disorders in a cohort subjected to whole-exome sequence analysis (WES).

Material and methods: Data from 484 patients were retrospectively analyzed using a gene panel (*ALDOB, FBP1, GALE, GALK1, GALM, GALT, LCT, SLC2A2, SLC5A1, SI*) for congenital monosaccharide-disaccharide metabolism disorders. WES was performed on 107 patients for segregation and 377 for clinical features using the xGen Exome Research Panel v2 kit. The study encompassed pathogenic, likely pathogenic, and variant of uncertain significance (VUS) variants.

Results: Among 484 patients, 17.35% carried 99 variants (67 distinct) in the analyzed genes. Pathogenic/likely pathogenic allele frequency stood at 0.013, while VUS allele frequency was 0.088 (total 10%). Variants were discerned in 19.6% (21/107) during segregation analysis and 16.7% (63/377) in clinical cases. Notably, 44% (37/84) of patients harboring mutations manifested at least one relevant phenotype. Carriage frequencies ranged from 1:25 (*SI* gene) to 1:968 (*GALE* gene), with the estimated disease frequency spanning from 1:2500 to 1:3748000.

Conclusion: This study underscores clinical manifestations in heterozygous carriers of recessive genetic disorders, addressing gaps in carrier frequencies and phenotypic effects for congenital monosaccharide-disaccharide metabolism disorders. Its implications extend to shaping national health policies and enriching international literature.

Keywords: *Genotype-phenotype correlation inborn metabolic disorders carrier frequency population genetics nutrigenetics*

Topic: *Other*

PP-75

ASSOCIATION OF THE *FABP2* ALA54THR POLYMORPHISM WITH OBESITY IN YOUNG NORTH MACEDONIANS

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Background: Genetic predisposition and specific single-nucleotide polymorphisms (SNPs) play a role in the risk of obesity. The Ala54Thr polymorphism of the *FABP2* gene, which encodes the IFABP protein, has been associated with obesity and obesity-related metabolic disorders. We assessed the association between obesity-related SNPs in the *FABP2* gene and obesity-related parameters in the North Macedonian population.

Material and Methods: A total of 107 individuals aged 18 to 40 participated in this study. Obesity was defined using the BMI index. Anthropometric parameters, including waist circumference, tricep skinfold, and waist-to-hip ratio, were collected. Blood samples were collected to measure glucose, total cholesterol and triglycerides. The Ala54Thr allelic variant was determined using PCR and RFLP. Statistical analyses were performed using R, with p = 0.05. Using Fisher's Exact Test we assessed genotype and weight category relationships. With ANOVA, we examined genotypes vs. anthropometric and biochemical parameters.

Results: 42 participants had the Ala/Ala genotype, 47 had the Ala/Thr genotype, and 18 had the Thr/Thr genotype for the *FABP2* Ala54Thr polymorphism. The Ala allele frequency was 0.612, and the Thr allele frequency was 0.388. The Ala/Thr genotype was more prevalent among overweight individuals (p-value = 0.01). Significant association was found between genotype and waist circumference and waist/hip ratio (p-values 0.03 and 0.05), but not with tricep skinfold (p-value = 0.95). No significant relationship was observed between genotypes and biochemical parameters.Conclusions:The study reveals an association between the *FABP2* Ala54Thr polymorphism and obesity-related disorders in the North Macedonian population.

Keywords: *Obesity, FABP2 genotype, polymorphism, BMI*

Topic*: Other*

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VDR GENE POLYMORPHISMS – FIRST EXPERIENCE OF OUR LABORATORY

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Background. Vitamin D is required to maintain normal serum calcium and phosphate levels that help normal bone mineralization, nerve conduction, muscle contraction, immune function, cell proliferation, and differentiation. High prevalence of vitamin D serum deficiency has been described in several autoimmune diseases, including multiple sclerosis and rheumatoid arthritis. Many studies showed that supplementation with vitamin D may not improve the vitamin D deficiency due to genetic variation. The aim of our study was to analyze SNPs in the VDR gene in the Macedonian population.

Material and methods. Fifty patients were referred to the Institute of Immunobiology and Human Genetics with different diagnosis like vitamin D deficiency, multiple sclerosis, rheumatoid arthritis, osteoporosis ect., to be tested for SNPs in genes related to vitamin D metabolism. The presence of 28 SNPs in 7 genes: GC, *CYP27B1, DHCR7, CYP2R1, CYP24A1, VDR* and *COL1A1* were analyzed using reverse line strip (RLS) kit from Vienna Lab, Vienna.

Results. We analyzed 31 female and 19 male patients, with an age range from 1 to 59 years. We analyzed 5 SNPs in the VDR gene. The TT genotype in rs10783219 had frequency of 16%, the TT genotype in FokI (rs2228570) 24%, AA genotype in Bsml (rs1544410) 26%, AA genotype in ApaI (rs7975232) 42% and CC genotype in TaqI (rs731236) 18%. The association of different SNPs with different diseases wasn't performed due to the small sample size.

Conclusion. Recent studies confirm the genetic risk to the carriers of VDR SNPs in autoimmune diseases. Nevertheless, to evaluate the real risk in our population we need to determine the frequency of the different SNPs in the healthy Macedonian population.

Keywords: *Vitamin D, VDR gene, autoimmune disease*

Topic: *Other*

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