ABSTRACTS OF THE 10TH CROATIAN HUMAN GENETICS CONFERENCE & 3RD CROATIAN PERSONALIZED AND PRECISION MEDICINE CONFERENCE

ORAL PRESENTATIONS

Presentation number: CSHG/CSPPM OP 01 Abstract number: 104-ISABS-2026

CROATIA'S PIONEERING ROLE FIRST SYSTEMATIC DNA-BASED IDENTIFICATION OF MASS GRAVE VICTIMS

Anđelinović Šimun[1], Primorac Dragan[2,3,4,5,6,7,8,9,10,11,12]

[1]University Hospital Center Split, Split, Croatia; [2]St. Catherine Specialty Hospital, Zagreb, Croatia; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, United States of America; [4]Eberly College of Science, The Pennsylvania State University, University Park, PA, United States of America; [5]Medical School, University of Split, Split, Croatia; [6]Medical School, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [7]Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, New Haven, CT, United States of America; [8]Sana Medical School, Coburg, Germany; [9]Medical School, University of Rijeka, Rijeka, Croatia; [10]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [11]Medical School, University of Mostar, Mostar, Bosnia and Herzegovina; [12]National Forensic Sciences University, Gandhinagar, India

simun.andjelinovic@unist.hr

The application of large-scale DNA-based identification in the context of armed conflict emerged in the early 1990s in response to unprecedented forensic challenges posed by mass graves and severely degraded human remains following the wars in Croatia and Bosnia and Herzegovina. This historical perspective examines the origins, methodological innovations, and lasting scientific impact of the first systematic uses of DNA technology for the identification of victims recovered from mass-fatality sites during active conflict and post-conflict period. These pioneering efforts were initiated between 1993 and 1994 at the Department of Pathology and Forensic Medicine of the University Hospital in Split, representing one of the earliest organized forensic DNA identification programs. By integrating classical forensic disciplines with early PCR based DNA profiling methods, and by establishing a structured kinship reference database, Croatian scientists developed a comprehensive and robust framework for victim identification. This work was carried out in close collaboration with leading forensic experts from the USA, enabling the transfer and adaptation of emerging molecular technologies to an active wartime environment. On December 6, 1995, during a Congressional Hearing on Intelligence and Security entitled "Mass Graves and Other Atrocities in Bosnia", Dr. Barbara Wolf formally acknowledged the Croatian DNA identification efforts, an exceptional endorsement of a forensic initiative developed outside established Western forensic systems. As part of this presentation, we will also examine the Duboki Jarak case, the first instance in Croatia in which a court (Military Court in Zagreb, April 18, 1994) formally mandated DNA analysis for the identification of victims of a mass-fatality event occurring under active wartime conditions. Notably, these applications preceded the formal incorporation of DNA analysis into international DVI guidelines later in the decade.

Keywords: forensic genetics, DVI, DNA identification, military compound explosion

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DYSPLASIA EPIPHYSEALIS HEMIMELICA: PERSONALIZED AND MULTIPLE TREATMENT MODALITIES FOR A SINGLE RARE DISEASE

Šimić Jovičić Marijana[1], Vlaić Josip[1], **Antičević Darko**[2,3]

[1]Department of Paediatric Orthopaedics, Children's Hospital Zagreb, Zagreb, Croatia; [2]St. Catherine Specialty Hospital, Zagreb, Croatia; [3]School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

darko.anticevic@gmail.com

Dysplasia epiphysealis hemimelica (DEH), also known as Trevor's disease, is a non-hereditary developmental bone disease mostly diagnosed in the first decade of a patient's age. Genetic tests for *EXT1* and *EXT2* gene expression can be used for diagnosis, as in multiple osteochondromas. The clinical experience with this condition is limited due to its very rare incidence (1:1,000,000). DEH is characterized by a benign, abnormal growth of the joint cartilage that produces an irregular intra-articular mass within the joint, causing limited function and deformity of the joint and limb length discrepancy. Clinical and radiological features are generally sufficient for a correct diagnosis if one has an early suspicion. If left untreated, degenerative arthritis with all its consequences will occur. This report aims to underline a personalized treatment approach and to present mid-term outcomes of the clinical and therapeutic course in three children. A single bone or multiple bones in a single limb may be affected. In a generalized form, it usually involves multiple bones and joints in two or more limbs or even the axial skeleton. A retrospective clinical and radiological analysis of three children with different challenging localizations of the disease was performed, i.e., lateral femoral condyle, scaphoid bone, and generalized form. We used different surgical modalities, e.g., arthroscopic resection, temporary hemi-epiphysiodesis, and corrective osteotomy as treatment methods. Ten-year clinical follow-up results were good and very good. Functional and radiological outcomes in two patients (scaphoid bone, femoral condyle) were very good. In generalized DEH, outcomes were less satisfactory due to multiple affected sites and more frequent surgeries. In children with symptomatic DEH, treatment is individualized based on lesion location, size, and age. Clinical observation until puberty is recommended, as lesions may grow until skeletal maturity.

Keywords: dysplasia epiphysealis hemimelica, Trevor's disease, osteochondral lesions, personalized surgical treatment

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GENETIC DIAGNOSIS OF RARE NEUROLOGICAL DISORDERS: CURRENT TRENDS AND FUTURE DIRECTIONS

Babić Božović Ivana[1,2], Maver Aleš[1], Bergant Gaber[1], Kovanda Anja[1], Lovrečić Luca[1], Peterlin Borut[1]

[1]Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Department of Genomic Medicine, Clinical Hospital Centre Rijeka, Rijeka, Croatia

ivana.babic.bozovic@kclj.si

Rare neurological disorders are predominantly genetic and represent a major diagnostic challenge. Ongoing European initiatives are targeting current limitations in genetic diagnosis of rare neurological disorders, including technology limitations, challenges in variant interpretation, lack of standardisation, insufficient integration of multi-omics approaches, inequalities in access to testing and specialised knowledge. The main focus of European collaborative frameworks is on advancing and standardisation of diagnostic approaches, pathways, and healthcare system factors. As a full member of European Reference Networks for Rare Neurological and Neuromuscular Disorders we will showcase the use of advanced diagnostic strategies, including exome and genome sequencing, cross-border data sharing, expert consultation via the Clinical Patient Management System, RNA sequencing for functional validation, and iterative reanalysis of genomic data. These approaches led to the resolution of previously unsolved cases and refinement of diagnostic pathways. Our experience highlights that the key determinants of successful diagnosis are not only technological advances but also access to collaborative networks, data integration, and multidisciplinary expertise. Ongoing efforts, including participation in European registries and expansion of multi-omics approaches, effective implementation and validation of artificial intelligence- based interpretation tools, and the development of learning healthcare systems aim to further improve diagnostic equity and efficiency. In conclusion, combining state-of-the-art genomic methods with structured European collaboration represents a critical step toward standardized, more accurate and timely diagnosis of RNDs.

Keywords: rare diseases, neurological disorders, neuromuscular disorders, genetic diagnosis, European Reference Networks

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THE HIDDEN LANGUAGE OF CANCER: PREDICTING CLINICAL OUTCOMES THROUGH GENOMIC SIGNALS

Bulić Luka[1,2,3], Brlek Petar[1,2,4], Primorac Dragan[1,2,5,6,7,8,9,10,11,12,13]

[1]St. Catherine Specialty Hospital, Zagreb, Croatia; [2]School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [3]Algebra Bernays University, Zagreb, Croatia; [4]Department of Molecular Biology, Faculty of Science, University of Zagreb, Zagreb, Croatia; [5]International Center for Applied Biological Research, Zagreb, Croatia; [6]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [7]Eberly College of Science, The Pennsylvania State University, State College, PA, United States of America; [8]School of Medicine, University of Split, Split, Croatia; [9]The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, New Haven, CT, United States of America; [10]Sana Kliniken Oberfranken, Coburg, Germany; [11]School of Medicine, University of Rijeka, Rijeka, Croatia; [12]School of Medicine, University of Pittsburgh, Pittsburgh, PA, United States of America; [13]Gandhinagar Campus, National Forensic Sciences University, Gandhinagar, India

luka.bulic@svkatarina.hr

Cancer is increasingly recognized as a dynamic and heterogeneous biological system shaped by interactions between germline predispositions and somatic genomic alterations. Advances in high- throughput sequencing, combined with artificial intelligence (AI), have enabled the extraction of clinically relevant patterns from complex genomic data, moving oncology from descriptive classification toward predictive modeling of disease behavior. Germline variants influence susceptibility, DNA repair capacity, and pharmacogenomic response, while somatic alterations define tumor phenotype, clonal evolution, and therapeutic vulnerabilities. AI-driven approaches, including machine learning and deep learning models, provide powerful tools for integrating these genomic layers with clinical data, capturing nonlinear relationships and improving predictive performance beyond traditional biomarker-based strategies. Recent developments have demonstrated that AI-based genomic models can stratify patients according to survival outcomes, predict recurrence risk, and anticipate response to targeted therapies and immunotherapy. In addition, circulating tumor DNA enables dynamic monitoring and early detection of minimal residual disease, further enhancing predictive accuracy. The integration of multi-omics data within AI frameworks represents a key step toward more precise and individualized prediction. Despite these advances, challenges remain, including data heterogeneity, limited generalizability, and issues of interpretability and clinical validation. Addressing these barriers is essential for successful implementation. Integrating germline and somatic genomic information through AI-driven models represents a critical step toward predictive oncology, enabling more accurate forecasting of clinical outcomes and more personalized cancer management.

Keywords: next-generation sequencing, precision oncology, artificial intelligence, machine learning, molecular tumor profiling

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IMPLEMENTATION OF NEXT-GENERATION SEQUENCING IN ROUTINE CARDIOLOGY PRACTICE: A RETROSPECTIVE STUDY FROM CLINICAL HOSPITAL CENTER RIJEKA

Hodak Kristian[1], Hrvatin Nenad[1], Babić Božović Ivana[1,2,3], Maver Aleš[3], Vodnjov Nina[3], Mladenić Tea[2], Dević Pavlić Sanja[2], Benko Koraljka[4,5], Čubranić Zlatko[4,5], Ružić Alen[4,5], Vraneković Jadranka[2], Ostojić Saša[2], Peterlin Borut[1,2,3]

[1]Department of Genomic Medicine, Clinical Hospital Centre of Rijeka, Rijeka, Croatia; [2]Department of Medical Biology and Genetics, Faculty of Medicine in Rijeka, Rijeka, Croatia; [3]Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; [4]Clinic for Cardiovascular Diseases, Clinical Hospital Center Rijeka, Rijeka, Croatia; [5]Department of Internal Medicine, Faculty of Medicine in Rijeka, University of Rijeka, Rijeka, Croatia

kristian_ho@hotmail.com

To assess the diagnostic yield, clinical indications, and utility of next-generation sequencing in adult cardiology patients at the Clinical Hospital Center Rijeka. This preliminary retrospective study included adult patients referred for genetic testing for cardiac diseases between 2023 and 2025. Genetic testing was offered to all patients with suspected inherited cardiovascular disease referred by the Clinic for Cardiovascular Diseases, including cardiomyopathies and cardiac channelopathies. Whole exome sequencing with phenotype-driven bioinformatic gene panels tailored to the specific cardiac conditions was applied. Medical data were collected from the hospital information system. There were 189 adult participants included in the study, consisting of 65 female (34.39%) and 124 male (65.61%). Regarding clinical indications, 15 (7.94%) had arrhythmogenic cardiomyopathy, 76 (40.21%) had dilated cardiomyopathy, 59 (31.22%) had hypertrophic cardiomyopathy, 6 (3.17%) had noncompaction cardiomyopathy, 1 (0.53%) had restrictive cardiomyopathy, 8 (4.23%) were classified as cardiomyopathy, and 24 (12.70%) were referred as suspected cardiac channelopathy. We successfully identified a causative genetic variant in 36 of the 189 patients, corresponding to an overall diagnostic yield of 19.05%. Causative variants were detected in the following genes: *MYBPC3, TNNT2, LMNA, MYL2, MYH7, KCNH2, TTN, PKP2, DSP, TPM1,* and *DMD*. In addition, a pathogenic heterozygous trinucleotide repeat expansion in the *DMPK* gene was detected in one patient. Our preliminary results support the integration and clinical utility of whole exome sequencing into routine practice for accurate diagnosis, prognosis, and management of inherited cardiac disorders. While genetic testing provides meaningful diagnostic insights, its effectiveness in routine clinical practice remains highly dependent on careful patient selection and detailed phenotyping, underscoring the growing role of medical genetics specialists.

Keywords: genetic testing, cardiomyopathies, cardiac channelopathies, heart rhythm disorders, whole exome sequencing

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FROM SEQUENCING TO THERAPY: IMPLEMENTING COMPREHENSIVE GENOMIC PROFILING IN ROUTINE CLINICAL PRACTICE

Kunac Nenad[1], Galeković Mia[1], Anđelinović Šimun[1]

[1]University Hospital of Split, Split, Croatia

nkunac@kbsplit.hr

The goal of this report was to evaluate the implementation of comprehensive genomic profiling (CGP) in routine diagnostics at the Department of Pathology, University Hospital Split. Material and methods included analysis of 1,093 samples (FFPE, blood and cfDNA) using next-generation sequencing (NGS)-based platforms, covering tumor-specific panels, homologous recombination repair/deficiency (HRR/HRD), myeloid and hereditary panels, and combined DN A/RNA CGP approaches. Results demonstrated successful detection of a wide range of genomic alterations, including SNVs, indels, CNVs, translocations, and gene fusions, as well as key immuno -oncology biomarkers such as tumor mutational burden (TMB), microsatellite instability (MSI), and homologous recombination deficiency (HRD). Integration of HRD testing enabled patient selection for PARP inhibitor therapy, while bioinformatics tools improved interpretation in low tumor content samples. Implementation also resulted in optimized workflows and high reproducibility. The introduction of CGP into routine diagnostics represents a significant advancement toward precision and personalized medicine, improving tumor characterization, therapeutic decision-making, and patient outcomes.

Keywords: comprehensive genomic profiling, next-generation sequencing, HRD, precision medicine, molecular diagnostics

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Y CHROMOSOME STORY AND CROATIAN HERITAGE: MODERN CROATIAN GENETIC POOL VS ANCIENT GENETIC DATA

Marjanović Damir[3,2,1], Novak Mario[1,4], Šarac Jelena[1,3], Havaš Auguštin Dubravka[1], Novokmet Natalija[1], Primorac Dragan[5,6,7,8,9,10,11,12,13]

[1]Institute for Anthropological Research, Zagreb, Croatia; [2]International Burch University, Sarajevo, Bosnia and Herzegovina; [3]Faculty of Biotechnology and Drug Development, University of Rijeka, Rijeka, Croatia; [4]Department of Archaeology and Heritage, Faculty of Humanities, University of Primorska, Koper, Slovenia; [5]St. Catherine Specialty Hospital, Zagreb, Croatia; [6]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [7]School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [8]Medical School, University of Split, Split, Croatia; [9]Department of Biochemistry & Molecular Biology, The Pennsylvania State University, State College, PA , United States of America; [10]The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, West Haven, CT , United States of America; [11]Regiomed Kliniken, Coburg, Germany; [12]Medical School, University of Rijeka, Rijeka, Croatia; [13]National Forensic Sciences University, Gandhinagar , India

dmarjanovic@inantro.hr

Due to its turbulent demographic history, marked by extensive settlement and gene flow from diverse regions of Eurasia, Southeastern Europe (SEE) has consistently served as a genetic crossroads between East and West and a junction for the migrations that reshaped Europe's population. SEE, including modern Croatian territory, was a crucial passage from the Near East and even more distant regions and human populations in this region, as almost any other European population represents a remarkable genetic mixture. Our views of its history have been mostly renewed in the last few decades by extraordinary data obtained from Y-chromosome studies. A substantial majority, exceeding three-quarters of the present-day Croatian male population likely traces its ancestry to "Old Europeans" who came here before and after the Last Glacial Maximum. The remaining part of the population is the offspring of the people arriving in this part of Europe through the southeastern migratory route in the last 10,000 years, mainly during Neolithization. In recent times, the international research community, bringing together geneticists and archaeologists, has steadily released a growing number of ancient genomes from this region, shedding more light on its complex past population dynamics and shaping the genetic pool in Croatia and this part of Europe. We believe this presentation will help us to summarize almost three decades of scientific efforts within the analysis of the genetic structure of the Croatian population in more detail, as well as the aspects of its demographic history.

Keywords: Y chromosome, old Europeans, present-day population, ancient data

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GENETIC CAUSES OF LISSENCEPHALY SPECTRUM: INSIGHTS FROM CHROMOSOMAL MICROARRAY AND CLINICAL/WHOLE-EXOME SEQUENCING

Meašić Ana-Maria[1,2,3], Vulin Katarina[1,2,3], Bobinec Adriana[1,2,3], Morožin Pohovski Leona[1,2,3], Sansović Ivona[1,2,3], Mikloš Morana[1,2,3], Kero Mijana[4], Tripalo Batoš Ana[5], Odak Ljubica[1,2,3], Barišić Ingeborg[6]

[1]Department of Medical and Laboratory Genetics, Endocrinology and Diabetology with daily care unit, Children's Hospital Zagreb, Zagreb, Croatia; [2]Scientific Centre of Excellence for Reproductive and Regenerative Medicine (CERRM), University of Zagreb School of Medicine, Zagreb, Croatia; [3]European Reference Network on congenital malformations and rare intellectual disability ERN-ITH-ACA, Zagreb, Croatia; [4]Department of Hematology, Oncology, Clinical Immunology, and Genetics, University Hospital of Split, Split, Croatia; [5]Department of Pediatric Radiology, Children's Hospital Zagreb, Zagreb, Croatia; [6]Polyclinic Sinteza, Zagreb, Croatia

ana-maria.measic@kdb.hr

Lissencephaly is a rare malformation of cortical development caused by abnormal neuronal migration. It represents a spectrum that includes agyria, pachygyria, and subcortical band heterotopia. Lissencephaly is considered as a predominantly genetic disorder, with at least 31 genes currently known to be associated with the condition. Our aim was to determine the diagnostic yield of comprehensive genetic testing in a cohort of patients with neuroimaging findings suggestive of the lissencephaly spectrum disorders and to characterize novel pathogenic variants contributing to the genetic architecture of the spectrum. We reviewed clinical and genetic findings in 23 patients with neuroimaging features suspected of the lissencephaly spectrum, seen at the Children's Hospital Zagreb between 2016 and 2025. Clinical data were obtained from medical records and outpatient assessments by clinical geneticists. Genetic testing included chromosomal microarray, clinical exome sequencing and whole-exome sequencing. A molecular diagnosis was established in 16 of 23 patients (69.5 %). The pathogenic variants involved genes related to microtubule function (*PAFAH1B1, DCX, TUBA1A, TUBB2B, DYNC1H1*), and variants in transcriptional and regulatory genes (*FOXG1, WDR62*). Five novel variants were detected in well-established lissencephaly genes (*DCX, PAFAH1B1, TUBA1A, FOXG1* and *WDR62*). Although most cases involved single-gene variants, three patients had pathogenic copy number variants (1q43q44, 22q11.21 and Xq22.3q23 deletions). Exome sequencing when used as a first-line test, complemented by chromosomal microarray, provides high diagnostic yield in patients with lissencephaly spectrum disorders. This integrated approach facilitates precise diagnosis, informs prognosis, enables targeted follow-up, and supports comprehensive genetic counselling.

Keywords: lissencephaly, pachygyria, subcortical band heterotopia, copy number variants, exome sequencing

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ARTIFICIAL INTELLIGENCE IN CYTOGENETICS: PROGRESS IN AUTOMATED KARYOTYPE ANALYSIS

Vraneković Jadranka[1], **Mladenić Tea**[1], Barišić Anita[2], Starčević Čizmarević Nada[1], Babić Božović Ivana[3,2]

[1]University of Rijeka, Faculty of Medicine, Rijeka, Croatia; [2]Clinical hospital Rijeka, Rijeka, Croatia; [3]Clinical Institute of Genomic Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia

tea.mladenic@uniri.hr

Computer systems for karyotype analysis have evolved in parallel with advances in digital microscopy, image processing, and artificial intelligence. In the 1980s and 1990s, early digital systems enabled storage and visualization of chromosome images, but analysis remained largely manual, requiring cytogeneticists to crop, arrange, and classify chromosomes with minimal software support. From the 1990s to around 2010, semi-automated systems introduced automated metaphase detection, chromosome segmentation, and preliminary classification based on morphological features such as length, centromere position, and banding patterns. However, expert validation was still necessary to confirm final results. After 2010, major improvements in image analysis and machine learning enabled advanced cytogenetic workstations capable of rapid slide scanning and efficient analysis of large numbers of metaphase spreads. More recently, deep learning methods, particularly convolutional neural networks, have enabled highly accurate automatic detection, segmentation, and classification of chromosomes. These developments have significantly improved the speed, reproducibility, and standardization of karyotype analysis in clinical and research cytogenetics. The aim of this study is to outline the evolution of computer systems for karyotype analysis and to highlight the role of artificial intelligence in improving efficiency, accuracy, and standardization.

Keywords: computer system detection, deep learning methods, karyotype analysis methods, metaphase chromosome

Presentation number: CSHG/CSPPM OP 10 Abstract number: 53-ISABS-2026

CLINICAL FEATURES, GENETIC LANDSCAPE AND MANAGEMENT OF OSTEOGENESIS IMPERFECTA PATIENTS IN CROATIA

Odak Ljubica[1], Vulin Katarina[1], Veršić Mirela[2], Sansović Ivona[1], Meašić Ana-Maria[1], Mikloš Morana[1], Jovović Lada[1], Morožin-Pohovski Leona[1], Antičević Darko[3], Brlek Petar[3], Primorac Dragan[3,4,5,6,7,8,9,10,11,12,13]

[1]Children's Hospital Zagreb, Zagreb, Croatia; [2]Special Hospital for Chronic Diseases of Children in Gornja Bistra, Gornja Bistra, Gornja Bistra, Croatia; [3]St. Catherine Specialty Hospital, Zagreb, Croatia; [4]International Center for Applied Biological Research, Zagreb, Croatia; [5]School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [6]Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [7]Eberly College of Science, The Pennsylvania State University, State College, University Park, Pennsylvania, United States of America; [8]School of Medicine, University of Split, Split, Croatia; [9]The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, New Heaven, Connecticut, United States of America; [10]Sana Kliniken Oberfranken, Coburg, Germany; [11]School of Medicine, University of Rijeka, Rijeka, Croatia; [12]School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America; [13]Gandhinagar Campus, National Forensic Sciences University, Gandhinagar, India

ljubica.odak7@gmail.com

The aim of the study is to evaluate clinical and molecular features and treatment of osteogenesis imperfecta patients (OI) in a cohort of Croatian patients. For this study, we made a retrospective analysis of OI patients that were diagnosed and treated in the Children's Hospital Zagreb. The clinical evaluation encompassed detailed phenotype assessment and stratification according to the modified Sillence classification system. We analyzed the total number of fractures, presence of associated anomalies and developmental abnormalities and use of bisphosphonate therapy. The molecular genetic testing was performed using the NextSeq Illumina exome sequencing (ES) and chromosomal microarray (CMA) using the Agilent 60K oligonucleotide. Variants were classified according to the ACMG/AMP guidelines. In the period 1998-2026 there were 22 patients with clinical diagnosis of OI. The most common OI type was type I detected in 12 patients, type III was present in four patients, type IV in two, type VI in three and type II in one patient. The total number of fractures ranged from 1 fracture to more than 100 fractures. Severe deformities were present in five patients. Mitral valve abnormalities were present in three patients. Three patients had neurodevelopmental abnormalities. The genetic basis of OI in these patients were alterations in *COL1A1* (12), *COL1A2* (2), *SERPINF* (3) and *IFITM5* (1). Fourteen patients received bisphosphonate therapy with variable response. Our study represents the largest cohort of OI patients in Croatia. The clinical presentation showed variable disease severity ranging from the sporadic fractures to severe bone disease with multiple deformities and loss of ambulation. The elucidation of genetic basis in these patients revealed the autosomal dominant and recessive form of disease. The variable response to bisphosphonate therapy underscores the necessity of additional treatment approaches.

Keywords: osteogenesis imperfecta, genetic testing, clinical features, therapy

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LEGAL DETERMINANTS IN MEDICAL GENETICS

Primorac Damir[2,3], † Kačer Hrvoje[1], Mateša Blanka[1]

[1]Faculty of Law, University of Split, Split, Croatia; [2]Faculty of Forensic Sciences, University of Split, Split, Croatia; [3]Faculty of Law, University of Mostar, Mostar, Bosnia and Herzegovina

damir.primorac@primorac-partners.com

Every occurrence and every phenomenon, as a rule, possesses various aspects including a legal aspect. This equally applies to medicine in general (indeed, it is precisely on this basis that a distinct branch of law, namely medical law), has emerged and consequently to its numerous specialized fields, including medical genetics. Medical genetics is a scientific discipline characterized by continuous and almost extraordinary progress. Medical (health) law represents a significant challenge for the average legal practitioner (and non-lawyers), primarily due to the complexity and constant expansion of medical terminology, the scope of which is directly proportional to the overall advancement and increasing specialization within medicine. In this context, the criminal law dimension of these issues is of particular importance, as is the role of court-appointed medical experts in criminal proceedings. Criminal offences against human health are regulated in Chapter XIX "Criminal Offences Against Human Health" of the Criminal Code of the Republic of Croatia. The protected legal interest underlying these offences is human health itself. Considering the significance and specificity of such offences in the contemporary world, the legislature was fully justified in regulating criminal offences against human health within a separate chapter of the Criminal Code of the Republic of Croatia. Within the framework of this topic, particular attention is devoted to the criminal offence of Unauthorized Removal and Transplantation of Human Body Parts, as prescribed under Article 182 of the Criminal Code. It is indisputable that medicine and medical research are developing on a daily basis, thereby simultaneously creating opportunities for various forms of human health abuse. For this reason, by prescribing this and other criminal offences within the aforementioned chapter, the legislature sought to provide the highest possible level of protection for human health and bodily integrity.

Keywords: medical law, people's health, criminal law aspects, removal and transplantation of human body parts, court experts

POSTER PRESENTATIONS

Presentation number: CSHG/CSPPM PP 01 Abstract number: 101-ISABS-2026

FROM KNOWLEDGE TO ACTION: EMPOWERING FUTURE HEALTHCARE PROFESSIONALS IN COLORECTAL CANCER PREVENTION

Blažanović Suzana[1,2], **Čebohin Maja**[1,2], Tomas Lidija[1,2], Kralik Kristina[5], Bojanić Kristina[1,2,3], Kirner Damir[4], Kuna Roguljić Lucija[1], Volarić Nikola[2,1], Včev Aleksandar[1,2], Smolić Martina[1], **Smolić Robert**[1,2]

[1]Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [2]Mursa Medical Center, Osijek, Croatia; [3]Health Center Osijek- Baranya County, Osijek, Croatia; [4]Clinical Hospital Center Osijek, Osijek, Croatia; [5]Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

sblazanovic@fdmz.hr; mcebohin@fdmz.hr; rsmolic@fdmz.hr

Colorectal cancer (CRC) is a major public health burden, and healthcare students are future promoters of prevention and screening. This study assessed knowledge, attitudes, and behaviours related to CRC prevention and screening among healthcare students. A cross-sectional study included 160 nursing, physiotherapy, and dental medicine students. Overall knowledge was good, with a median of 11 correct answers out of 13. Nursing students had higher knowledge scores than other groups (P=0.03). Formal education on CRC during studies was strongly associated with better knowledge (P<0.001), while information from healthcare professionals was also linked to higher scores (P=0.02). Attitudes toward prevention were generally positive, especially regarding its importance, screening benefits, trust in the healthcare system, and intention to participate in screening. Formal education was associated with more positive attitudes, including perceived benefits, self-efficacy, trust, and social influence. Nursing students showed stronger intention to participate in screening (P=0.003), while senior students perceived higher personal risk (P=0.003). Knowledge was positively correlated with information-seeking and discussing prevention with others. Main barriers were lack of knowledge, fear, and embarrassment. These findings highlight formal education as a key driver of knowledge, attitudes, and preventive behaviours. Better integration of prevention and screening into healthcare curricula may strengthen promotion of early detection. Acknowledgement: Funded by the European Union – NextGeneration EU through programme funding of the University of Osijek (UNIOS) – Institutional Project (Project code: 581-UNIOS-46) to R.S. The views and opinions expressed are solely those of the authors and do not necessarily reflect the official positions of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Keywords: colorectal cancer, healthcare students, knowledge, attitudes, screening

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ASSOCIATION OF *MTHFR C677T* AND *A1298C* POLYMORPHISMS WITH OVARIAN RESERVE AND OVARIAN STIMULATION OUTCOMES IN INFERTILE WOMEN WITH AUTOIMMUNE THYROIDITIS

Dević Pavlić Sanja[1], Sušanj Šepić Tina[2], Smiljan Severinski Neda[2]

[1]Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia; [2]Department of Human Reproduction, Clinic for Gynecology and Obstetrics, University Hospital Centre Rijeka, Rijeka, Croatia

sanja.devic@uniri.hr

Variability in the methylenetetrahydrofolate reductase (*MTHFR*) gene has been implicated in reproductive dysfunction and may influence ovarian physiology in women with autoimmune thyroiditis (AIT), a population in which infertility is increasingly recognized. This prospective genotyping study aimed to evaluate the frequency of the *MTHFR C677T* and *A1298C* polymorphisms and their association with ovarian reserve (OR) and response to controlled ovarian hyperstimulation (COH) in infertile women with AIT. Genomic DNA was extracted from peripheral blood samples, amplified by polymerase chain reaction (PCR), and genotyped using restriction fragment length polymorphism (RFLP) analysis. Associations between *MTHFR* polymorphisms and OR in AIT patients undergoing assisted reproductive technology were assessed. In addition, differences in COH outcomes across genotypes were evaluated, including the proportion of MII oocytes, fertilization rate, total number of retrieved oocytes, and the proportion of day 3 and day 5 embryos, using linear regression and group comparison analyses. A statistically significant difference was observed in both genotype distribution and allele frequency of the *MTHFR C677T* polymorphism ($p=0.00065$ and $p=0.00006$, respectively) between infertile AIT patients with diminished OR and those with preserved OR. No significant differences were found in the distribution of *MTHFR A1298C* genotypes between the same patient groups ($p>0.05$). Furthermore, the combined genotypes of both polymorphisms did not show a significant association with COH outcomes. The present results suggest that the *MTHFR C677T* polymorphism may represent a potential factor associated with diminished OR in infertile women with AIT. Accordingly, this polymorphism may have clinical relevance in the diagnostic and prognostic evaluation of infertility associated with AIT.

Keywords: autoimmune thyroiditis, gene, infertility, methylenetetrahydrofolate reductase, polymorphism

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MILD PHENOTYPIC PRESENTATION OF RUBINSTEIN–TAYBI SYNDROME TYPE 1 IDENTIFIED BY WHOLE EXOME SEQUENCING: A CASE REPORT

Hrvatin Nenad[1,2], Hodak Kristian[1], Butorac Ahel Ivona[3], Babić Božović Ivana[1,4,5]

[1]Department of Genomic Medicine, University Hospital Centre Rijeka, Rijeka, Croatia; [2]St. Catherine Specialty Hospital, Zagreb, Croatia; [3]Department of Pediatrics, University Hospital Centre Rijeka, Rijeka, Croatia; [4]Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia; [5]Clinical Institute of Genomic Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia

nenad.hrvatin@svkatarina.hr

Rubinstein-Taybi syndrome type 1 (RTS1) is a rare genetic disorder caused by pathogenic variants in the *CREBBP* gene, characterized by distinctive facial features, broad thumbs and halluces, growth restriction, and varying degrees of intellectual disability. However, phenotypic expression can be highly variable, and mild presentations may remain unrecognized without advanced genetic testing. We report a female patient referred for genetic evaluation at 7 years of age following whole exome sequencing (WES) performed due to speech delay and developmental cognitive delay. Previous genetic investigations, including karyotype, *FMR1* testing, and chromosomal microarray, were normal. The patient had been followed by a pediatric neurologist since early childhood due to speech delay. Electroencephalography revealed paroxysmal irregular spike-wave complexes and treatment with lamotrigine was initiated. Brain MRI and an extensive metabolic workup were unremarkable. Developmental history showed mild global delay, with relatively preserved motor milestones but persistent speech and cognitive impairment. Multidisciplinary assessment identified behavioral immaturity and autism-like features. WES identified a heterozygous likely pathogenic variant in *CREBBP* (c.3832G>A, p.Glu1278Lys) gene, confirming RTS1. Physical examination revealed only subtle dysmorphic features, including highly arched eyebrows, high-arched palate, and mild micrognathia without classic hallmark features such as broad thumbs or halluces. This case highlights a mild and atypical presentation of RTS1, emphasizing the importance of genomic testing in patients with unexplained developmental delay – even in the absence of classic phenotypic features. The findings support the concept of variable expressivity in *CREBBP*-related disorders and expand the phenotypic spectrum of RTS1. Early genetic diagnosis is essential for appropriate management, surveillance, and genetic counseling.

Keywords: whole exome sequencing, *CREBBP*, Rubinstein-Taybi syndrome type 1, mild phenotype, developmental delay

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ROLE OF MITOCHONDRIAL DNA MUTATIONS IN ACUTE MYELOID LEUKEMIA TREATMENT RESPONSE: A REVIEW OF THE PATHOPHYSIOLOGICAL MODEL

Laslo Dorian[1]

[1]Laboratory of Protein Dynamics, Ruđer Bošković Institute, Zagreb, Croatia

dorian.laslo.md@gmail.com

Mitochondrial DNA (mtDNA) mutations have emerged as important regulators of cancer cell metabolism and survival, particularly in acute myeloid leukemia (AML), a heterogeneous hematologic malignancy characterized by variable treatment outcomes. Increasing evidence suggests that mitochondrial dysfunction contributes to leukemogenesis and influences sensitivity to chemotherapy. This abstract aims to synthesize recent findings on the role of mtDNA mutations in AML treatment response, with emphasis on specific mitochondrial genes and their functional consequences. Recent studies demonstrate that mtDNA mutations in AML frequently involve genes encoding components of the oxidative phosphorylation system, including *MT-ND1, MT-ND4*, and *MT-ND5* (Complex I), *MT-CYB* (Complex III), and *MT-CO1* (Complex IV). Mutations in MT-ND genes impair electron transport chain efficiency, leading to reduced ATP production and increased reactive oxygen species (ROS), which promote genomic instability and survival signaling. Alterations in *MT-CYB* and *MT-CO1* further disrupt mitochondrial respiration and enhance metabolic reprogramming toward glycolysis. Additionally, mutations in *MT-ATP6* (Complex V) affect ATP synthesis, contributing to altered energy homeostasis and resistance to apoptosis. Variations in mtDNA copy number and heteroplasmy levels modulate the severity of these effects and correlate with treatment response. These mitochondrial alterations support leukemic cell adaptation to chemotherapeutic stress and are particularly relevant in leukemic stem cells, which rely on oxidative phosphorylation. Importantly, targeting these dysfunctional pathways with mitochondrial inhibitors has shown potential to restore chemosensitivity and overcome resistance. In conclusion, mutations in key mtDNA-encoded respiratory genes play a critical role in AML treatment response by driving metabolic adaptation and resistance mechanisms. These alterations represent promising biomarkers and therapeutic target.

Keywords: apoptosis, gene, leukemia, mutation, mitochondrial DNA

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FETAL GENETICS AND SPONTANEOUS PRETERM BIRTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mladenić Tea[1], Vukojević Gabrijel[1], Mladenić Dora[1], Dević Pavlić Sanja[1]

[1]Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Croatia, Rijeka, Croatia

tea.mladenic@uniri.hr

Spontaneous preterm birth (sPTB), defined as delivery before 37 weeks of gestation without medical induction, remains a major contributor to perinatal morbidity and mortality worldwide. The role of fetal genetic predisposition in sPTB is increasingly recognized but not yet fully elucidated. The aim of this study was to systematically evaluate the role of fetal genetic variations in sPTB. A comprehensive literature search of PubMed and Scopus databases was conducted up to June 2025 following PRISMA 2020 guidelines. Eligible studies included case-control, cross-sectional, and cohort studies assessing associations between fetal genetic variants and sPTB. Data extraction and risk of bias assessment were performed using Cochrane criteria. Meta-analyses were conducted for variants investigated in at least three independent studies using Comprehensive Meta-Analysis Software. A total of 52 studies were included in the qualitative synthesis, of which 15 met criteria for meta-analysis. Across studies, over 145 SNPs in 62 genes were reported as significantly associated with sPTB. Meta-analysis identified a statistically significant association only for the gene Vitamin D Receptor (*VDR*) FokI (C>T) polymorphism under dominant (CC vs CT+TT) and overdominant (CC+TT vs CT) models, while *TNF*-α, *IL6*, and *TLR4* variants showed no significant associations. Genome-wide studies identified several loci reaching genome- wide significance, but replication across populations was limited. These findings suggest that fetal genetic factors contribute modestly to sPTB risk, with vitamin D–related pathways representing a potential mechanism. However, the overall evidence remains inconsistent due to methodological variability and limited replication. Future large-scale, multi-ethnic studies integrating fetal and maternal genetics are needed to clarify genetic contributions and improve risk prediction.

Keywords: fetal blood, genetic association studies, genetic variation, meta-analysis, preterm birth

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SEMAGLUTIDE ATTENUATES STEATOSIS AND PROINFLAMMATORY SIGNALING ASSOCIATED WITH MASLD PROGRESSION AT THE HEPATOCYTE LEVEL

Petrović Ana[1], Hefer Marija[1], Matić Anita[1], Kralik Kristina[1], Omanović Kolarić Tea[1], Kuna Roguljić Lucija[1], Smolić Martina[1]

[1]Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

anapetrovic@fdmz.hr

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a major global health burden, affecting approximately 25-40% of the adult population worldwide. The complex pathophysiology of MASLD is closely associated with obesity, insulin resistance, and type 2 diabetes. Current therapeutic options remain limited, with pharmacological treatment largely restricted to advanced stages such as metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis. This study investigated the effects of semaglutide in an in vitro MASLD model using HepG2 cells exposed to oleic acid. Semaglutide (2-20 nM) significantly improved cell viability ($p < 0,01$), reduced intracellular lipid accumulation ($p < 0,01$), and decreased triglyceride levels across all concentrations compared to the MASLD model. At the protein level, semaglutide significantly reduced PPAR-α levels at 10 and 20 nM ($p < 0,05$), while TNF-α concentrations were significantly decreased at all tested concentrations ($p < 0,05$) relative to oleic acid treatment. At the gene expression level, semaglutide significantly downregulated PPAR-γ expression at all concentrations ($p < 0,05$), and reduced TNF-α expression at 5 and 10 nM ($p < 0,05$). These findings demonstrate that semaglutide attenuates both steatotic and inflammatory alterations in an in vitro MASLD model. Modulation of TNF-α suggests a key role in reducing early inflammatory signalling, which may be critical in limiting disease progression. Overall, the results support the potential of semaglutide to act at the hepatocyte level in mitigating early-stage MASLD and preventing progression toward MASH, highlighting its relevance beyond currently approved indications.

Keywords: semaglutide, MASLD, MASH, HepG2, hepatic steatosis

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COMPUTATIONAL DRUG DISCOVERY ASSESSMENT OF CARVACROL AGAINST *PSEUDOMONAS AERUGINOSA* USING BIOINFORMATICS AND CHEMINFORMATICS

Slivšek Goran[1,2,3,4], Mijač Sandra[1,2,3], Matković Nives[5], Fabijanec Marija[1], Marinović Marin[4], Petković Silvija[2], Brstilo Nevija[3], Brstilo-Čičković Marlena[3], Verbanac Donatella[1], Crnolatac Ivo[3], Jonjić Antonija[6], Čoklo Miran[6], Dolanc Ivan[6]

[1]Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia; [2]Faculty of Medicine, University of Zagreb, Zagreb, Croatia; [3]Ruđer Bošković Institute, Zagreb, Croatia; [4]Rijeka University Hospital Centre, Rijeka, Croatia; [5]Faculty of Medicine, University of Split, Split, Croatia; [6]Institute for Anthropological Research, Zagreb, Croatia

goran.slivsek@xnet.hr

Natural products often exhibit pleiotropic and multi-target effects, making them promising candidates for antibacterial drug discovery against antibiotic-resistant bacteria such as *Pseudomonas aeruginosa*, whose carbapenem-resistant strains are listed in the 2024 World Health Organization Bacterial Priority Pathogens List. This study evaluated carvacrol as a potential antibacterial agent against *P. aeruginosa* using an in silico drug discovery framework integrating bioinformatics and cheminformatics approaches for early-stage drug development. Physicochemical descriptors, pharmacokinetic properties, and drug-likeness were assessed with the Swiss Absorption, Distribution, Metabolism, and Excretion web tool (SwissADME). P. aeruginosa protein structures were obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) based on literature relevance, binding pockets were identified with the Computed Atlas of Surface Topography of Proteins (CASTp), and molecular docking was performed in triplicate using AutoDock Vina 1.1.2. Binding poses and intermolecular interactions were further analysed using the Python Molecular Graphics System (PyMOL 3.1.6.1), University of California, San Francisco Chimera (UCSF Chimera 1.19), and BIOVIA Discovery Studio Visualiser 2025. Carvacrol demonstrated a favourable in silico profile, met key drug-likeness criteria consistent with Lipinski's Rule of Five, and showed reproducible interactions with the selected protein targets. These findings support prioritising carvacrol as a potential antibacterial agent against P. aeruginosa, justifying further preclinical evaluation. They also highlight the effectiveness of bioinformatics-guided target selection, cheminformatics profiling, and structure-based computational chemistry as a resource-efficient approach for hit identification, lead prioritisation, and candidate profiling, potentially reducing early attrition before in vitro and in vivo assessments.

Keywords: antibacterial agent, antibacterial drug resistance, carvacrol, drug discovery, *Pseudomonas aeruginosa*

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THE ROLE OF (−)-EPICATECHIN IN OXIDATIVE STRESS MODULATION IN MASLD

Hefer Marija[1], Petrović Ana[1], Tomičić Vice[1], Filipović Nikolina[2], Šarić Stjepan[2], Kovač-Andrić Elvira[2], **Smolić Martina**[1]

[1]Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [2]Department of Chemistry, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

msmolic@fdmz.hr

The aim of this study was to evaluate the role of (-)-epicatechin (EPI) in modulating oxidative stress and lipid accumulation in an in vitro model of metabolic dysfunction-associated steatotic liver disease (MASLD). The levels of glutathione (GSH), lipid hydroperoxides (LOOHs), conjugated dienes (CDs), and intracellular triacylglycerols were determined to assess oxidative stress and lipid accumulation. MASLD was induced in HepG2 cells using oleic acid. Preventive and therapeutic experimental models were established by pre- and post-treatment with EPI (10-50 μM). Oxidative stress was assessed by measuring intracellular GSH levels and lipid peroxidation products (CDs and LOOHs) using spectrophotometric methods. Lipid accumulation was quantified by determining intracellular triacylglycerol concentrations using the enzymatic GPO-PAP method. Oleic acid treatment caused an increase in the CD and LOOH concentrations, along with increased triacylglycerol accumulation. Treatment with EPI resulted in a dose-dependent preservation of GSH levels and a reduction in lipid peroxidation markers, indicating attenuation of oxidative stress. Additionally, EPI decreased intracellular triacylglycerol content, thereby alleviating MASLD progression. (-)-Epicatechin mitigates oxidative stress and lipid accumulation in steatotic HepG2 cells by increasing antioxidant capacity and reducing lipid peroxidation. Therefore, these results support its potential role as a modulator of redox balance and lipid metabolism in MASLD. Acknowledgement: Funded by the European Union – NextGeneration EU through programme funding of the University of Osijek (UNIOS) – Institutional Project (Project code: 581-UNIOS-47) to M.S. The views and opinions expressed are solely those of the authors and do not necessarily reflect the official positions of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Keywords: (-)-epicatechin, MASLD, GSH, conjugated dienes, lipid hydroperoxides

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SELECTIVE CYTOTOXIC EFFECTS OF CHAGA EXTRACT ON CANCER CELLS

Tomičić Vice[1], Pejaković Lovro[1], Hefer Marija[1], Omanović Kolarić Tea[1], Kuna Roguljić Lucija[1], Raguž-Lučić Nikola[1], Smolić Robert[1,2], **Smolić Martina**[1]

[1]Faculty of Dental Medicine and Health Osijek, Osijek, Croatia; [2]Mursa Medical Center Osijek, Osijek, Croatia

msmolic@fdmz.hr

The aim of this study was to evaluate the anticancer activity of Inonotus obliquus (chaga) extract in different human cancer cell lines compared to normal cells. Chaga extract was prepared using 80% ethanol extraction from chaga powder, followed by filtration and drying. Antioxidant capacity was assessed using the DPPH assay. Human cancer cell lines (CLS-354, Detroit-562, Huh-7, HepG2) and normal human fetal lung fibroblasts (MRC-5) were cultured under standard conditions and treated with chaga extract (5-100 μg/mL) for 24 and 48 hours. Metabolic activity was determined using the MTS assay, while apoptotic changes were evaluated by propidium iodide (PI) and Hoechst staining using fluorescence microscopy. Chaga extract demonstrated antioxidant activity in the DPPH assay. Treatment for 48 hours resulted in a dose-dependent decrease in metabolic activity in cancer cell lines, indicating cytotoxic effects, while minimal effects were observed after 24 hours. The extract showed selective toxicity toward cancer cells compared to normal MRC-5 cells. Fluorescence staining revealed morphological changes characteristic of late apoptosis in treated cancer cells, particularly at higher concentrations. Chaga extract exhibits selective anticancer effects in vitro, reducing metabolic activity and inducing apoptosis in cancer cell lines, while showing no significant effects in normal cells. Therefore, these results support further investigation of chaga extract as a source of bioactive compounds with potential applications in cancer therapy. Acknowledgement: Funded by the European Union – NextGeneration EU through programme funding of the University of Osijek (UNIOS) – Institutional Project (Project code: 581-UNIOS-47) to M.S. The views and opinions expressed are solely those of the authors and do not necessarily reflect the official positions of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Keywords: chaga extract, Inonotus obliquus, anticancer activity, cancer cells, natural compounds

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SGLT2 INHIBITORS: A NEW ALLY AGAINST MASLD IN TYPE 2 DIABETES

Khaznadar Farah[1,2], Khaznadar Omar[3], Hefer Marija[1], Jurić Ana[4], Hrženjak Ana[4], Kralik Kristina[5], Petrović Ana[1], Steiner Justinija[6], Bojanić Kristina[1,7,8], Smolić Martina[1,2], **Smolić Robert**[1,9]

[1]Department of Translational Medicine, Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [2]Department of Pharmacology, Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [3]Department of Radiology, "Dr. Juraj Njavro" National Memorial Hospital Vukovar, Vukovar, Croatia; [4]Department of Internal Medicine, General County Hospital Našice, Našice, Croatia; [5]Department of Medical Statistics and Medical Informatics, Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [6]Directory, Health Center Osijek, Osijek, Croatia; [7]Department of Radiology, Health Center Osijek, Osijek, Croatia; [8]Department of Biophysics and Radiology, Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; [9]Mursa Medical Center, Osijek, Croatia

rsmolic@fdmz.hr

Type 2 diabetes mellitus (T2DM) is often associated with metabolic dysfunction–associated steatotic liver disease (MASLD), for which effective treatments remain limited. This study evaluated the effects of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on liver fibrosis, steatosis, and metabolic biomarkers in patients with T2DM-related MASLD. A total of 67 patients were followed for six months after initiating SGLT2i therapy. Serum PPARα, PPAR, SREBP1, and MTTP levels were measured, while liver fibrosis and steatosis were assessed using 2D-SWE and UGAP. After six months, MTTP levels significantly increased (198.4 → 428.9 ng/L; $p<0.001$), while PPAR levels decreased (895.0 → 565.4 ng/L; $p<0.001$). Liver stiffness improved, as indicated by reduced 2D-SWE values (6.22 → 6.10 kPa; $p=0.001$), which showed an inverse correlation with MTTP ($\rho=-0.268$; $p=0.03$). UGAP values were positively correlated with 2D- SWE ($\rho=0.365$; $p=0.002$) and with leukocyte count, triglycerides, and liver enzymes, while demonstrating a negative association with HDL cholesterol ($p\leq0.01$). Significant improvements were also observed in fasting glucose, HbA1c, INR, waist circumference, and BMI ($p\leq0.04$). SGLT2i therapy was associated with early improvements in liver steatosis, fibrosis, and metabolic control, accompanied by favorable changes in MTTP and PPAR, suggesting improved hepatic lipid metabolism. Larger controlled studies are needed to confirm these findings. Acknowledgement: Funded by the European Union – NextGeneration EU through programme funding of the University of Osijek (UNIOS) – Institutional Project (Project code: 581- UNIOS-46) to R.S. The views and opinions expressed are solely those of the authors and do not necessarily reflect the official positions of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Keywords: SGLT2 inhibitors, MASLD, T2DM, PPARs, MTTP