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**2nd B&H SYMPOSIUM
OF LABORATORY GENETICISTS
AND MOLECULAR BIOLOGISTS
(WITH INTERNATIONAL PARTICIPATION)**



The Official Publication of the
Institute for Genetic Engineering and Biotechnology
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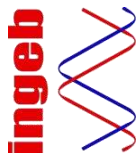
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**2ND B&H SYMPOSIUM OF LABORATORY GENETICISTS AND MOLECULAR BIOLOGISTS
(WITH INTERNATIONAL PARTICIPATION)**

10TH - 11TH MAY 2024, BANJA LUKA, BOSNIA AND HERZEGOVINA

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**2nd B&H SYMPOSIUM OF LABORATORY GENETICISTS AND
MOLECULAR BIOLOGISTS (WITH INTERNATIONAL
PARTICIPATION)**

May 10th 2024	Friday - FIRST DAY	
8:30-9:00	Registration of participants	
9:00-9:20	Opening and welcome speech	Radoslav Dekic, PhD, Dean of FNSM, Banja Luka Stojko Vidovic, PhD, Medical Faculty Banja Luka Marija Vukovic, PhD, University Clinical Center of the Republic of Srpska, Banja Luka
9:20-9:40	Trends in psychiatric genetics	Lejla Kapur Pojskic, PhD, INGEB, Sarajevo
9:40-10:00	Neurodegenerative diseases –challenges and perspectives in molecular approach treatment	Jasmin Ramic, PhD, INGEB, Sarajevo
10:00-10:20	Molecular-genetic diagnostics autism spectrum disorders	Nela Maksimovic, PhD, Institute for Human Genetics, Belgrade University, Medical Faculty
10:20-10:30	Discussion	
10:30-11:00	Coffee break	
11:00-11:30	Genomics as a basis for personalized medicine	Sonja Pavlovic, PhD, IMGGE, Belgrade
11:30-12:00	Detection of copy number variants in genome and their significance in human diseases	Dijana Perovic, PhD, Institute for Human Genetics, Belgrade University, Medical Faculty
12:00-12:30	Cytogenetics in the era of molecular karyotyping	Leona Morožin Pohovski, PhD, Children's Hospital Zagreb
12:30-13:00	The role of genomic instability in the promotion and progression of malignant tumors - diagnostic and prognostic significance	Nikola Tanic, PhD, The University of Belgrade, Institut for Biological Research “ Sinisa Stankovic“, Institut of National Interest for Republic of Serbia, Belgrade, Republic of Serbia

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13:00-13:15	Sponzorsko predavanje Profy: OPTIMIZE YOUR MSI WORKFLOW WITH PROMEGA	Kriti Pathak, Promega GmbH, Walldorf, Germany
13:15-14:15	Lunch	
14:15-14:40	Conventional and molecular diagnostics of myeloproliferative neoplasms and acute myeloid leukemia – the experience of Clinic of Hematology UCCS	Vesna Djordjevic, PhD, University Clinical Center of Serbia, Belgrade
14:40-15:05	Diagnostics of chronic lymphocytic leukemia and multiple myeloma: from cytogenetic to NGS	Marija Dencic, PhD, Medical Faculty, Belgrade
15:05-15:25	Conventional cytogenetic analysis in chronic lymphocytic leukemia	Jelica Jovanovic, spec.geneticist, University Clinical Center of Serbia, Belgrade
15:25-15:40	Cytogenetic and molecular-genetic aberrations in acute lymphoblastic leukemia in adults- the experience of Clinic of Hematology UCCS	Sandra Bizic Radulovic, spc.geneticist, University Clinical Center of Serbia, Belgrade
15:40-15:50	Disccusion	
15:50-16:15	Genetic influences on metabolic diseases development	Malgorzata Wrzosek, PhD, Collegium Medicum, Jan Kochanowski University, Kielce, Poland 2) Department of Biochemistry and Pharmacogenomics, Faculty of Pharmacy, Medical University of Warsaw, Warsaw, Poland
16:15-16:30	Human genetic variants modulating the course of COVID-19 infection in a subset of Bosnian-Herzegovinian patients.	Adna Asic, PhD, Verlab Research Institute for biomedical engineering, medical devices and artificial intelligence
16:30-16:40	Disccusion	
16:40-17:30	Poster Presentation	
20:00-24:00	Gala Dinner	Restaurant Integra-14.floor

**2nd B&H SYMPOSIUM OF LABORATORY GENETICISTS AND
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May 11th 2024	Saturday - SECOND DAY	
9:00-11:00	Satellite symposium-“ Pharmacogenomics in the era of next-generation sequencing ”.	PharmGenHub project granted by EU throughout program Horizon Widera 2021 - Twinning Western Balkan
11:00-11:30	Discussion	
11:30-12:00	Coffee break	
12:00-12:30	Pharmacogenomics and pharmacotranscriptomics of acute myeloid leukemia in childhood: on the way to personalized medicine	Branka Zukic, PhD, IMGGE, Belgrade
12:30-12:50	Significance of TPMT genotyping in clinical practice	Vanja Vidovic, PhD, Medical faculty, Banja Luka
12:50-13:10	Genotipization of promotor variants of UGT1A1 gene as a pharmacogenetic marker in clinical practice	Marija Vukovic, PhD, University Clinical Center of Republic of Srpska, Banja Luka
13:10-13:25	Sponzorsko predavanje Mikro&Polo: A Novel Digital PCR Tool for Parallel Detection of Multiple Hallmark Mutations in BRAFV600 and EGFR exon19	Dr. Ellen Bruske
13:25-13:30	Discussion	
13:30-14:30	Lunch	
14:30-14:50	Application of molecular karyotyping in prenatal diagnostics	Jadranka Vranekovic, PhD, University of Rijeka, Faculty of Medicine
14:50-15:10	Genetic causes of male infertility; karyotyping and Y microdeletion analysis	Nada Starcevic Cizmarevic, PhD, University of Rijeka, Faculty of Medicine
15:10-15:30	Subfertility and sterility of couples: mutations associated with thrombophilia - more than a coagulation disorder and why both partners should be tested after re-occurring spontaneous abortions	Zeljko Popovic, PhD, FNSM; GenoLab, Laboratory of Medical Biochemistry and Molecular Diagnostics, Novi Sad
15:30-15:45	Pros and cons of dietary antioxidants: interindividual variability of flavonoids genotoxicity	Maida Hadžić, PhD, INGEB, Sarajevo

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15:45-16:00	Assessment of Immunomodulatory and Epigenetic Effects: A Comparative Study of Cytokine Profiles between Plant-Based and Omnivorous Diets	Marta Despotovic, research assistant, Institute for Medical Research, Belgrade
16:00-16:10	Discussion	
16:10-17:00	Declaration of the best poster, Closing ceremony	
	Parallel sessions: The posters will be displayed continuously in the entrance hall of the Amphitheater. Presenting authors will be available for questions and discussion personally.	

POSTERS

KOŽIK BOJANA (*Laboratory for Radiobiology and Molecular Genetics, Vinča Institute of Nuclear Sciences, National Institute of Republic of Serbia, University of Belgrade, Belgrade, Serbia*): SPATIAL EXPRESSION OF ZEB1 GENE AS A POTENTIAL PROGNOSTIC MARKER IN RECTAL CANCER

KRAJNOVIĆ MILENA (*"Vinča" Institute of Nuclear Sciences - National Institute of the Republic of Serbia, University of Belgrade, Laboratory for Radiobiology and Molecular Genetics, Mike Petrovića Alasa 12-14, 11001 Belgrade, Serbia*): SEQUENCE VARIABILITY OF HCV CORE REGION AND HOST GENETIC AND EPIGENETIC FACTORS CAN PREDICT THE RESPONSE TO COMBINED PEG-IFN/RBV THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION GENOTYPE 1B

TOVILOVIĆ-KOVAČEVIĆ GORDANA (*Institute for Biological Research "Siniša Stanković" – National Institute of the Republic of Serbia, University of Belgrade, Belgrade, Serbia*): ANTIHEPATOMA ACTIVITY OF METHANOL EXTRACTS FROM *THYMUS PANNONICUS* IN VITRO SHOOT CULTURES

BOŽOVIĆ ANA (*Vinča Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade, Belgrade, Serbia*): ERB IS A POSSIBLE BIOMARKER OF BREAST CANCER

ROLJIĆ ALEKSANDRA (*Pan-European University Apeiron, Banja Luka, Bosnia and Herzegovina*): CORRELATION OF GENETIC FACTORS WITH SPORTS PREDISPOSITIONS

ANDJELKOVIC MARINA (*Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia*): CHARACTERIZATION OF 16 NOVEL GENETIC VARIANTS IN GENES ASSOCIATED WITH EPILEPSY

MALEŠEVIĆ BOJANA (*University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina*): A RARE TRISOMY OF CHROMOSOME 4 IN ACUTE MYELOID LEUKEMIA - CASE REPORT

DEVANTIER-DU PLESSIS CARLA (*Medical Faculty, University of Sarajevo, Sarajevo, Bosnia and Herzegovina*): DETERMINING SIBSHIP INDICES WITH 15 STR LOCI: CENTRAL BOSNIA STUDY

BLAGOJEVIĆ DANIJELA (*Public Health Institution Hospital "Sveti Vračevi", Bijeljina, Bosnia and Herzegovina*): CHALLENGES IN SARS-CoV-2 DIAGNOSTICS BY REAL TIME RT-PCR

IGNJATOVIĆ ĐURĐICA (*Institute for Biological Research "Siniša Stanković" - National Institute of Republic of Serbia, University of Belgrade, Belgrade, Republic of Serbia*): EFFECTS OF PRENATAL DEXAMETHASONE TREATMENT AND MODERATE POST-WEANING FRUCTOSE CONSUMPTION ON RECOGNITION MEMORY IN ADULT MALE WISTAR RAT OFFSPRING

SOFTIĆ ADNA (*Verlab Research Institute for Biomedical Engineering, Medical Devices and Artificial Intelligence, Sarajevo, Bosnia and Herzegovina*): ENHANCING SPORTS PERFORMANCE BY INSIGHTS FROM GENETIC TESTING OF YOUNG ATHLETES FROM BOSNIA AND HERZEGOVINA

VUČIĆ GORDANA (*Laboratory for Immunohistochemical and Molecular Diagnostics, Institute of Clinical Pathology, University Clinical Center, Banja Luka, Bosnia and Herzegovina*): FREQUENCY OF V600E MUTATION IN BRAF GENE AMONG PATIENTS WITH METASTATIC MELANOMA ON THE TERRITORY OF BOSNIA AND HERZEGOVINA

ŠNJEGOTA DRAGANA (*Faculty of Natural Sciences and Mathematics, University of Banja Luka, Banja Luka, Bosnia and Herzegovina*): THE INFLUENCE OF SEX ON THE GENETIC STRUCTURE OF THE JACKAL (*CANIS AUREUS*) OF BOSNIA AND HERZEGOVINA

BRKLJAČIĆ JELENA (*Institute for Biological Research "Siniša Stanković" - National Institute of Republic of Serbia, University of Belgrade, Belgrade, Republic of Serbia*): DIETARY SUPPLEMENTATION WITH LIOPHILISED STRAWBERRY IMPROVES INSULIN SENSITIVITY AND REDOX STATUS IN MOUSE MODEL OF DIET INDUCED OBESITY

KULIĆ JOVAN (*Faculty of Medicine Foča, University of East Sarajevo, Foča, Republic of Srpska, Bosnia and Herzegovina*): THE ROLE OF ANGIOTENSIN I CONVERTING ENZYME INSERTION/DELETION POLYMORPHISM ON COVID-19 DISEASE SUSCEPTIBILITY

KRISTEL KLAASSEN (*Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Republic of Serbia*): GENETIC LANDSCAPE OF PHENYLKETONURIA IN SERBIA

VIRIJEVIC MARIJANA (*Clinic of Hematology University Clinical Center of Serbia, Faculty of Medicine University of Belgrade, Belgrade, Republic of Serbia*): NEW TERT VARIANT IN A FAMILY WITH APLASTIC ANEMIA

CIMESA MLADEN (*International Burch University, Department of Genetics and Bioengineering, Sarajevo, Bosnia and Herzegovina*): MICRORNA SIGNATURES IN ALZHEIMER'S DISEASE: A REVIEW OF DIAGNOSTIC POTENTIAL

ŠUŠKALO NEVENA (*University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina*): CASE REPORT OF INHERITED TRANSLOCATION T(12;13)(Q24.33;Q21.2)

MARJANOVIC IRENA (*Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Republic of Serbia*): NEW GATA3 VARIANT IN A PATIENT WITH BARAKAT SYNDROME

GABELJIĆ NUSRETA (*International Burch University, Sarajevo, Bosnia and Herzegovina*): ADVANCING ALZHEIMER'S DISEASE MANAGEMENT THROUGH PERSONALIZED MEDICINE: INTEGRATING GENETIC, NEUROINFLAMMATORY, AND BIOMARKER INSIGHTS

KONJHODŽIĆ RIJAD (*Alea Genetic Center, Sarajevo, Bosnia and Herzegovina*): OPTIMIZING CUSTOM-DESIGNED PRIMERS FOR COMPLETE MITOCHONDRIAL GENOME SEQUENCING WITH ILLUMINA® NEXTERA® XT SYSTEM AND CONFIRMATORY SANGER SEQUENCING

MASLIĆ SRETENKA (*University Clinical Centre of the Republic of Srpska, Department of Medical Genetics, Banja Luka, Bosnia and Herzegovina*): CASE REPORT: PRENATAL DETECTION OF PSEUDOISODICENTRIC CHROMOSOME 18Q

ZEKAVICA MAJA (*Department of Laboratory Diagnostics, University Hospital Medical Center "Zvezdara", Belgrade, Republic of Serbia*): TUMOR NECROSIS FACTOR ALPHA GENE POLYMORPHISMS -238G>A AND -308G>A AS GENETIC MARKERS FOR THE DEVELOPMENT OF ALCOHOL RELATED LIVER CIRRHOSIS

CURRENT TRENDS IN PSYCHIATRIC GENETICS

Pojškić Lejla

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Psychiatric Genetics (PG) is the (sub)field of Genetics with focus of understanding the heritability and organic nature of the mental disorders. The main orientation of PG efforts worldwide is in fostering basic and applied research on the ethical, legal and social implications of genetic and genomic research for individuals, families and communities. The PG is in that sense faced with technological and ethical barriers that need to be thoroughly assessed before the PG tests are put in clinic. The survey on the current pan-European capacities in PG was assessed through EnGage network of professionals. The most important findings are that there are no available guidelines for the clinical implementation of Psychiatric GC/GT; 58.6% and 26.5% of the respondents already provide PsychGC and PsychGT, respectively, either themselves or within their clinics/institutions; also there are significant differences between the regions in our study for the implementation and access to the facilities. Interestingly, but not surprisingly, discrepancies in PsychGC and GT offered within a country are widely present. Overall data shows that there is very heterogeneous knowledge and implementation throughout Europe of available techniques, guidelines, and sources of information in general for GC and GT, but also reflecting the early implementation of these for major psychiatric disorders.

Keywords: Psychiatric Genetics (PG); Psychiatric Genetics Counselling (PsychGC); Psychiatric Genetics Testing (PsychGT)

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NEURODEGENERATIVE DISEASES (ND) -CHALLENGES AND PERSPECTIVES IN MOLECULAR APPROACH TREATMENT

Ramić Jasmin, Pojskić Lejla, Lojo Kadrić Naida, Tomić Nikolina, Šarić Medić Belmina

Univerzitet u Sarajevu - Institut za genetičko inženjerstvo i biotehnologiju, Sarajevo, Bosna i Hercegovina

Neurodegenerative disorder are, for now, incurable disease and in treatment of this kind of disease physicians are mainly concentrated on symptom treatment. Few experimental investigations are in progress, and new technology and using AI promising if not much better treatment then better risk assessment in patients with this kind of disease. Advance in genome editing and different and for now experimental ways in drug delivery, from other side, promises new and improved methods for disease like Huntington's disease (HD). In this case autosomal dominant inheritance pattern of disease is caused by an inherited CAG trinucleotide expansion in huntingtin (HTT) gene, are usually with no treatment for disease itself but for emerging symptoms of disorder. The diagnosis of HD is usually established in a proband with symptoms of disease by the identification of an abnormal CAG trinucleotide repeat expansion in HTT gene by molecular genetic testing.

Keywords: neurodegenerative disorder, symptom treatment, risk assessment, experimental ways in drug delivery, genome editing

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MOLECULAR-GENETIC DIAGNOSTICS OF AUTISM SPECTRUM DISORDERS

Maksimović Nela, Perović Dijana, Damjanović Tatjana

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Autism spectrum disorders (ASD) are among the most common neurodevelopmental disorders, with a frequency as high as 1 in 59 children. These disorders are complex, extremely genetically heterogeneous, caused by both inherited and de novo gene variants, and in some cases, their interaction with environmental factors. Over the past decade, mutations in hundreds of genes have been identified that contribute to the severe communication, social interaction, and behavioral problems characteristic for ASD patients. However, they explain only up to 40% of cases and patients with the same or similar pathogenic gene variants can show significant differences in phenotype. Besides gene mutations, variations in modifier genes, copy number variations in the genome as well as epigenetic changes may have a key role in the manifestation of the ASD phenotype. There is a great necessity for genetic testing in this group of patients since the obtained results can influence the further course of therapy and clinical monitoring of patients. Genetic testing that is usually offered to patients with ASD includes testing for Fragile X syndrome, chromosomal microarray and whole exome sequencing. However, even in highly developed countries less than 50% of the patients get tested. Despite numerous researches, there are still no suitable diagnostic markers or specific therapies for the treatment of patients with ASD. At this moment, different researches are being conducted at the level of gene transcription, non-coding RNA, disorders in signal transport, epigenetic post-translational modifications of proteins, connections between the nervous and digestive systems, neuroinflammation, etc., all of which represents the theoretical basis for the next step, which should be personalized therapy. Some of the current research approaches in the field of therapy are: CRISPR activation and gene replacement, application of antisense oligonucleotides and drugs from the group of small molecules.

Keywords: autism spectrum disorders, genetic testing, gene mutations, CNVs, epigenetic modifications

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GENOMICS AS A BASIS FOR PRECISION MEDICINE

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Although medicine always aimed to be personalized, true implementation of personalized medicine in health care practice has started recently. Fascinating progress of molecular genetics has strongly contributed to this great achievement of modern medicine. Personalized medicine, also known as genome-based medicine and precision medicine, uses the knowledge of molecular basis of the disease in order to individualize treatment for each patient. Development of novel powerful high-throughput technologies has enabled better insight into “oms” landscape of many diseases, resulting in application of precision medicine approaches in their treatment. There are four cornerstones of modern precision medicine: “omics”-based diagnostics, pharmacogenomics, specific molecular targeted, gene and cellular therapy and predictive genomics. One of the most important successes of precision medicine is a discovery of novel diagnostic molecular markers. Furthermore, numerous newly discovered molecular markers have contributed to more precise classification of patients in distinct prognostic groups, leading to specific, more successful treatment protocols. Development of pharmacogenomics platforms and application of molecular-targeted therapy have led to the individualization of therapy, tailored to genetic profile of a disease in each patient. The development of gene therapies which can cure or prevent a disease by targeting disease-causing molecular defect has confirmed that the precision medicine has responded successfully to a great challenge. Additionally, cellular and tissue therapies have opened new possibilities for personalized treatment of many patients. Growing knowledge in predictive genomics leads to the preventive medicine, the most important goal of modern medicine. There is no doubt that we are getting closer to full implementation of precision medicine in every day clinical practice.

Keywords: genomics, precision medicine, molecular diagnosis, pharmacogenomics, molecular targeted therapy, gene therapy, stem cell therapy

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DETECTION OF COPY NUMBER VARIANTS IN GENOME AND THEIR SIGNIFICANCE IN HUMAN DISEASES

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Copy number variations (CNVs) are middle-sized quantitative genomic variants. They are recognized as an important source of normal variations in the genome as well as a cause of a number of diseases, which has led to a recent surge in interest in their detection in clinical diagnostics. The classical definition of CNVs includes gain or loss of genetic material between 1 kb and 5 Mb. An increase in the resolution of genomic tests during the last decades has been followed by a decrease in the size of altered genomic regions designed as CNV, with the current lower limit of ≥ 50 bps. A change in dosage of the gene(s) intolerant to haploinsufficiency or exhibit triplosensitivity is obvious and the most common CNV disease-causing mechanism. Alternatively, it could be disruption of a gene or its regulatory elements, a positional effect, or demasking the recessive allele. The phenotype resembles monogenic disease, or it could be part of contiguous gene syndromes, also known as microdeletion and microduplication syndromes (MDDs). Recurrent MDDs, with similar boundaries, originate mostly from non-allelic homologous recombination in hot-spot genomic regions rich in segmental duplications, while non-recurrent MDDs could happen in any part of the genome and be caused by other mechanisms based on DNA repair or errors during DNA replication. Large-scale CNVs, more than 5 Mb in size, could be detected by classical karyotyping. Middle- and low-scale ones require locus-specific techniques like FISH and MLPA, or molecular karyotyping and new-generation sequencing methods for genomic coverage. Array comparative genomic hybridization (a-CGH) is a reliable and gold standard technique for genomic CNV detection in most laboratories today. We aim to present our 5-year laboratory experience in CNV detection and interpretation in postnatal diagnostic settings using the CGH methodology.

Keywords: copy number variations, detection, array-CGH

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ROLE OF CYTOGENETICS IN THE ERA OF MOLECULAR KARYOTYPING

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Molecular karyotyping, also “array-based Comparative Genomic Hybridization” (aCGH) or “chromosomal microarray” (CMA), is a molecular cytogenomic technique for the detection of chromosomal copy number changes that enables to scan through an entire genome with significantly greater resolution compared to classical karyotyping. It was introduced into clinical practice in 2004, and nowadays it has become the method of choice in routine genetic diagnostic. The method is based on the co-hybridization of differently fluorescently labelled DNA fragments from the test and control samples with oligonucleotide DNA probes spotted onto a glass slide. It allows for the analysis of the entire genome at a resolution approximately 50-1000 times higher than routine karyotyping. The level of resolution is determined by considering both probe size and the genomic distance between DNA probes. Probes can be targeted to specific regions where known microdeletion/duplication syndromes are located (targeted array), or the probes can be dispersed throughout the entire genome at larger or smaller intervals (whole genomic array). It is also possible to design custom probes for specific genes or chromosomal regions. The advantages of this method are significant. It detects submicroscopic rearrangements throughout the genome as well as mosaicism, and it is simpler and faster compared to classical cytogenetics. In comparison to routine karyotyping, aCGH analysis eliminates subjectivity in interpretation. However, a significant limitation of the aCGH method is the inability to detect chromosomal changes such as balanced translocations, ring chromosomes, and paracentric or pericentric inversions, as well as cell lines in mosaicism and some ploidies. Since classical karyotyping allows the qualitative determination of the structural alteration, accurately specifying numerical and microscopically visible balanced and unbalanced chromosomal aberrations of the entire genome, cytogenetic remains the “gold standard” in laboratory diagnosis of chromosomal alteration.

Keywords: cytogenetics, chromosomal microarray, balanced translocation, ring chromosome, mosaicism

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THE ROLE OF GENOMIC INSTABILITY IN CANCER PROMOTION AND PROGRESSION - DIAGNOSTIC AND PROGNOSTIC VALUE

Tanić Nikola

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Cancer development is a multistage process that results from an accumulation of mutations. Since spontaneous mutation rates in human cells are considerably lower than the large number of mutations observed in cancer cells, cancer cells must be a manifestation of mutator phenotype. The mutator phenotype, also referred to as genomic instability, designates the increased mutation rate that occurs in neoplastic cells. The induction of genomic instability phenotype is emerging to be a crucial early event in carcinogenesis that enables an initiated cell to evolve into a cancer cell by achieving a greater proliferative capacity and genetic plasticity, which can overcome host immunological resistance, localized toxic environments and a suboptimal supply of micronutrients. Three distinct forms of genomic instability have been identified, microsatellite instability (MIN), chromosomal instability (CIN) and single nucleotide instability (SNI). It is of great importance, for the choice of therapy regiment and disease outcome, to determine which form of instability is present in particular cancer cells. We applied AP-PCR to measure genomic instability in samples of patients with Non-Small Cell Lung Cancer (NSCLC), Anaplastic Astrocytomas (AA), Glioblastoma Multiforme (GBM), Head and Neck Squamous Cell Carcinomas (HNSCC) and their premalignant lesions leukoplakias. AP-PCR is a PCR-based DNA fingerprinting method for DNA profiling that utilizes arbitrarily chosen primers to co-amplify multiple and independent sequences under low stringency conditions during the first cycles. The unbiased nature of AP-PCR profiling allows for the screening of anonymous regions of a genome without any prior knowledge of its structure and provides information about two distinct types of DNA alterations: qualitative changes – MIN phenotype and quantitative changes – CIN phenotype. Moreover, we identified some unique genetic alterations that have never been associated with these types of cancer before.

Keywords: DNA profiling, genomic instability, NSCLC, AA, GBM, HNSCC, leukoplakia

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CONVENTIONAL AND MOLECULAR DIAGNOSTICS OF MYELOPROLIFERATIVE NEOPLASMS AND ACUTE MYELOID LEUKEMIA - EXPERIENCE OF CLINIC OF HEMATOLOGY UKCS

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Myeloproliferative neoplasms (MPN) are a heterogeneous group of clonal disorders of hematopoietic stem cells, characterized by increased proliferation of one or more cell lines of the myeloid lineage in the bone marrow. The classification of MPN includes four subgroups of the disease: Philadelphia positive (Ph+) MPN or chronic myeloid leukemia (CML); classic Philadelphia negative (Ph-) MPN (polycythemia vera (PV), essential thrombocytosis (ET) and primary myelofibrosis (PMF)); non-classic Ph- MPN (chronic neutrophilic leukemia (CNL) and chronic eosinophilic leukemia (HEL)); unclassified MPN. The cytogenetic marker for CML is a Ph chromosome and the molecular marker is a BCR/ABL fusion gene. At the Clinic of Hematology of the University Clinical Center of Serbia (CH UCCS), a Ph chromosome is detected by a conventional cytogenetic analysis of the cells from bone marrow aspirate. Detection of BCR/ABL gene is performed by molecular cytogenetic analysis, fluorescent in situ hybridization (FISH) and molecular genetic analysis, reverse transcription and polymerase chain reaction (RT-PCR). Detection of minimal residual disease, residual BCR/ABL, is performed by Real Time PCR and RQ-PCR analysis. Molecular markers for classical Ph- MPN are the “driver” mutations in JAK2, MPL and CALR genes. At the CH UCCS the analyses applied for diagnosis of classical Ph-MPN (PV, ET, PMF) are: conventional cytogenetics and Real Time PCR (detection of the “point” mutation V617F in JAK2 gene). Acute myeloid leukemia (AML), a disease of the myeloid lineage stem cells, is caused by gene alterations that lead to neoplastic changes and clonal proliferation of bone marrow cells. Genes and mutations responsible for developing of AML are classified into three classes: class I (proliferative advance genes): FLT3, KIT, RAS, PTNPN11, JAK2; class II (genes responsible for blocking differentiation and apoptosis): PML/RARA, RUNX1/RUNX1T1, CBFB/MYH11, MLL, CEBPA, NPM1; class II (epigenetic modification genes): DNMT3, TET2, IDH1, IDH2, ASXL1. At the CH UCCS classical cytogenetics and RT-PCR analysis are used for detecting recurrent chromosomal and genes aberrations for AML:t(15;17)- PML/RARA; t(8;21)- RUNX1/RUNX1T1; inv(16)/t(16;16)-CBFB/MYH11. Rearrangements of MLL genes are detected by FISH analysis. PCR and RFLP (Restriction Fragment Length Polymorphism) analyses are used for detecting FLT3-ITD and FLT3-TKD (D835) mutations. A Real Time PCR analysis is applied for detecting mutations in the NPM1 gene.

Keywords: myeloproliferative neoplasms, acute myeloid leukemia, cytogenetics, RT-PCR

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DIAGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA AND MULTIPLE MYELOMA: FROM CYTOGENETICS TO NEXT-GENERATION SEQUENCING

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Chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) are lymphoproliferative neoplasms in which genetic testing plays a very important role in determining a precise prognosis and selecting a targeted therapy. Over the past three decades, a significant development of genetic methods has taken place, which has contributed to the discovery of a large number of biomarkers in these diseases. Along with the understanding of CLL and MM pathogenesis, the development of highly effective therapeutics took place in the field of pharmacogenomics, which are used today with great success for the treatment of these hematological diseases. In CLL, the first research in the field of genetics involved the application of the standard cytogenetic method, which was successfully replaced by the fluorescent in situ hybridization (FISH) method at the end of the 1990s. Further, diagnostics developed in the direction of the application of sequencing methods, which proved to be the most sensitive for the detection of certain gene variants. However, despite the application of modern methods, cytogenetic testing in CLL has gained importance in recent years, thanks to newly discovered mitogens that initiated cell division in the vast majority of B-CLL lymphocytes. In MM, the FISH technique is still considered the gold standard for the detection of recurrent aberrations, although even with this method there are limitations in terms of the impossibility of detecting gene variants. Patients with CLL and MM can have multiple changes in the genome, which can be an additional challenge for setting a precise prognosis of the disease. Today, it is of the greatest importance to choose a sufficiently sensitive genetic method that will enable the detection of a possible relapse after the applied therapy or to assess the minimal residual disease after the patients achieve clinical remission.

Keywords: chronic lymphocytic leukemia, genetic testing, precision medicine, chromosome aberrations

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CONVENTIONAL CYTOGENETIC ANALYSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic Lymphocytic Leukemia (CLL) is the predominant adult leukemia in the Western world. Over three decades ago, conventional cytogenetic analysis provided initial insights into CLL's genetic diversity and the prognostic significance of specific chromosomal abnormalities. However, due to the low mitotic index of cultured B-cells, conventional cytogenetics could only detect clonal aberrations in 40-60% of CLL cases. The introduction of fluorescence in situ hybridization (FISH) significantly enhanced CLL management by identifying genomic lesions in 80% of patients and enabling the recognition of high-risk cohorts. Discovery of novel, potent B-cell mitogens like CpG-oligonucleotides, has enhanced our capacity to detect clonal cytogenetic aberrations in more than 90% of patients, deepening our understanding of clinically relevant cytogenetic anomalies. At the Laboratory for cytogenetics and molecular genetics, Clinic for Hematology, UCCS, FISH analysis for CLL began in 2012, followed by the introduction of conventional cytogenetic analysis in late 2018. Both methodologies utilize peripheral blood samples, ensuring non-invasiveness for patients. Immunostimulatory CpG-oligonucleotides (DSP-30) combined with Interleukin 2 (IL-2) serve as B-cell mitogens in our protocol. To date, conventional cytogenetic analysis has been performed on 439 CLL patients, including 277 males and 162 females, with an average age of 64.9 years (range: 24-86). Notably, 42 patients (9.57%) lacked metaphases suitable for conventional cytogenetic analysis, but had FISH results available. Among the 397 patients with both cytogenetic and FISH results, aberrations were detected in 272 patients (68.5%). Of the 125 patients with a normal karyotype, FISH identified aberrations in 82 patients (65.6%). In the subgroup with normal FISH results (79/439), conventional cytogenetic analysis revealed aberrations in 25 individuals. The combined application of both methods enhances genetic aberration detection in our CLL patient cohort. Conventional cytogenetic analysis unveiled a novel high-risk subset characterized by a complex-aberrant karyotype (≥ 5 aberrations), requiring immediate and intensive treatment.

Keywords: chronic lymphocytic leukemia, conventional cytogenetics, immunostimulatory CpG-oligonucleotides, complex karyotype

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CYTOGENETIC AND MOLECULAR-GENETIC ANALYSIS OF ABERRATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA IN ADULTS-THE EXPERIENCE OF CLINIC OF HEMATOLOGY, UCCS

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Acute lymphoblastic leukemia (ALL) is a heterogeneous malignant disease caused by various genetic alterations in lymphoid progenitor cells, which disturb processes of their proliferation, differentiation, and/or apoptosis. The most common genetic alterations in ALL are aneuploidy, chromosomal translocations, and mutations in genes for transcription factors, cell cycle regulators, and tumor suppressors. This study described genetic alterations detected in ALL patients diagnosed and treated in Clinic of Hematology, UCCS between 2003-2023. Genetics analysis included 317 adult ALL patients, of which 240 were diagnosed with B-cell (B-ALL) and 77 with T-cell (T-ALL). Cytogenetic analysis was performed on unstimulated bone marrow cells using the HG-banding technique. BCR-ABL1 gene rearrangements were additionally tested in 120 patients using the method of Reverse Transcription Polymerase Chain Reaction (RT-PCR). The median age of analyzed patients was 44 (range 18-83). Study group consisted of 161 (51%) males and 156 (49%) females. Karyotyping was unsuccessful in 30 (9.4%) patients due to an absence of metaphase cells in analyzed samples. Frequencies of cytogenetic abnormalities among successfully analyzed samples were 62.7% and 47.1% in B-ALL and T-ALL patients, respectively. The t(9;22)(q34;q11) was the most frequent aberration, detected in 62 (28.5%) of B-ALL patients, while hyperdiploidy was detected in 26 (11.9%), the t(4;11)(q21;q23) in 15 (6.9%), and t(1;19)(q23;p13) in 2 (0.8%) of B-ALL patients. The main aberrations in T-ALL patients were der(2), del(6q), del(13q), and a translocation involving chromosomes 11 and 14. In patients with confirmed BCR-ABL1 fusion, 64.7% had BCR-ABL1 minor (e1a2) and 29.4% had BCR-ABL1 major (b3a2 or b2a2) transcript, while two patients (5.9%) had co-expression of these transcripts. The results showed many genetic aberrations in our ALL patients, mostly with a poor prognosis. In clinical practice, identification of genetic markers by various genetic analyzes contributed to a better diagnosis, selection of therapy, and monitoring of the disease.

Keywords: acute lymphoblastic leukemia, cytogenetic analysis, chromosomal aberration, Translocation, BCR-ABL1 fusion transcript

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GENETIC INFLUENCES ON METABOLIC DISEASES DEVELOPMENT

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There are numerous genetic variants identified in Genome-Wide Association Study (GWAS), that can affect metabolic diseases (type 2 diabetes, obesity and cardiovascular disease). Individual predisposition to multifactorial, common metabolic diseases reflects the combined effects of hundreds of genetic risk loci, environmental exposures and lifestyle decisions. The main type 2 diabetes-risk alleles are at the TCF7L2 (transcription factor 7-like 2) locus, for example rs7903146. TCF7L2 gene encodes the TCF4 transcription factor, that regulates the transcription of the target genes of the Wnt/beta-catenin signaling pathway, which affects lipid and glucose metabolism, embryonic development of pancreatic islets and the maturation of pancreatic β -cells. Among the genes associated with obesity, the fat mass and obesity-associated (FTO) gene plays a special role with risk alleles, such as rs9930609 A and rs9930506 G, respectively. The FTO gene is expressed mainly in the hypothalamus and plays an important role in energy homeostasis and in the regulation of adipose tissue mass by influencing lipolysis and differentiation of preadipocytes. The FTO gene is recognized as associated with enhanced adiposity and seems to influence the risk of obesity. The evidence of strong genome-wide selection for cardiometabolic traits is limited. Among various genes involved in blood pressure regulation, the angiotensin-converting enzyme (ACE) gene and endothelial nitric oxide synthase (NOS3) gene seem to be of particular importance. New insights into molecular mechanisms related to changes in gene expression that have important implications for understanding genotype-phenotype maps are also available. There is no doubt that further knowledge is required for the future development of clinically relevant guidelines and new methods for the early detection, prevention, treatment, and prognosis of metabolic diseases. Advances in human genetics for complex diseases are associated with providing causal pathways and mechanisms of studied diseases that are still, in many respects, unexplained.

Keywords: genetic variants, type 2 diabetes, obesity, cardiovascular disease

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HUMAN GENETIC VARIANTS MODULATING THE COURSE OF COVID-19 INFECTION IN A SUBSET OF BOSNIAN-HERZEGOVINIAN PATIENTS

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COVID-19 has been a major focus of scientific research since early 2020. Due to its societal, economic, and clinical impact worldwide, research efforts aimed, among other questions, to address the effect of host genetics in susceptibility and severity of COVID-19. We, therefore, performed next-generation sequencing of coding and regulatory regions of 16 human genes, involved in maintenance of the immune system or encoding receptors for viral entry into the host cells, in a subset of 60 COVID-19 patients from the General Hospital Tešanj, Bosnia and Herzegovina, classified into three groups of clinical conditions of different severity (“mild,” “moderate,” and “severe”). We confirmed that the male sex and older age are risk factors for severe clinical picture and identified 13 variants on seven genes (CD55, IL1B, IL4, IRF7, DDX58, TMPRSS2, and ACE2) with potential functional significance, either as genetic markers of modulated susceptibility to SARS-CoV-2 infection or modifiers of the infection severity. Our results include variants reported for the first time as potentially associated with COVID-19, but further research and larger patient cohorts are required to confirm their effect. Such studies, focused on candidate genes and/or variants, have a potential to answer the questions regarding the effect of human genetic makeup on the expected infection outcome. In addition, loci we identified here were previously reported to have clinical significance in other diseases and viral infections, thus confirming a general, broader significance of COVID-19-related research results following the end of the pandemic period.

Keywords: ACE2, COVID-19, host genetics, IRF7, SARS-CoV-2, TMPRSS2

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PHARMACOGENOMICS AND PHARMACOTRANSCRIPTOMICS OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDHOOD: ON THE WAY TO PERSONALIZED MEDICINE

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Personalized medicine is focused on research disciplines that contribute to the individualization of therapy, such as pharmacogenomics and pharmacotranscriptomics. Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. It is one of the pediatric malignancies with the highest cure rate, but still a lethal outcome due to therapy accounts for 1–3% of deaths. Further improvement of treatment protocols is needed through the implementation of pharmacogenomics and pharmacotranscriptomics. The research study was aimed at discovering pharmacogenetic and pharmacotranscriptomic markers of response to therapy with thiopurine and glucocorticoid drugs, methotrexate and vincristine in children with ALL in Serbia. Blood and bone marrow samples from children with ALL were collected at the University Children's Hospital in Belgrade. Variants in the studied genes were detected by PCR and Sanger sequencing. The expression level of NUDT15 in mononuclear cells was determined by real-time PCR. Next-generation sequencing using cancer panel TruSeq Amplicon, Illumina was also performed to assess drug resistance. Correlation of pharmacomarkers with clinical parameters was performed using statistical tests. A polygenic risk score based prediction model for the development of methotrexate-induced hepatotoxicity was developed. A number of molecular markers responsible for the efficacy, side effects and toxicity of drugs used to treat ALL, ie. glucocorticoids, vincristine, asparaginase, anthracyclines, thiopurines and methotrexate. Their application in clinical practice is still insufficient. Research efforts should be focused on analyzing data and designing predictive models that use machine learning algorithms. Bioinformatics tools and the implementation of artificial intelligence will help personalized medicine come to life in clinical practice.

Keywords: pharmacogenomics, pediatric acute lymphoblastic leukemia, personalized medicine

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SIGNIFICANCE OF TMPT GENOTYPING IN CLINICAL PRACTICE

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Hematotoxicity caused by the use of thiopurine drugs in patients with pediatric acute lymphoblastic leukemia and inflammatory bowel diseases is associated with genetic variability in the Thiopurine S-methyltransferase (TPMT) gene. This enzyme affects the catalysis of anti-tumor and immunosuppressive agents that are used in these conditions. Among the numerous allelic variants present within this gene, alleles *2, *3B and *3C are the most frequent in the Caucasian population, and carriers of these alleles have reduced TPMT enzyme activity, which eventually leads to hematotoxicity, especially to severe myelosuppression. The importance of genotyping patients for whom therapy is indicated, and whose mechanism of metabolism depends, among other factors, on the activity of TPMT, is very important in order to prescribe an adequate dose of the drug, as well as to prevent unnecessary toxic effects. So far, 28 samples have been genotyped in the Laboratory for Molecular Biology and Genetics, Center for Biomedical Research, Faculty of Medicine, University of Banja Luka, of which *1/*3A genotype was detected in 4 patients, and 24 patients were carriers of the normal genotype (*1/*1), which is consistent with the frequency in other European populations. Patients carrying the *1/*3A genotype are considered to be intermediate metabolizers, and for them the initial dose is indicated to be 30 to 80% of the normal starting dose, and precise dosage depends, besides genotype, on the other clinical characteristics of the patient. Bearing in mind the availability of molecular genetic analyses, it would be very important to implement an individual approach to each patient when prescribing a certain therapy, with the aim of the successful treatment outcome and prevention of side effects.

Keywords: TMPT, allelic variants, *2, *3B, *3C, hematotoxicity

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GENOTIPIZATION OF PROMOTOR VARIANTS OF UGT1A1 GENE AS A PHARMACOGENETIC MARKER IN CLINICAL PRACTICE

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The uridine-diphospho-glucuronosyl transferase 1A1 enzyme (UGT1A1) has the exclusive role in glucuronidation of bilirubin, as well as significant role in the metabolism of numerous pharmaceuticals such as antineoplastic drugs used in oncology (irinotecan, belinostat, epirubicin, 5-fluorouracil), then atazanavir and ritonavir in the treatment of HIV infection, and analgesic/antipyretic acetaminophen which is widely used. The frequency of clinically significant UGT1A1 variants shows racial and ethnic specificity. The most common variants are related to the TATA box of the UGT1A gene promoter and differ in the number of TA repeats. Wild type UGT1A1 contains 6 TA repeats (TA6), while variants with 5, 7 or 8 TA repeats are designated UGT 1A1*36 (TA5), UGT1A1*28 (TA7) and UGT1A1*37 (TA8). The transcription activity of the promoter decreases accordingly to a higher number of repeats compared to TA6. According to the frequency in populations, UGT1A1*28 allele is classified to be a pharmacogenetic marker. In this study, 121 healthy subjects from the general population of the Republic of Srpska were analyzed. For the analysis of the TA variants in the UGT1A1 promoter region, PCR methodology was used. In the population of the Republic of Srpska, genotypes UGT1A1 6/6TA, 6/7TA and 7/7 TA occur with a frequency of 45%, 45% and 31% respectively, and the frequency of the UGT1A1*28 allele in general population is 0,44. Considering the extremely high incidence of UGT1A1*28 alleles in general population of the Republic of Srpska, and its vital role and importance in the metabolism of numerous drugs, it has been concluded that UGT1A1*28 allele is a significant pharmacogenetic marker in this population and that UGT1A1 (TA)_n genotype analysis is recommended to be performed in routine clinical practice before introducing into therapy the drugs in which the metabolism UGT1A1 enzyme is involved.

Keywords: UGT1A1*28, pharmacogenetic marker, frequency, population, Republic of Srpska

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APPLICATION OF MOLECULAR KARYOTYPING IN PRENATAL DIAGNOSTICS

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Karyotype analysis, fluorescence in situ hybridization (FISH) and microarray comparative genomic hybridization (array CGH) are currently the mainstay of invasive prenatal diagnosis of chromosomal abnormalities. Currently, array CGH is recommended by scientific organizations as a first-line test in the prenatal diagnosis of fetuses with sonographic abnormalities. The aim of this study was to present the results of array CGH in prenatal diagnosis. In this retrospective study, a total of 348 amniotic fluid samples from pregnant women with various indications were collected between 2018 and 2023. A total of 348 karyotypes were performed, together with 63 FISH and 43 array CGH analyses. The median maternal age was 33 [range 21 – 44 years] and the median gestational week was 19 [range 13 – 37 weeks]. The most common indication for array CGH was sonographic fetal anomaly, which was present in 84% (36/43) of cases. Soft ultrasound markers were observed in 19% (7/36) and hard markers in 81% (29/36) of cases. Abnormal molecular karyotype results were found in 18% (8/43) of the participants. Our results suggest that the use of the microarray method improves the detection rate of pathogenic single-copy losses in fetuses with sonographic abnormalities, although counselling prior to analysis is crucial.

Keywords: chromosomal abnormalities, microarray comparative genomic hybridization, molecular karyotyping, prenatal diagnosis

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GENETIC CAUSES OF MALE INFERTILITY; KARYOTYPING AND Y MICRODELETION ANALYSIS

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About 15% of couples fail to conceive within a year and seek medical treatment for infertility. Infertility affects both men and women. In half of infertile couples, factors associated with male infertility, together with abnormal sperm parameters, are likely to be the cause. The sperm of infertile men have an increased rate of aneuploidy, structural chromosomal abnormalities and DNA damage. Current routine clinical practice is based on the analysis of chromosomes and genomic DNA from peripheral blood samples. Testing for AZoospermia Factor (AZF) deletions of the Y chromosome is an important part of the diagnostic workup of azoospermic and severely oligozoospermic men. Karyotype analysis is also indicated in men with severely impaired spermatogenesis. The aim of the study was to analyze the results of karyotyping and Y microdeletion analysis and to present selected cases with detected chromosomal aberrations (confirmed by the FISH method) and Y-chromosome microdeletions simultaneously. One case is a terminal deletion of Yq, the other is a rare translocation of the sex-determining region Y (SRY gene) to the X chromosome, resulting to a 46,XX testicular disorder of sex development. A total of 148 karyotypes and 90 Y microdeletion analyzes were performed in infertile men (with different referral reasons) and included in the retrospective study from September 2020 to 2023. Determining the genetic factors of infertility helps to assess the risk of a particular chromosomal or genetic disorder and to choose the best method of assisted reproduction accordingly, if at all possible. Various cases require further molecular cytogenetic analysis as well as detailed clinical evaluation, interpretation and appropriate genetic counseling.

Keywords: chromosomal aberrations, male infertility, Y-chromosome microdeletions

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SUBFERTILITY AND STERILITY OF COUPLES: MUTATIONS ASSOCIATED WITH THROMBOPHILIA - MORE THAN A COAGULATION DISORDER AND WHY BOTH PARTNERS SHOULD BE TESTED AFTER RE-OCCURRING SPONTANEOUS ABORTIONS

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Thrombophilia is a state when blood has an increased tendency to the formation of a blood clot or thrombus, due to the existence of disorders in blood clotting. Blood clotting disorders can be acquired or congenital e.g. genetically determined. Anyone with a genetic predisposition to thrombophilia has a higher risk of developing venous thrombosis compared to people who do not carry specific genetic mutations. A significant percentage of people have this genetic tendency, but the thrombus is formed only in a few people and in specific conditions, such as pregnancy. Namely, pregnancy, due to its specificity, significantly predisposes women and/or the fetus to thrombosis. However, genetic testing for the detection of SNPs associated with thrombophilia is recommended for women only, even though fetuses are composed of two haploid combinations - from a mother and a father. Thus, the fetus can be paternally predisposed to thrombotic events, which can significantly complicate pregnancy, especially in women who themselves do not have significant mutations associated with thrombophilia. Furthermore, apart from the possible metabolic effect of specific SNP mutation, a combination of multiple SNPs on patient hemostasis, and metabolism in general, must be taken into account as well, since their additive effects might cause miscarriage, post-partal complications, and slower maternal recovery.

Keywords: thrombophilia, SNP mutations, paternal mutations, pregnancy, miscarriage

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PROS AND CONS OF DIETARY ANTIOXIDANS: INTERINDIVIDUAL VARIABILITY OF FLAVONOIDS GENOTOXICITY

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The protective role of antioxidants in cells is to stabilize and neutralize free radicals which induce harmful effects, including genetic material. Plant flavonoids, being recognized antioxidants, are commonly found in the daily human diet. The recommended optimal dosage of flavonoids is estimated to be between 1 to 2 g per day. Various plant flavonoids are commercially available as dietary supplements, however, there is a notable oversight regarding their potential harmful impact on genetic material. Research conducted at the University of Sarajevo - Institute for Genetic Engineering and Biotechnology has revealed significant insights into the effects of luteolin, a particular flavonoid, on human peripheral blood lymphocytes when administered as a single dose in vitro. This study unveiled detrimental pro-oxidative effects at the cytogenetic level across different sample groups. Notably, various genetic abnormalities, including chromosomal and chromatid breaks, as well as chromosome pulverization, were observed following exposure to luteolin. It was found that a concentration of 50 μM of luteolin itself increased frequency of structural chromatid-type aberrations in two out of five peripheral blood samples when compared with negative control ($F=2.571$; $p=0.053$), suggesting interindividual variability in response to its bioactive effects. Luteolin displayed both pro- and anti-oxidative properties, exhibiting an unexpected inverse effect. Altogether, luteolin demonstrated inhibitory properties by significantly reducing ($p<0.05$) the frequency of genotoxicity biomarkers, such as micronuclei and nuclear buds induced by genotoxic agents in all samples. This reduction suggests an upregulation of hTERT and an enhanced capacity for damage repair. The results of this research aim to raise awareness among the public regarding the potential adverse harmful effects of dietary antioxidants, whether consumed naturally or in the form of commercially available supplements. Additionally, these findings underscore the importance of recognizing interindividual variations in response to such substances, underscoring the influence of genetic predispositions and implications.

Keywords: luteolin, genetic damage, chromosomal aberrations, nutrition

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ASSESSMENT OF IMMUNOMODULATORY AND EPIGENETIC EFFECTS: A COMPARATIVE STUDY OF CYTOKINE AND BIOCHEMICAL PROFILES BETWEEN PLANT-BASED AND OMNIVOROUS DIETS

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Ongoing nutritional debates question the role of meat, dairy, grains and legumes in a healthy diet. However, there would seem to be disagreement in the scientific community that following a plant-based diet is beneficial for one's health. There is a growing body of scientific evidence linking chronic low-grade inflammation to increased susceptibility to various diseases. This chronic inflammation is closely associated with a dysfunctional and dysregulated immune response, contributing to conditions like cancers, neurological disorders, cardiovascular diseases, obesity and other serious health complications. Recent scientific inquiries have revealed convincing evidence suggesting that plant-based dietary sources possess a wealth of essential vitamins, minerals and a diverse range of phytonutrients, which all together are linked with lower levels of inflammatory markers. As these markers provide a broader understanding of the body's inflammation levels, it's essential to study how they react to nutrition. Phytonutrients have been extensively documented to have pleiotropic effects on cellular physiology. These changes lead to a modulation of gene expression patterns, ultimately resulting in favorable immunological outcomes. This study intended to examine the links between a plant-based diet and inflammatory biomarkers, immunological and hematological status, compared to an omnivorous diet. Specifically, how dietary preferences affect the circulating levels of pro- and anti-inflammatory chemokines and cytokines: IL-1 β , IFN- α 2, IFN- γ , TNF- α , MCP-1, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, IL-23 и IL-33. Additionally, we assessed leukocytes, erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, iron, neutrophils, lymphocytes, monocytes, eosinophils and basophils, along with their absolute counts. The study included 70 omnivores and 70 individuals on a plant-based diet for over 2 years, comprising 60 vegans and 10 lacto-ovo vegetarians, all of whom were healthy participants. Stratification ensured comparability in gender, age, physical activity, smoking status, BMI, and waist circumference, excluding interfering factors. Cytokine levels were assessed using flow cytometry and a LEGEND plex immunoassay kit. Hematological and immunological markers were measured using automated analyses, including enzymatic methods and spectrophotometry. Statistically significant differences were observed between the two groups in circulating levels of several pro-inflammatory cytokines: IFN- α 2 ($p < 0.05$), IFN- γ ($p < 0.001$), TNF- α ($p < 0.05$), IL-6 ($p < 0.05$), IL-8 ($p < 0.05$), IL-12 ($p < 0.05$) and IL-17A ($p < 0.01$), notably lower in the plant-based cohort. However, levels of IL-1 β , MCP-1, IL-10, IL-18, IL-23, and IL-33 showed no significant differences. Additionally, leukocytes ($p < 0.05$), MCHC ($p < 0.001$), lymphocytes ($p < 0.001$) and eosinophils total count ($p < 0.05$) were significantly lower in the plant-based group, while other immunological and hematological markers did not differ significantly. These findings highlight the diverse benefits of plant-based nutrition in bolstering immune health by reducing systemic inflammation markers, which possess immunomodulatory effects and promote positive gene expression. This supports the adoption of plant-based diets for improved health outcomes.

Additionally, these results provide valuable insights into the therapeutic and preventive potential of plant-based dietary choices, which can profoundly impact overall well-being through epigenetic mechanisms, modulating immune function towards reduced inflammation. These effects are likely influenced by dietary factors like fiber, phytonutrients, and gut microbiota interactions, resulting in a more balanced cytokine profile.

Keywords: plant-based; vegan; nutrition; immunonutrition; immunology; cytokines; inflammation.

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Plenary lecture - Sponsored

OPTIMIZE YOUR MSI WORKFLOW WITH PROMEGA

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As global biotechnology leader, Promega specializes in supporting scientists for more than 40 years with a wide range of innovative products including high quality reagents, enzymes, cell-based assays, and instruments. These products serve the scientists in basic research, applied research, drug discovery, agriculture, forensics, and molecular diagnostics. Promega has also been a leader in Microsatellite Instability (MSI) research for over 15 years. With precision performance and expert support, the Promega MSI Analysis workflow is the gold standard for MSI testing. The goal of identifying functional evidence of genomic instability (loss of DNA mismatch repair system) is associated with research in hereditary cancers called Lynch Syndrome. Recently, the role of MSI as a biomarker has been expanded past its classical association with Lynch Syndrome, to also becoming a solid tumor, tissue agnostic marker for patient selection for cancer immunotherapeutic called immune checkpoint inhibitors. Promega offers the full workflow from the extraction to data analysis to optimize your workflow. The MSI Analysis System, v 1.2, has been the first commercially available kit used in clinical and molecular diagnostics research since 2004 and is a leader in MSI clinical research. The new LMR MSI Analysis System shares four markers with the MSI Analysis System, v1.2, but incorporates an expanded panel of markers that includes long mononucleotide repeat (LMR) markers which offer larger-sized shifts and could help reveal instability in challenging samples. Our manual and automated purification systems, fluorescence-based quantification instrument Quantus™ Fluorometer and our Spectrum Compact capillary electrophoresis instrument accompany our MSI kits and complete this workflow.

Keywords: MSI, LMR MSI, biomarker, cancer, Lynch syndrome, immunetherapeutic, capillary electrophoresis

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Plenary lecture - Sponsored

A NOVEL DIGITAL PCR TOOL FOR PARALLEL DETECTION OF MULTIPLE HALLMARK MUTATIONS IN BRAFV600 AND EGFR EXON19

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The identification of genetic mutations driving cancer becomes more and more important, especially in the background of precision medicine and AI leading to more and more personalized investigations and treatments. We would like to emphasize the critical task of identifying genetic mutations in genes such as BRAF and EGFR, which are important in various cancer types. Our new method for digital PCR (dPCR) reflects a highly sensitive method to analyze key mutations in cancer-associated genes in more detail. Our research focuses on a pioneering digital PCR (dPCR) approach meticulously designed to concurrently detect hallmark mutations in BRAF and EGFR genes that are pivotal in diverse cancer types by introducing the innovative dPCR PanCancer Kits for use in research. The optimized assays for use on the QIAcuity® dPCR system specifically target eight V600 hallmark mutations in BRAF and twenty-three exon 19 deletions in EGFR in parallel. A reference gene is included for PCR efficiency control and genome copy number quantification. Our optimized dPCR setups demonstrate exceptional sensitivity, allowing for the detection of multiple mutations in a single channel, even at allelic frequencies down to 0,1%. Across various sample types, including blood, plasma and FFPE we demonstrate the dPCR PanCancer Kits' versatility in various research applications. Beyond their utility in screening samples before or after next-generation sequencing, they prove effective in the ongoing monitoring of cancer cells or organoids. This simultaneous assessment of mutations facilitates processes, reduces time, costs, and preserves precious sample material. The adaptable nature of our technology suggests the potential development of analogous assays for other cancer-associated genes. Our work highlights the dPCR PanCancer Kits as a robust and efficient technological advancement, offering a nuanced understanding of critical mutations in BRAF and EGFR-driven cancers.

The dPCR PanCancer Kits are intended for molecular biology applications. They are not intended for the diagnosis, prevention, or treatment of a disease.

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SPATIAL EXPRESSION OF *ZEB1* GENE AS A POTENTIAL PROGNOSTIC MARKER IN RECTAL CANCER

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The prognosis of rectal cancer (RC) can be influenced by various factors, including the location of the tumor. Studies have shown that the position of the tumor within the rectum can impact the recurrence and overall survival rates. Tumor localization in RC is also associated with gene expression alterations. *ZEB1* is a transcriptional factor that promotes tumor invasiveness via regulation of the epithelial-mesenchymal transition process and plays a significant role in RC by influencing tumor aggressiveness. This study aimed to evaluate the location-specific expression of the *ZEB1* gene and its prognostic role in RC patients. This preliminary study included 45 untreated RC patients who underwent curative resection. In 10 patients, the tumor was located in the low rectum (0-5 cm), while 35 tumors were positioned within the mid and upper rectum (5-15 cm). We isolated mRNA from postoperative tumor FFPE samples. TaqMan® gene expression assay was used for quantitative real-time PCR analysis of *ZEB1* gene expression. The preliminary analysis revealed that relative *ZEB1* gene expression was significantly higher in upper RC locations than among low-positioned tumors (0.00198 vs. 0.000947, $p=0.024$). We did not find a significant difference in overall survival (OS) and disease-free survival (DFS) among RC patients based on the tumor location and *ZEB1* expression ($p > 0.05$ in both cases). However, among 35 patients with upper-positioned tumors, we noted that patients with elevated *ZEB1* expression had shorter DFS than patients with low *ZEB1* expression (48.062 ± 6.557 vs. 61.682 ± 6.095 months), although the observed difference was not statistically significant ($p=0.270$). Our results indicate the importance of evaluating spatial *ZEB1* expression in RC and suggest its potential prognostic role, especially in determining the survival time without disease recurrence in RC patients. However, further research on a larger number of samples is needed to confirm these findings.

Keywords: Rectal cancer, *ZEB1* expression, prognosis

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SEQUENCE VARIABILITY OF HCV CORE REGION AND HOST GENETIC AND EPIGENETIC FACTORS CAN PREDICT THE RESPONSE TO COMBINED PEG-IFN/RBV THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C INFECTION GENOTYPE 1B

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Variations in the hepatitis C virus (HCV) core gene are related to the progression of liver fibrosis and therapy response. However, the influence of individual amino acid (aa) substitutions at different positions of HCV Core protein on the response to combined pegylated interferon/ribavirin (PEG-IFN/RBV) therapy and disease progression is not yet fully understood. The HCV Core protein can inactivate various genes in the host genome by affecting the methylation of their promoters, leading to liver damage and carcinogenesis. Two genes whose methylation status is affected by the HCV Core protein are the tumor suppressor genes *RASSF1A* and *p16*. We have previously shown that the methylation status of these two genes, together with the single nucleotide polymorphism (SNP) rs12979860 near the interleukin-28 beta subunit (*IL-28B*) gene, influences the response to combined therapy. Herein, we investigated a possible association between detected aa substitutions in HCV Core protein and response to combined therapy, liver disease progression, *IL28B* genotype, and the methylation status of the *RASSF1A* and *p16* genes. In 29 examined patients we found no association between individual aa substitutions and therapy response. However, we observed that patients with HCV Core aa substitutions at position 75 and CT/TT *IL28B* genotypes were non-responders (NR) ($p=0.023$), which was associated with the presence of unmethylated *RASSF1A* gene. In contrast, even 75% of patients with aa substitutions at position 91 and CC *IL28B* genotype achieved a sustained virologic response (SVR) ($p=0.030$), and 70% of them had methylated *RASSF1A* gene. There was no significant association between the methylation status of the *p16* gene and aa variations in the HCV core region. Our results suggest that combined analysis of aa substitutions in HCV Core protein, *IL28B* genotype, and methylation status of the *RASSF1A* gene may help predict response to PEG-IFN/RBV therapy in patients with chronic hepatitis C genotype 1b.xx

Keywords: HCV; Core protein; *IL28B*; *RASSF1*; *p16*; methylation; therapy response

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ANTIHEPATOMA ACTIVITY OF METHANOL EXTRACTS FROM *THYMUS PANNONICUS* IN VITRO SHOOT CULTURES

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Thymus pannonicus All. (Lamiaceae) is a perennial plant native to Central and Eastern Europe and Russia. The dried herb is traditionally used to treat mild respiratory and gastrointestinal illnesses, due to enrichment with monoterpenes and sesquiterpenes. Other secondary metabolites found in *Thymus* species, namely phenolic acids, flavonoids, flavone glucuronides, show numerous additional health-promoting effects (antioxidant, antidiabetic, anticancer). In this work, the antihepatoma activity of methanol extracts from in vitro shoot cultures of *T. pannonicus* citral chemotype on human HEPG2 hepatoma cells was evaluated. Two methanol extracts were investigated: E1 – derived from shoots grown on a medium without plant growth regulators and E2 – derived from shoots grown in the presence of the plant hormone indole-3-acetic acid (1mg/ml). Quantitative spectrophotometric analysis revealed that total phenolic and flavonoid contents were higher in E2 (540.4mg/g and 9.84mg/g, respectively) than in E1 (265.4mg/g and 6.52mg/g, respectively). Further analysis using HPLC identified rosmarinic acid (RA) as the dominant phenolic acid in both extracts, with E2 containing a slightly higher amount of RA than E1. The extracts reduced growth of HEPG2 cells in a dose- and time-dependent manner with moderate IC₅₀ values (IC₅₀(E1)=81.1µg/ml; IC₅₀(E2)=77.8µg/ml, MTT, 96h), as shown by cell viability tests. Similarly, RA, used as a control, suppressed the growth of HEPG2 cells with an IC₅₀=30.8µM (MTT, 96h). Flow cytometry of propidium iodide-stained cells showed that *T. pannonicus* extracts and RA arrested HEPG2 cells in the G2/M phase of the cell cycle, while fluorimetric measurement of cells loaded with dihydrorhodamine revealed mild elevation of intracellular ROS content induced by both extracts after 48h of treatment. Considering high content of RA in both extracts and similar antiproliferative effect of RA, E1 and E2 on HEPG2 cells, it could be proposed that RA is the active compound responsible for moderate antihepatoma activity of the investigated *T. pannonicus* extracts.

Keywords: *Thymus pannonicus*, in vitro shoot cultures, methanol extracts, rosmarinic acid, antihepatoma activity, antiproliferative effectx

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ERB IS A POSSIBLE BIOMARKER OF BREAST CANCER

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Breast cancer (BC) is the most common cancer among women worldwide. The diagnosis and treatment decisions depend on the three biomarkers: oestrogen receptor alfa, progesterone receptor and human epidermal growth factor 2. The foremost treatment line is Nolvadex (tamoxifen). Yet approximately 30% of patients do not respond to tamoxifen treatment. The discovery of oestrogen receptor beta (*ERβ*) opened the door for another BC biomarker's introduction. The studies show that the *ERβ* usually behaves like a tumour suppressor and that its expression is a favourable parameter of the patient survival and treatment response. Our study aimed to assess the prognostic and predictive role of *ERβ* in BC. It encompassed 118 BC samples from patients operated at the Institute of Oncology and Radiology of Serbia from 2002 to 2004. Overall (OS) and disease-free survival (DFS) data were collected between 2002 and 2022. We used the Western blot method for *ERβ*1 protein detection. The *ERβ*1 mRNA and *ERβ* delta5 mRNA isoforms were detected by quantitative PCR method with TaqMan Assays. The extracted DNA was subjected to a two-step MSP MethEvaGreen procedure, using primers we designed to detect specific *ERβ* gene promoter ON methylation. Patient groups were divided into low and high-expression groups based on median values. Our results showed that in the high methylation index group, OS and DFS of patients who received adjuvant Nolvadex treatment were significantly longer than those who did not ($p=0.001$, $p=0.033$, respectively). In the low methylation index group, the DFS of patients who received radiotherapy was significantly shorter than those who did not ($p=0.037$). However, in the low *ERβ* mRNA expression group, the DFS of patients who received radiotherapy was significantly shorter than those who did not ($p=0.028$). Our results show that *ERβ* could be a significant additional parameter in the BC prognosis and treatment decisions. Further analyses are needed.

Keywords: Oestrogen receptor beta, Nolvadex, methylationx

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CORRELATION OF GENETIC FACTORS WITH SPORTS PREDISPOSITIONS

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The limit of each individual to perform a given type of exercise depends on the nature of the task and is influenced by a variety of factors, including psychology, environment and genetic makeup. Sports performances can be ultimately defined as a polygenic trait. Genetics in sports can determine predisposition in sports, discover health risks, and adapt the practice to genetic status. The main genetic markers for the survey of sport genetic predisposition are *ACTN3*, *ACE*, *PPARA- δ* , *HIF-1*, and mtDNA. Through this pilot project, we examined genetically conditioned traits in three different sports (basketball, football, and track and field (T&F)) and compared results with the control non-athletic group. In our study were examined 110 of examinees (60 men, and 50 women). 69% were active in professional sports, and 31% were control group. In men, basketball players are 8.3% taller than the common population in Bosnia and Herzegovina, but the control non-athletic group was 1.3% smaller than the common population in BIH. BMI was the smallest in T&F group with 19,8 BMI and the control group had the highest value with 34 BMI. In the women's group, all groups have a close height value to the average of the common population in BIH. BMI of football players and T&F women was 21,26 but in the control group was significantly higher with 24,7. Endurance as the main quality was declared by 71%, 17% and 38,5% of basketball, T&F and football players, respectively. Speed as the main quality declared by 83%, 61,5% and 28,6% by T&F, football and basketball players respectively. Positive family history in sports reveals a high concordance with success in sports and that is the indicator that besides genetic predisposition, support and a positive, stimulating environment have crucial influence on sports success. This study will continue with analyzing the correlation of our results with specific genetic markers.

Keywords: Genetic predispositions, sport, height, BMI, genetic marker

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CHARACTERIZATION OF 16 NOVEL GENETIC VARIANTS IN GENES ASSOCIATED WITH EPILEPSY

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Childhood epilepsies are caused by heterogeneous underlying disorders where approximately 40% of the origins of epilepsy can be attributed to genetic factors. The application of next-generation sequencing has revolutionized molecular diagnostics and has enabled identification of disease-causing genes and variants in childhood epilepsies. In our study, 55 children with epilepsy of unknown etiology were analyzed combining clinical-exome and whole-exome sequencing. Molecular genetic cause of epilepsy was identified in 31 patients and the overall diagnostic success rate was 56%. We identified variants in 23 different genes associated with epilepsy that correlate well with the observed phenotype. This includes genes such as *ASH1L*, *CILK1*, *KCNMA1*, *RHOBTB2* and *SLC13A5*, which have only recently been associated with epilepsy. Half (51.6%) of solved patients carried novel variants. These sixteen novel variants were characterized using various *in silico* algorithms including Phyre2, EzMol, Aminode and MutPred2 for structure prediction. Interestingly, identification of a causative gene directed attention to 15 individuals, including six individuals who carry entirely novel genetic variants, for whom therapeutic options may be available (*ALDH7A1*, *GRIN1*, *KCNQ2*, *PNPO*, *SCN1A* and *SCN2A*). Described novel variants will contribute to better understanding of the European genetic landscape, while insights on genotype-phenotype correlation will contribute to better understanding of childhood epilepsies around the globe. Given the expansion of molecular-based approaches, each newly identified genetic variant could become a potential therapeutic target.

Keywords: childhood epilepsy, monogenic disease, clinical-exome sequencing, whole-exome sequencing, novel genetic variants

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A RARE TRISOMY OF CHROMOSOME 4 IN ACUTE MYELOID LEUKEMIA - CASE REPORT

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Acute myeloid leukemia (AML) is a malignant disease of the bone marrow characterized by the uncontrolled formation of blood cells of the myeloid lineage, usually leukocytes, extremely rarely erythrocytes. In the Public Institution of the University Clinical Center of the Republika Srpska, 1576 bone marrow cytogenetic analyses were performed for ten years, of which 112 (7.1%) patients were diagnosed with AML. In the population of Republika Srpska, the incidence of AML from 2013-2023 is 0.9% per 100,000 inhabitants. Among 112 patients diagnosed with AML, there were two cases with a rare trisomy of chromosome 4. In the first case, a 66-year-old patient was diagnosed with AML M5, with leukocytosis, monocytosis, anemia, and thrombocytopenia, as well as elevated inflammation parameters. Cytogenetic analysis revealed the presence of a pathological clone with trisomy 4, which was dominant with a karyotype - 47,XX,+4[26]/46,XX[4]. In the second case, it was a 42-year-old male patient diagnosed with AML M4 with anemia and thrombocytopenia, marked fatigue and tachycardia. Cytogenetic analysis revealed a dominant pathological clone with trisomy of chromosome 4, accompanied by trisomy of chromosome 8, and the case was described with karyotype 48,XY,+4,+8[12]/46,XY[8]. The first patient died 3 months after the diagnosis, while the second patient was sent for treatment to another institution outside BiH. The prognosis of the disease outcome in patients with AML in whom trisomy 4 is present is controversial. Still, according to the recommendations of the National Comprehensive Cancer Network and the European LeukemiaNet (ELN), solo trisomy 4 in AML is classified as an intermediate-risk group. This can also be used as a prognostic factor to identify patients in whom allogeneic hematopoietic stem cell transplantation may benefit survival and success of the treatment course.

Keywords: AML, cytogenetic analyses, trisomy 4

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DETERMINING SIBSHIP INDICES WITH 15 STR LOCI: CENTRAL BOSNIA STUDY

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This study evaluated the effectiveness of 15 specific short tandem repeat (STR) loci which determined the sibling relationships within the isolated community of Vukotići village, Bosnia and Herzegovina. The aim was to calculate the reliability indicators (sensitivity, specificity, positive predictive value, and negative predictive value) at different Combined Sibship Index (CSI) levels. This was utilised to identify siblings within this population. The study furthermore sought to establish threshold values for the “gray zone”, the area of uncertain CSI values, to enhance forensic analyses and enable comparisons with previous research in Bosnia and Herzegovina. Thirty-eight participants from Vukotići village provided buccal mucosal cell samples for genetic analysis. DNA extraction was carried out using the Miller protocol in 2010. This was followed by quantification with the QUANTIFILER DNA Identification kit. STR loci amplification was conducted using the PowerPlex™16 Kit, with results compared to previous research. Sibship relationships were assessed through likelihood ratios for each locus, and the cumulative sibship index was calculated. Analysis of buccal samples produced usable DNA profiles for all 38 samples across 15 STR loci and amelogenin. The threshold values for CSI were explored, with CSI=1 and CSI=3 identified as reliable thresholds for determining sibling relationships within small local populations. Genetic diversity analysis using STR polymorphisms revealed genetic uniformity among the village populations. Regardless of employing a different genetic analyser, all the profiles were fully detected for all 15 loci. CSI=1 and CSI=3 values accurately identified these sibling relationships and confirmed the absence of biological sibling connections in related and unrelated pairs, with 100% accuracy.

Keywords: short tandem repeats, sibling relationships, genetic diversity, reliability indicators, isolated community

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CHALLENGES IN SARS-COV-2 DIAGNOSTICS BY REAL TIME RT-PCR

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COVID-19 pandemic caused by coronavirus 2 respiratory virus (SARS-CoV-2) required fast and effective diagnostics for the purpose of preventing the spread of the disease and outbreak monitoring and control. Therefore, prompt, accurate and reliable testing was of particular importance. Indubitably, the most representative, the most sensitive and the fastest method for detection of SARS CoV-2 is Real Time RT-PCR (RT-qPCR). During the pandemic there were numerous different assays, reagents, protocols and reporting procedures under the question mark because of lack of certified standards, standardization of RNA extraction and reporting procedures. In practice, the reliability of RT-qPCR results depend on a number of parameters that include sample collection and processing, method of RNA extraction, choice of assay, choice of instrument, analysis method and operator intervention. Here we present the various challenges which we encountered during our work and emphasize comparative analysis by different assays, as well as automated versus manual RNA extraction. Sampling, adequate manipulation load, the quality of the assay and interpretation of the result are extremely important. Our results revealed that manual viral RNA extraction should be a method of choice for high sensitivity. In addition, amplification assays targeting three SARS-CoV-2 genes are much more efficient from those targeting one. Unfortunately, RT-qPCR (originally quantitative method) was exclusively used as qualitative diagnostic test for SARS-CoV-2. We think that the ideal testing regimen would involve not just qualitative detection of SARS-CoV-2 but reliable and meaningful quantitative reporting of viral load. For such a thing, a consensus at the level of the world medical community is necessary regarding the most important thing: defining the cut-off value for a clinically significant viral load. It has never been done and therefore many people, all over the world, were sentenced to house arrest for no reason at all.

Keywords: SARS-CoV-2, RT-qPCR, viral load

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EFFECTS OF PRENATAL DEXAMETHASONE TREATMENT AND MODERATE POST-WEANING FRUCTOSE CONSUMPTION ON RECOGNITION MEMORY IN ADULT MALE WISTAR RAT OFFSPRING

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During prenatal development, glucocorticoids control fetal growth and maturation of fetal tissues. Synthetic glucocorticoids are frequently administered to pregnant women at risk for preterm delivery. Despite their beneficial effects on lung maturation and fetal survival, their impact on the developing brain is less clear. Among postnatal factors that might have a profound effect on both the cognitive capacity and behavior of the offspring, high fructose consumption is particularly concerning in the young population. The present study aimed to investigate the effects of prenatal dexamethasone exposure additionally challenged with postnatal fructose overconsumption on anxiety and recognition memory performance in male Wistar rat offspring. Pregnant female rats were treated with three doses of dexamethasone (0.5 mg/kg/b.m.) during late gestation (16th-18th gestational day), corresponding to clinical human exposure. Male offspring were supplemented with a moderate dose of fructose, similar to those found in sugar-sweetened beverages (10% solution), from weaning till adulthood. Recognition memory and anxiety-like behavior were assessed using a novel object recognition test, and elevated plus maze, respectively. Hippocampal synaptic plasticity was estimated by the levels of GAP-43, synaptophysin, postsynaptic density protein 95 (PSD-95), and its activating phosphorylation (pPSD-95-Ser295). Prenatal dexamethasone treatment induced an anxiolytic-like effect, stimulation of exploratory behavior, and the improvement of recognition memory associated with an increase in GAP-43 protein level in the hippocampus. Fructose overconsumption after weaning did not modify the effects of prenatal glucocorticoid exposure in the applied experimental model, suggesting that fetal programming had a prevailing influence. According to our results, prenatal dexamethasone treatment may induce changes in reactions to novel situations in male Wistar rats which might represent advantageous fetal developmental adaptation to a new environment, while increased exploratory behavior, reduced anxiety, and improved ability to recognize novel objects could improve survival in an adverse postnatal environment.

Keywords: prenatal, dexamethasone, fructose, novel object recognition, hippocampus, synaptic plasticity, programming

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ENHANCING SPORTS PERFORMANCE BY INSIGHTS FROM GENETIC TESTING OF YOUNG ATHLETES FROM BOSNIA AND HERZEGOVINA

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The combined model of testing the athletes encompasses the assessment of basic motor skills, psychological stress testing, and genetic testing, whereby genetic predisposition is important for determining the athletes' predisposition for specific disciplines and risk of sports-related injuries. The insertion/deletion (I/D) allele of the angiotensin-converting enzyme gene (ACE) (rs1799752) is one of the most studied polymorphisms, with the I allele linked to enhanced performance in runners and rowers and generally in disciplines requiring endurance, while the D allele is associated with sports requiring strength and power. The ACTN3 (alpha-actinin-3) rs1815739 polymorphism is linked to athletic performance, with the 577R allele associated with lower risk of training-related injuries and a better response to intensive exercises and training process, while the 577X variant is found in fewer athletes and is associated with increased likelihood of injuries due to intensive training process, thus requiring additional caution. We are hereby presenting the first results of genetic testing of 32 young Alpine skiers over these two genetic polymorphisms. DNA isolation from whole blood samples was done using the PureLink™ Genomic DNA Mini kit, followed by amplification of target polymorphisms using real-time PCR with TaqMan SNP assays. Regarding ACTN3 genotypes, 58.1% of successfully analyzed participants were C/C homozygotes (577RR), 32.3% were T/C heterozygotes (577RX), and 9.7% were T/T homozygotes (577XX). The results were inconclusive for one participant. Regarding ACE testing, 25 participants were successfully genotyped and none of them carried Alu sequence (i.e., all participants were D/D homozygotes). The results of genetic testing could serve as valuable guidance for optimizing training based on the obtained results, potentially reducing the frequency of athletes' injuries.

Keywords: genetic testing of athletes, ACE, ACTN3, strength and endurance, power, sports-related injury

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FREQUENCY OF V600E MUTATION IN *BRAF* GENE AMONG PATIENTS WITH METASTATIC MELANOMA ON THE TERRITORY OF BOSNIA AND HERZEGOVINA

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Melanoma is one of the most aggressive types of cancer in humans, ranking fifth in terms of frequency among all types of cancer worldwide. In our study on mutation detection in the *BRAF* gene, real time PCR method was used, along with Cobas 4800 *BRAF* V600 mutation test, showing that more than half of metastatic melanomas have this mutation. The analysis included data on detection of *BRAF* V600E mutation in a total of 393 FFPE samples from patients with metastatic melanoma (MM) in the period from 2014 to 2018 in Bosnia and Herzegovina. Pathohistological and molecular analysis of all samples was conducted at Laboratory for Immunohistochemistry and Molecular Diagnostics of Institute of Clinical Pathology of University Clinical Centre in Banja Luka. Our study on frequency of V600E *BRAF* gene mutation in patients with MM in Bosnia and Herzegovina was conducted using parameters such as: gender of patients; concentration of isolated DNA from FFPE samples; success rate of *BRAF* V600E mutation detection; relationship between gender of patients with *BRAF* V600E mutation and presence of *BRAF* V600E mutation in patients of different age categories. The results of study show that a sufficient amount of DNA was successfully isolated from a large number of samples for further mutation testing. Over a five-year period, the gender ratio of patients with MM was 60.56% male to 39.44% female. Percentage of presence of *BRAF* V600E mutation was 54.35%, while 45.65% of FFPE samples from patients did not have this mutation. In terms of gender, there were 49.06% *BRAF*⁺ samples compared to 50.94% *BRAF*⁻ in males; while in females, there were 61.54% *BRAF*⁺ samples compared to 38.46% *BRAF*⁻. Average age of all patients with MM whose samples were tested was 58.62 years. The age category with highest number of patients at 27.45% is between 55 and 65 years old. *BRAF* V600E oncogene mutations are the most commonly detected molecular changes in patients with melanoma and are used to achieve best therapy for their treatment, in line with new therapeutic options.

Keywords: metastatic melanoma (MM); molecular analysis; *BRAF* V600E mutation; gender and age categories of patients

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THE INFLUENCE OF SEX ON THE GENETIC STRUCTURE OF THE JACKAL (*CANIS AUREUS*) OF BOSNIA AND HERZEGOVINA

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The European golden jackal (*Canis aureus*) occupies a wide geographical range, spanning across northern and eastern Africa, northeastern Europe, and parts of southern Asia. In the past two decades, there has been a notable expansion of jackal populations into lowland areas in the northern regions of Bosnia and Herzegovina, with individuals migrating from Serbia and northeastern Croatia, thus establishing a stable population. A comprehensive population genetic study conducted by Nikitović et al. (2023) revealed intriguing insights into the genetic makeup of Bosnian jackals. Despite the absence of a discernible spatial pattern, the study revealed moderate genetic variability and the presence of two genetic clusters within the population. Intrigued by these findings, our study aimed to delve deeper into the genetic dynamics, specifically investigating whether sex plays a role in shaping the genetic structure of the jackal population in Bosnia and Herzegovina. Our analysis focused on 47 individuals sampled from the northern regions of Bosnia and Herzegovina. To determine the sex of the specimens, we employed molecular techniques, amplifying the Amelogenin gene using The Canine Genotypes™ Panel 1.1 kit (Finnzymes, Thermo Fisher Scientific, Finland). We used 16 microsatellite loci to assess genetic structure and variability and employed various software including GenAlEx v6.5 for genetic variability parameters (Na, Ne, He, Ho, HWE), STRUCTURE v.2.3.4 for population structure analysis, Structure Harvester for determining the optimal number of genetic clusters, and Clumpak for visualizing results from STRUCTURE analyses. Our dataset comprised 18 females and 29 males, for which basic genetic parameters appeared similar. However, STRUCTURE analysis revealed the presence of four genetic clusters (K=4) without a clear spatial pattern. Despite this, our findings conclusively demonstrate that sex does not significantly influence the genetic structure of the jackal population in Bosnia and Herzegovina.

Keywords: amelogenin, Bosnia and Herzegovina, *Canis aureus*, population structure, sex

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DIETARY SUPPLEMENTATION WITH LIOPHILISED STRAWBERRY IMPROVES INSULIN SENSITIVITY AND REDOX STATUS IN MOUSE MODEL OF DIET INDUCED OBESITY

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Healthy dietary habits with abundant fruit consumption may reduce prevalence and positively affect development and progression of various chronic diseases including obesity and insulin-resistance related diseases. Strawberry (*Fragaria × ananassa* Duch.) represent a valuable source of vitamins, minerals, fatty acids, dietary fiber, and various bioactive polyphenolic compounds such as anthocyanins and flavonoids which are known for their antioxidant and anti-inflammatory activities. In this study we evaluated the effect of newly introduced strawberry cultivar „Aprika” supplemented in the form of lyophilized powder, on obesity-related metabolic alterations in high-fat-diet fed mice. We hypothesized that chronic (8 weeks) supplementation of lyophilized strawberries in the amount comparable to two servings per day in humans, would ameliorate insulin resistance associated with obesity in C57BL/6 mice. Furthermore, we hypothesized that strawberry meal consumed at 7PM i.e. before active feeding period of mice (which corresponds to early breakfast in humans) would induce more pronounced beneficial effects compared to meal consumed at 7AM i.e. at the end of the active feeding period (which corresponds to late dinner in humans). High fat diet induced hyperglycaemia, hyperinsulinaemia, insulin resistance and obesity; and disturbed hepatic insulin signaling. Lyophilized strawberries, only when consumed before feeding period, reduced body weight gain and improved insulin sensitivity induced by high-fat diet (evidenced by lower area under the curve after an intraperitoneal GTT, reduced serum insulin levels and an insulin resistance index (IR-HOMA). Strawberry meals consumed after active feeding period had no such effect. However, strawberries, regardless of the time of consumption, restored protein level of Insulin receptor substrate 1 (IRS1) in the liver and increased hepatic antioxidant enzymes level. In conclusion, strawberries improve insulin sensitivity and raise hepatic antioxidant capacity in mouse model of diet induced obesity. Nevertheless, more beneficial effects were achieved when strawberries were consumed before active feeding period, as an early breakfast.

Keywords: high-fat diet, insulin resistance, antioxidant, polyphenols, strawberry

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THE ROLE OF ANGIOTENSIN I CONVERTING ENZYME INSERTION/DELETION POLYMORPHISM ON COVID-19 DISEASE SUSCEPTIBILITY

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The outbreak of COVID-19 caused by SARS-CoV-2 has led to a global health crisis, highlighting the urgent need for understanding the factors influencing disease susceptibility and severity. Among the various genetic factors under investigation, the angiotensin I converting enzyme (ACE) insertion/deletion (I/D) polymorphism has garnered significant attention due to its potential association with COVID-19. ACE, a key component of the renin-angiotensin system (RAS), plays a crucial role in regulating blood pressure and fluid balance. The ACE gene I/D polymorphism has been implicated in various cardiovascular and respiratory diseases due to its influence on ACE levels and activity. In our study, we aimed to investigate connection between ACE gene I/D polymorphism with asymptomatic and symptomatic COVID-19 patients. The study featured two groups, asymptomatic and symptomatic COVID-19 patients, each with 100 subjects. DNA was extracted, PCR-amplified, and analyzed by gel electrophoresis. Results revealed a statistically significant association ($p=0.050$) between examined groups in the frequency of the II genotype. Significantly, higher number of asymptomatic COVID-19 patients (25%) had II genotype when compared to the patients with COVID-19 symptoms (14%). However, no statistical significance was observed for the DD and ID genotypes. Interestingly, the D allele was significantly ($p=0.039$) more often present in group with COVID-19 symptoms (64%) when compared to the asymptomatic group (54.5%). Notably, no statistical significance was found for the I allele. Presented results confirmed the significant relationship between ACE (I/D) polymorphism, specifically the D allele and risk of COVID-19 symptomatic disease

Keywords: ACE gene I/D polymorphism, COVID-19 disease, asymptomatic and symptomatic COVID-19 patients

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GENETIC LANDSCAPE OF PHENYLKETONURIA IN SERBIA

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Phenylketonuria (PKU) is the most frequent inborn disorder of amino acid metabolism caused by variants in human phenylalanine hydroxylase gene (*PAH*). In this study, a total of 109 PKU patients from Serbia were included, who were classified into three phenotypic categories in accordance with pre-treatment plasma phenylalanine level: classic PKU, mild PKU and mild hyperphenylalaninemia. For genetic analyses, we combined Sanger sequencing, MLPA and next generation sequencing to identify disease-causing variants in *PAH* gene, which were further classified using ACMG classification. Additionally, we used *in silico* and/or eukaryotic expression studies to assess the effect of novel genetic variants identified in our patients. Disease-causing variants were identified in 217 of 218 alleles, reaching detection rate of 99.5%. We detected a total of 32 different variants, of which 29 previously described and three novel ones: p.Gln226Lys, p.Pro244His and p.Pro416Leu. *In silico* and/or eukaryotic expression studies confirmed pathogenic effect of all novel genetic variants. The most frequent variant was p.Leu48Ser (31.2%), followed by p.Arg408Trp (13.8%), p.Ile306Val (9.2%), p.Glu390Gly (5%), p.Pro281Leu (4.6%), and p.Arg261Gln (3.2%). All detected disease-causing variants were classified as pathogenic using ACMG classification. Our study brings the updated spectrum of molecular genetic data, variant classification and detailed phenotypic characteristics for PKU patients from Serbia. Therefore, our study contributes to better understanding of molecular landscape of PKU in Europe and to general knowledge on genotype–phenotype correlation in PKU.

Keywords: phenylketonuria; phenylalanine hydroxylase; variant; genotype-phenotype correlation

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NEW TERT VARIANT IN A FAMILY WITH APLASTIC ANEMIA

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TERT gene, the most frequently mutated gene in patients with telomere biology disorders (telomeropathies), encode telomerase reverse transcriptase enzyme. Heterozygous variants in the TERT gene impair telomerase activity by haploinsufficiency and pathogenic variants are associated with bone marrow failure syndrome and acute myeloid leukemia predisposition. TERT variants show incomplete penetrance and can also be found in asymptomatic family members. Due to the rarity of the disease and the small number of clinical trials, telomeropathies are often unrecognized and misdiagnosed. To report a novel variant in TERT gene in familial hematopoietic disorder. Methodology: Next Generation Sequencing of DNA isolated from peripheral blood of a patient (older sister) with clinical diagnosis of aplastic anemia, using TruSight One MiSeq platform (Illumina®) and segregation sequencing analysis of patient's mother and younger sister. We identified a novel missense heterozygous variant c.2605G>A p.(Asp869Asn) in TERT gene in a family of mother and two daughters. This variant results in replacement of aspartic amino acid on 869 position in TERT enzyme polypeptide chain by asparagine. It is located in highly conserved protein region and is very likely to disrupt the function of the enzyme. According to ACMG classification, detected variant is characterized as likely pathogenic, class 2. As patients with telomeropathies often have a history of macrocytosis and thrombocytopenia, often wrongly diagnosed as immune-mediated thrombocytopenia, myelodysplastic syndrome or aplastic anemia, our findings indicate that TERT rare variants pass under-recognized in these patients. For that reason, our findings point out the importance for routine deep genetics screening for TERT rare variants in patients with family history of different bone marrow failure syndromes. Which could identify clinically inapparent telomere biology disorder and improve outcomes through forehand diagnosis setting, genetic counseling and the precise therapy consideration.

Keywords: Aplastic anemia, TERT gene, next generation sequencing

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MICRORNA SIGNATURES IN ALZHEIMER'S DISEASE: A REVIEW OF DIAGNOSTIC POTENTIAL

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Alzheimer's disease (AD) stands as one of the most pressing health challenges of our time, characterized by progressive cognitive decline and neuronal degeneration. Despite decades of research, reliable diagnostic biomarkers for AD remain elusive. Recently, microRNAs (miRNAs) have emerged as promising candidates due to their stability in bodily fluids and their regulatory roles in key biological processes implicated in AD pathogenesis and beyond. Studies have shown that miRNAs are implicated in the regulation of amyloid precursor protein expression, tau phosphorylation, and brain-derived neurotrophic factor (BDNF) levels, all of which are key factors in AD pathology. MiRNAs are small non-coding RNAs, typically 18-22 nucleotides in length, that play crucial roles in post-transcriptional gene regulation by binding to target messenger RNA (mRNA) and modulating their expression levels. This review summarize and provides a comprehensive synthesis of the current literature on the potential of miRNAs as diagnostic and prognostic biomarkers for AD. Specific miRNAs, such as miR-153 and miR-455-3p, have been implicated in regulating key proteins associated with AD pathology, suggesting their potential as diagnostic markers. The dysregulation of miRNAs, such as miR-16, miR-17, and miR-206, has been observed in AD, indicating their potential as indicators of disease progression. We explore the dysregulation of specific miRNAs expression profiles in AD patients across various biological samples, including blood, cerebrospinal fluid, and brain tissue, such as miR-29a, miR-107, miR-125b, miR-132, and miR-146a. Additionally, we discuss the utility of miRNAs in distinguishing AD from other neurodegenerative disorders and in monitoring disease progression. Subsequently, we do effort to examine the challenges and limitations associated with miRNA-based biomarker research, including standardization issues and the need for large-scale validation studies. Finally, we try and equally important to highlight the future directions and clinical implications of miRNA-based biomarkers in the early detection, diagnosis, and management of AD.

Keywords: microRNAs, Alzheimer Disease, biomarkers

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CASE REPORT OF INHERITED TRANSLOCATION T(12;13)(Q24.33;Q21.2)

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Unbalanced chromosome rearrangements represent a significant number of genetic disorders, wherein often stemming from inherited parental structural chromosome rearrangement or spontaneous alterations. Genetic counseling and testing play crucial roles in identifying carriers of balanced reciprocal structural rearrangement, typically asymptomatic individuals. Here is presented a case study of a neonate with an unbalanced karyotype, elucidated through cytogenetic methods. The infant exhibited multiple congenital anomalies characterized by dyscrania, hypotelorism, postaxial hexodactyly of all extremities, chest deformity and cryptorchismus. This male newborn was third child of their parents, with unaffected older siblings. Cytogenetic analysis via GTG banding revealed a complex karyotype 46,XY,der(12)t(12;13)(q24.33;q21.2). The manifestation of the newborn's phenotype, suggests an influence of the 13q partial trisomy and 12q partial monosomy. Further analysis of the parents' karyotypes identified the father as a carrier of balanced reciprocal translocation: 46,XY,t(12;13)(q24.33;q21.2). Father's sister is also carrier of the same balanced structural chromosome rearrangement. In her first pregnancy, the fetus had an unbalanced karyotype 46,XY,der(13)t(12;13)(q24.33;q21.2). After that, a karyotype analysis of the closest relatives was indicated in the genetic counseling center, which the relatives did not follow. This case underscores the significance of cytogenetic analysis and genetic counseling in elucidating the etiology of complex chromosome rearrangements and their phenotype consequences in congenital disorders.

Keywords: unbalanced karyotype, partial trisomy 13q, genetic counseling

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NEW GATA3 VARIANT IN A PATIENT WITH BARAKAT SYNDROME

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Background: *GATA3* protein is a transcription factor involved in the embryonic development of parathyroid glands, kidney, thymus, inner ear, and central nervous system. Pathogenic heterozygous germline variants in the *GATA3* gene impair protein activity by haploinsufficiency leading to hypoparathyroidism, sensorineural deafness, and renal dysplasia- HDR or Barakat syndrome. So far, about 200 patients have been reported in the literature worldwide. A novel variant in *GATA3* gene was detected. Next -generation sequencing analysis of DNA isolated from peripheral blood of a 17-year-old patient with clinical diagnosis of bilateral sensorineural deafness, unilateral renal agenesis, developmental delay and double uterus, is performed using TruSight One panel and NextSeq 550 system (Illumina). A novel missense heterozygous variant c.989G>A p.(Arg330Lys) in *GATA3* gene was detected in a patient. This variant results in a replacement of amino acid arginine by lysine on position 330 in *GATA3* transcription factor protein. It is in a highly conserved zinc-finger protein region and is very likely to disrupt the function of the enzyme by haploinsufficiency. According to ACMG classification, the detected variant is characterized as likely pathogenic. Barakat syndrome is a clinically heterogeneous autosomal dominant disorder caused by pathogenic variants in the *GATA3* gene. So far, 93 *GATA3* pathogenic variants have been reported in the literature. *GATA3* variants show incomplete penetrance, causing great clinical variability. We present the patient, a heterozygous carrier of novel variant in *GATA3* gene, with no typical presentation of HDR syndrome, since hypoparathyroidism was clinically unapparent, and the patient had additional clinical manifestations – neurological developmental delay and a double uterus. Since prenatal ultrasound and neonatal hearing screening can identify renal or hearing defects, the presence of those symptoms should represent clinical indication for NGS testing which will result in earlier diagnosis of HDR and detection of other symptoms, enabling early intervention and genetic counseling.

Keywords: Barakat syndrome, *GATA3* gene, NGS.

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ADVANCING ALZHEIMER'S DISEASE MANAGEMENT THROUGH PERSONALIZED MEDICINE: INTEGRATING GENETIC, NEUROINFLAMMATORY, AND BIOMARKER INSIGHTS

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioral changes. It is the most common cause of dementia, affecting millions worldwide. In its most common form, it occurs in people over 65 years of age, who make up 60% of the total patients, making early detection crucial. Despite extensive research, effective treatments for AD remain elusive, prompting a shift towards personalized medicine approaches to better understand and manage the disease. Personalized medicine in AD is a rapidly evolving field with promise for improving diagnosis, treatment, and prevention. Genetic factors are crucial in AD susceptibility. Variations like decreased CD33 expression are associated with altered AD risk, affecting amyloid β peptide clearance, a key process in the disease. This highlights genetic information's potential to guide personalized treatment. Precision medicine in AD focuses on understanding neuroinflammatory mechanisms, fluid biomarkers, and genetics to tailor treatments. Utilizing advanced statistical analyses and biomarker data, researchers identify distinct patient clusters, aiding in personalized treatment discovery. Genetics play a crucial role, enabling risk prediction, improving diagnostic accuracy, and facilitating targetable disease mechanism discovery. Therapeutic strategies in AD are shifting towards personalized approaches, including subgrouping patients based on clinical or genetic similarities. This aims to develop more effective drugs targeting specific patient characteristics. However, transitioning from universal risk-reduction strategies to personalized interventions is still in progress. Precision medicine offers a clear path towards individualized interventions for AD and other neurodegenerative diseases. By tailoring treatments to each patient's unique characteristics, it can revolutionize AD diagnosis and therapy, leading to better outcomes. In conclusion, integrating genetic information, neuroinflammatory mechanisms, fluid biomarkers, and personalized treatment strategies paves the way for a more targeted approach to managing AD. Precision medicine represents a shift towards personalized care, considering individual variability in disease presentation and treatment response.

Keywords: Alzheimer's disease, precision medicine, genetic factors, biomarkers, early detection

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OPTIMIZING CUSTOM-DESIGNED PRIMERS FOR COMPLETE MITOCHONDRIAL GENOME SEQUENCING WITH ILLUMINA® NEXTERA® XT SYSTEM AND CONFIRMATORY SANGER SEQUENCING

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Mitochondrial DNA (mtDNA) has been of utmost importance in forensic practice as well as in the research of hereditary diseases. Next-generation sequencing (NGS) (multiparallel sequencing) has been discovered as a revolutionary technology for large-scale analysis of genomes and transcripts and is useful in numerous scientific areas. Next-generation sequencing of mitogenome has overcome the time and cost issues of Sanger sequencing methods. Validation of multiparallel sequencing and confirmatory Sanger sequencing of mitogenome are essential for robust mtDNA analysis. As of now, various optimizations have been performed, but none on mitogenome primers or sequencing reagents. The subject matter covers the optimization of novel designed two primer pairs for mitogenome amplification, while the results with Nextera XT primers yielded no results. The main objective of this research was primer design and optimization for whole mitochondrial DNA sequencing on MiSeq® instrument, as well as the confirmatory Sanger sequencing of the mitogenome. This study outlines the development of an optimal procedure for mitogenome sequencing using the Illumina Miseq technology, which can be applied in forensics and clinical settings. To confirm the NGS data, Sanger sequencing was performed using 32 custom-made primer pairs. The sequencing data was analyzed using Mitowizz, a recently developed and established bioinformatics software that allows prompt discovery of mutations associated with mitogenome diseases.

Keywords: primer optimization, sequencing, mtDNA, forensic science, clinical practice

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CASE REPORT: PRENATAL DETECTION OF PSEUDOISODICENTRIC CHROMOSOME 18Q

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Compared to chromosome disorders like trisomy 18 (Edwards syndrome) or terminal deletion syndromes of 18p and 18q, which have been sporadically observed, the occurrence of pseudoisodicentric chromosome 18 is even rarer. Here, we report a case of a woman who was referred for prenatal cytogenetic diagnostics. The echocardiographic report showed normal findings and the decision for prenatal cytogenetic diagnostics testing was based on a patient's age. Prenatal cytogenetic chromosomal analysis of a fetus was conducted using amniotic fluid by flask method. Both conventional GTG-banding analysis and CBG-banding analysis were conducted using Applied Spectral Imaging (ASI) software. Twenty metaphase cells of cultured amniocytes were analyzed. Karyotype analysis of a fetus revealed presence of a pseudoisodicentric chromosome 18q in all analyzed metaphases, 46,XX,psu idic(18)(18pter→18q22::18q22→18pter). As a result, the fetus had partial trisomy (18pter→18q22) and partial monosomy (18q22→18qter).

Keywords: prenatal diagnostics, pseudoisodicentric chromosome, karyotyping

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TUMOR NECROSIS FACTOR ALPHA GENE POLYMORPHISMS -238G>A AND -308G>A AS GENETIC MARKERS FOR THE DEVELOPMENT OF ALCOHOL RELATED LIVER CIRRHOSIS

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INTRODUCTION: Alcohol-related liver cirrhosis (ALC) is a progressive liver disease that may result from excessive alcohol abuse. Endotoxemia induced by ethanol consumption represents a strong stimulus for Kupffer cells to secrete Tumor necrosis factor- α (TNF- α). TNF- α induces an inflammatory response that often leads to chronic liver injury. It plays a key role in the pathogenesis of alcohol-related liver disease. Our study aimed to estimate the association of *TNF- α* promoter polymorphisms at two positions (-238G>A and -308G>A) with ALC susceptibility from one group of ALC patients from Serbia. A total of 118 patients with ALC and 131 sex and age-matched healthy controls were clinically examined and genetically tested. DNA was extracted from peripheral blood lymphocytes, and genotyping was performed using PCR-RFLP for both promoter variants. We determined the *TNF- α* genotypes of each participant by the presence of the relevant DNA fragments on agarose gel. Groups were compared using the Chi-Square test; binary logistic regression was used to obtain odds ratios. Concerning the -238G>A variant, a significant association between A allele carriers and risk of ALC (OR=2.36, 95% CI=1.15-4.83; p=0.019) was observed. We found only one patient with an AA genotype, so we compared the combined AA and GA genotypes with GG genotype. No significant differences were found in either genotype or allelic frequencies of the -308 *TNF- α* gene variant between the patients and controls (allele frequencies 15.7% vs. 13.4%, p=0.463). The -238 *TNF- α* -A allele was associated with a higher risk of developing ALC in our group of patients with ALC from Serbia. This variant could represent one of the genetic factors that confer a predisposition to develop ALC.

Keywords: *TNF- α* , promoter variants, alcohol-related liver cirrhosis, proinflammatory cytokine

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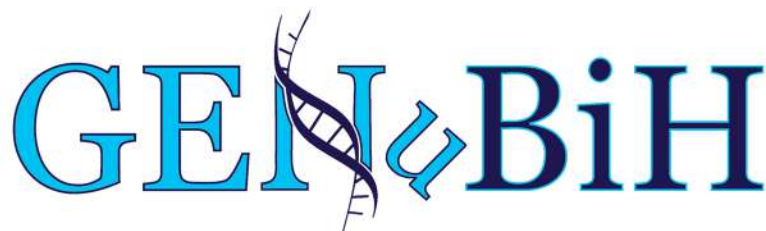
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