Volume 70 | Supplement 4 | 2024

ACTA MARISIENSIS
SERIA MEDICA

OFFICIAL PUBLICATION OF THE
GEORGE EMIL PALADE UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE, AND TECHNOLOGY OF TARGU MURES

THE XIVTH MEDICAL GENETICS CONFERENCE WITH INTERNATIONAL PARTICIPATION

Targu Mures, Romania
3-5 October 2024

BOOK OF ABSTRACTS

ISSN: 2668-7755 • Online ISSN: 2668-7763 • www.actamedicamarisiensis.ro

UNIVERSITY PRESS
19 99
TÂRGU-MUREȘ

Acta Marisiensis - Seria Medica

Volume 70 | Supplement 4 | 2024

THE XIVTH MEDICAL GENETICS CONFERENCE WITH INTERNATIONAL PARTICIPATION

Targu Mures, Romania
3-5 October 2024

BOOK OF ABSTRACTS

Acta Marisiensis - Seria Medica

Acta Marisiensis - Seria Medica (ISSN 2668-7755) is the official publication of the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, being published by University Press, Targu Mures.

The journal publishes high-quality articles on various subjects related to research and medical practice from the all the medical and pharmaceutical fields, ranging from basic to clinical research and corresponding to different article types such as: reviews, original articles, case reports, case series, letter to editor or brief reports. The journal also publishes short information or editorial notes in relation to different aspects of the medical and academic life.

Information for contributors

Manuscripts must be submitted via editorial manager system, available online at
https://ojs.actamedicamarisiensis.ro/

Correspondence

All correspondence should be addressed to the Editorial Office:
Acta Medica Marisiensis
George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures
38, Gh. Marinescu St, 540139 Tîrgu Mureş, Romania
Managing Editor Professor Adrian Man
or sent by e-mail to ammjournal@umfst.ro

Acta Marisiensis - Seria Medica is indexed in the following international databases:

· SCOPUS
· DOAJ
· EBSCO Discovery Service (since 01 July 2010, first indexed number - no.4/2010)
· National Library of Medicine
·Sciendo
·Baidu Scholar
· Celdes
· Google Scholar
· J-Gate
· Publons

DTP and Website Management
Editura Prisma

This journal is printed on environmentally-friendly ECF (elemental chlorine free) woodfree paper.

THE XIVTH MEDICAL GENETICS - CONFERENCE WITH INTERNATIONAL PARTICIPATION

Targu Mures, Romania 3-5 October 2024

Organizing Committee

Claudia Bănescu
Florin Tripon
Florin Burada
Ioana Streață
Alina Bogliș
Andrei Crauciuc
Beata Balla
Adriana Crișan
Camelia Chirteș
Anamaria Todoran-Butilă
Balazs Baczoni
Timea Forro
Damiana Codați
Corina Gutman
Vasile Păcurar
Adriana Bota
Alexandrina Dragomir
Daniela Vacariu

Scientific Committee

Maria Puiu
Mircea Covic
Marius Bembea
Florin Burada
Vlad Gorduza
Cristina Rusu
Claudia Bănescu
Vasilica Plăiașu
Emilia Severin
Camelia Al-Khzouz
Radu Popp
Adrian Trifa
Claudia Jurcă
Nicoleta Andreescu
Mariela Militaru
Adela Chiriță-Emandi
Andreea Cătană
Ioana Streață
Elena Braha
Diter Atasie
Georgeta Cozaru
Teodora Barbarii
Katalin Csép

ORAL PRESENTATIONS

IMPORTANCE OF GENETIC HETEROGENEITY IN PRACTICE OF MEDICAL GENETICS – CRANIOSYNOSTOSIS

Lavinia Caba[1], Eusebiu Vlad Gorduza[1]

[1] Medical Genetics Discipline, Medicine of Mother and Child Department, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Introduction: Craniosynostoses are congenital anomalies characterized by a premature fusion of cranial suture. Craniosynostoses present a complex etiology, with primary or secondary cases.

Material and Method: Primary craniosynostoses imply single suture (non-syndromic) or multiple sutures (non-syndromic and syndromic).

Results and discussion: In syndromic craniosynostoses the genetic factors are implied in 25% of all cases. These cases present cranial, cardiac, genital or limb congenital anomalies. Syndromic craniosynostoses are usually produced by de novo autosomal dominant mutations. The syndromic craniosynostoses are Apert, Crouzon, Pfeiffer, Saethre-Chotzen, Jackson-Weiss, Beare Stevenson, and Antley-Bixler, but are known more than 150 such diseases. The genes implied in monogenic forms of craniosynostoses are**:** *FGFR1* (Pfeiffer), *FGFR2* (Pfeiffer, Crouzon, Apert), *FGFR3* (Muenke), *TWIST1* (Saethre-Chotzen). In the last years, by using NGS techniques are discovered other genes, like *EFNB1, MSX2, FREM1, IGFR1, RUNX2, ALX4, ERF, EFNA4, LRIT3*. These data are concordant with complex pathogeny of syndromic craniosynostoses. Craniosynostoses present an important genetic heterogeneity explained by a high number of proteins that intervenes in several signaling pathways at cellular level.

Conclusions: The clinic diagnosis is difficult because are superpositions between different craniosynostoses. In these conditions, the best opportunity for diagnostic is the use of NGS with a specific panel of genes.

Keywords: craniosynostoses, genetic heterogeneity, de novo mutations, autosomal dominant inheritance, NGS

Acknowledgements: None

ORO-DENTAL ANOMALIES IN PATIENTS WITH RARE MONOGENIC DISORDERS

Emilia Severin[1], Sânziana Jurcă[2], Andreea Moldoveanu[1]

[1] "Carol Davila" University of Medicine and Pharmacy Bucharest
[2] Faculty of Medicine and Pharmacy, University of Oradea

Introduction: Oral and dental anomalies are frequent or occasional manifestations associated with genetic syndromes, suggesting that the same genes and signalling pathways regulating craniofacial and teeth development also play a role in other organs and tissues. Disruptions in these pathways, due to genetic mutations or environmental factors, can lead to various oro-dental anomalies. In monogenic disorders, these anomalies can be significant indicators for early diagnosis and personalised treatment. Objectives**:** To identify and describe the oro-dental and craniofacial anomalies in patients with monogenic disorders. To evaluate the impact of these anomalies on oral function and quality of life. To explore dental anomalies as diagnostic markers for rare diseases.

Material and Method: This study included patients clinically diagnosed with rare monogenic disorders, confirmed through genetic testing. Each patient underwent a detailed dental examination, panoramic radiographs, and genetic testing for pathogenic variants. Personal and family medical histories were also collected.

Results and discussion: Various severities of oro-dental anomalies were identified, including micrognathia, anomalies in tooth number (agenesis, supernumerary teeth), enamel hypoplasia, premature/delayed eruption, and abnormalities in tooth size. While many findings confirmed known anomalies, novel findings were also observed.

Conclusions: Given the high prevalence of oral and dental abnormalities in patients living with a monogenic disorder, comprehensive oral evaluations should be integral to care. Pediatric dentists should recognise these abnormalities for early diagnosis. Integrating genetic insights into dental practice is key to predictive, preventive, and personalised dental care.

Keywords: rare monogenic disorders, oro-dental anomalies, gene variants

Acknowledgements: The authors thank the patients and their families who generously participated in the study.

WHY DO PATIENTS NEED TO SHAPE THE RARE DISEASES ECOSYSTEM?

Dorica Dan[1,2], Maria Puiu[3], Dan Alexandru Tiberiu[2], Emilia Severin[4], Alexandra Loredana Dan[2]

[1] RONARD, RPWA, ARCrare
[2] NoRo Center
[3] Clinical Emergency Hospital for Children "Louis Țurcanu" Timișoara, Romania
[4] University of Medicine and Pharmacy "Carol Davila" Bucharest

Introduction: Patients need to be partners in shaping the RD ecosystem because they bring their everyday experiences in living with RDs, they can significantly contribute to improve information, care, research and treatment development and, they advocate for system change. Aim**:** To generate a translational knowledge agenda, which identifies and prioritizes needs assessment surveys, directly relevant to patient care and the system change.

Material and Method: Since the establishment of NoRo Center in 2011 we have created a multidisciplinary team at the center, composed of 30 professionals from different fields (doctors, social workers, special education teachers, speech therapists, kinetotherapists, psychologists, art therapist, nurses, etc.) that do therapies. They are also in contact with families for counseling, with all the centers of Expertise in Romania, with schools and kindergartens to ensure continuity of care in community and with community nurses and authorities, centers of expertise for case management and care coordination.

Results and discussion: Patient involvement at every stage ensured that their perspectives were integrated, solidifying patient-centeredness and integration of these perspectives in the local, regional and national strategies as part of the NCRD.

Conclusions: This collective endeavor reflects the collaborative spirit needed for rare disease care. This knowledge agenda will not only guide where we need to bridge the gaps but will also boost interdisciplinary collaboration to push the field of rare diseases consortium and change the system of care in Romania. Patient engagement, transparency, and a comprehensive approach make this knowledge agenda a pivotal step toward addressing the pressing integrated care needs and priorities in this domain.

Keywords: shaping the RD ecosystem, multidisciplinary team, translational knowledge agenda, system change, patients' engagement

Acknowledgements: Team of NoRo Center, members of RONARD, centers of expertise and community nurses network

---

EUROPEAN POLICIES AND REGULATIONS IN RARE DISEASES AND GENETICS

Maria Puiu[1,4], Ioana Streața[2,3,4]

[1] Timis Regional Center for Medical Genetics, Louis Turcanu Children's Emergency Clinical Hospital, Timisoara University of Medicine and Pharmacy in Craiova, Human Genomics Laboratory
[2] University of Medicine and Pharmacy in Craiova, Human Genomics Laboratory
[3] Dolj Regional Center for Medical Genetics, SCJU Craiova
[4] The center of expertise in congenital malformations with and without mental retardation, part of ERN ITHACA

Introduction: The complete sequencing of the human genome has revolutionized medicine. We are increasingly talking about a Genomic Medicine, with a great potential for diagnosis or prediction of diseases, their prevention and personalized, even genetic, treatment. However, many of the promising tools of genomic medicine are still in their infancy and their application may be limited by the limited knowledge we have, which prevents its use in the clinic.

Material and Method: We did not set out to describe genomic medicine, which has monumental potential and seems the key to a healthier future. And we do not insist that all this information revolves around our specialty. More and more information can mean the separation of Medical Genetics into the 2 specialties (Clinical Genetics and Clinical Laboratory of Medical Genetics), as many European countries have decided? It is a subject of reflection! Another hot topic is the fact that we train residents who lack skills from the start**:** either they only do cytogenetics or molecular or clinical genetics. Training in different university centers is very different. It is another topic of reflection! How can we standardize resident training and even their assessment?

Results and discussion: I was saying that there are still limits and frontiers in knowledge, that research is very important and perhaps more than in other specialties, an international collaboration is needed to expand the use of gene therapies and open new fronts for the fight against infectious, oncology, genetic, rare diseases.

Conclusions: Regarding the approach to rare diseases, Europe started a project that is still considered successful, a project that tries to concentrate expertise in rare diseases in centers affiliated to the 24 European Reference Networks (ERN). On January 1, 2024, a new EU4Health joint action on the European integration of Reference Networks in national healthcare systems (JARDIN) began its activity.

Keywords: genomic medicine, rare diseases, ERN, centers of expertise

Acknowledgements: Thanks to the organizers!

CLASSIC AND MODERN IN RASOPATHIES

Cristina Rusu[1], Monica Panzaru[1], Lacramioara Butnariu[1], Roxana Popescu[1]

[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Introduction: RASopathies are a group of disorders produced by mutations of the different genes involved in the RAS-MAPK pathway. The group includes classic disorders like Noonan, cardio-facio-cutaneous, Costello, Noonan with lentigines and neurofibromatosis, as well as other rare/new disorders.

Material and Method: We aim to present the common, evocative features for RASopathies in order to facilitate recognition in practice.

Results and discussion: The different entities will be presented briefly, with accent on the features that are characteristic for each of them. Each disorder will be illustrated with cases diagnosed in Iasi Regional Medical Genetics Centre, as well as the evolution of features in time. The updated network of genes and their involvement in different disorders will be presented. Finally, the testing protocol and the actual management plan will be discussed.

Conclusions: In conclusion, we present updated data on RASopathies to facilitate recognition and diagnosis in practice, but also to present our experience with the diagnosis and management of these patients.

Keywords: RASopathies, RAS-MAPK pathway, Noonan, diagnosis

Acknowledgements: None

LONG EXPERIENCE IN SOLVING RARE AND UNDIAGNOSED DISEASES – WHAT HAVE WE LEARNT? WHAT ABOUT THOSE LEFT BEHIND?

Vasilica Plaiasu[1], Diana Ozunu[1], Gabriela Motei[1]

[1] Regional Center of Medical Genetics Bucharest Romania

Introduction: Many of genetic diseases are extremely rare and have overlapping phenotype with other diseases. The diagnostic yield of rare genetic diseases could vary by the test methods, affected organ system, and patient population.

Material and Method: This retrospective of approx. 7000 patients' cohort study was conducted during 6 years (2018-2023) at the Regional Center of Medical Genetics Bucharest. The undiagnosed children were selected based on their phenotype with heterogeneous presentation to be evaluated by NGS technologies (gene panels, WES, WGS).

Results and discussion: A series of 374 unrelated undiagnosed patients were finally solved receiving a genetic diagnosis using the NGS technologies**:** genetic syndromes, neurodevelopmental disorders, inherited errors of metabolism, skeletal dysplasias, cardiovascular disorders, genodermatoses, inherited connective tissue disorders, neuromuscular conditions, retinal dystrophies etc. We identified a lot of challenges and barriers to the implementation of genomic medicine**:** limited infrastructure and technology in the real-world, limited resources to support the genomic testing by the public health system, poor genomic literacy amongst healthcare providers, cultural and societal beliefs. Implementation of genetic tests based on NGS methods in clinical practice is at a turning point because approximately 80% of rare diseases are estimated to have a genetic origin. The results offered many opportunities to help the patients and their families**:** diagnosis (also dual diagnosis), prognosis, genetic counseling, identifying research findings or actionable conditions.

Conclusions: Applying NGS technologies facilitates genetic diagnosis, eventually enabling us to better understand the ultra-rare disease and serve as a guide for establishing appropriate genetic counseling, surveillance, and management strategies.

Keywords: rare diseases, NGS technologies, undiagnosed conditions, challenges, genomics

Acknowledgements: The authors offer their sincere thanks to all the patients and their families for cooperation, also to all clinicians involved in diagnosis and management of the cases.

CO-OCCURRENCE OF TWO GENETIC DISEASES – A CLINICAL CHALLENGE FOR THE MEDICAL TEAM: FOUR UNRELATED CASES

Elena Emanuela Braha[1], Oana Popa[1], Ioana Nedelcu[1], Camelia Procopiuc[1], Andreea Brehar[1], Lidia Radomir[1], Adina Ghemigean[1,2], Sorina Schipor[1]

[1] National Institute of Endocrinology "C.I. Parhon" Bucharest
[2] University of Medicine and Pharmacy "Carol Davila" Bucharest

Introduction: The particularity of some genetic diseases underlines the need for consistent clinical experience and the value of the essential multidisciplinary approach in the management and taking care of patients.

Material and Method: We describe the coexistence of two different genetic conditions in four unrelated patients. Each patient is subjected to a diagnostic evaluation adapted to signs and symptoms, resulting in differential diagnosis and using appropriate genetic tests to allow an accurate diagnosis. The possibility of being affected by two genetic diseases must be considered when the clinical picture is inconsistent with the primary diagnosis. For these patients, a complete diagnosis improves their clinical management and genetic counselling.

Results and discussion: We diagnosed the coexistence of mosaic Turner syndrome (45,X/46,XX) with Grieg cephalopolysyndactyly syndrome (heterozygous status pathogenic mutation *GLI3* gene) - case 1; case 2 with osteogenesis imperfecta type 1 (heterozygous status, pathogenic mutation *COL1A1*) and dentinogenesis imperfecta, Shields type II (heterozygous status, pathogenic mutation *DSPP* gene); case 3 associates Paget disease of bone type 3 (heterozygous status pathogenic mutation in the *SQSTM1* gene) and Lynch syndrome type 1 (heterozygous status pathogenic mutation *MSH2*); case 4 associates mosaic Turner syndrome (45,X/46,X,+mar) with Kabuki syndrome type 1 (heterozygous *KMT2D* pathogenic mutation).

Conclusions: The rarity of these disease associations underlines the value of a correct and personalized medical evaluation and genetic counselling. In addition, it emphasizes how a multidisciplinary approach is essential in the management and treatment of patients to determine the most accurate prognosis and the best long-term care.

Keywords: coexistence genetic diseases, phenotype

Acknowledgements: To our patients

DOUBLE TROUBLE: BECKWITH-WIEDEMANN SYNDROME AND FAMILIAL LONG QT SYNDROME TYPE I

Codruta Diana Petchesi[1,2], Oana Alexandra Iuhas[2], Corina Mihaela Nagy[2], Mihaela Stefania Buzdugan[3], Cristina Adriana Buzlea-Zaha[3], Aurora Jurca[1], Claudia Maria Jurca[1,2], Marius Bembea[1]

[1] Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania
[2] Regional Center for Medical Genetics Bihor (part of ERN ITHACA), Bihor County
[3] Bihor County Clinical Emergency Hospital, Oradea, Romania

Introduction: Beckwith-Wiedemann syndrome is an overgrowth syndrome characterized by an increased risk of childhood cancer, often caused by changes in the imprinted gene loci on chromosome 11p15. Long QT syndrome type I is an autosomal dominant inherited disorder caused by the heterozygous loss of function of the *KCNQ1* gene.

Material and Method: We present a case of Beckwith-Wiedemann syndrome associated with familial long QT syndrome type I.

Results and discussion: MS-MLPA showed hypomethylation of the KvDMR locus (IC2), and Sanger sequencing revealed a pathogenic mutational variant in the *KCNQ1* gene. Not all the carriers of the pathogenic mutational variant in the *KCNQ1* gene and IC2 hypomethylation exhibit both genetic disorders.

Conclusions: Early diagnosis, close multidisciplinary monitoring, and adequate treatment are critical to the patient's optimal development and good prognosis.

Keywords: Long QT type I, Beckwith-Wiedemann, *KCNQ1*, IC2 hypomethylation

Acknowledgements: None

GENETIC COUNSELING – CHALLENGES, OPPORTUNITIES AND PERSPECTIVES

Florin Tripon[1]

[1] George Emil Palade University of Medicine, Pharmacy, Science and Technology from Targu Mures, Romania

Introduction: We live in the era of technology and this has several consequences on/for us. The Medical Genetics specialty is of the most actively medical specialty and several advances in the field were performed. The aim of this paper is to present the knowledge and the newest information regarding the genetic counseling.

Material and Method: The latest research papers and guides were used for the current study. **Results and discussion:** The genetic counseling polities differ significantly in several countries, and can be accorded by physicians in medical genetics or not. The new technologies, advantages, education structure, European polities, live style etc. may influence the genetic counseling.

Conclusions: Even if we are able to use the new technologies and several advances in the field of genetics will be do in the future, the genetic counseling it is very important and must be delivered to/ and understand by/ patients in the correct way.

Keywords: genetic counseling, counselor, medical genetics

Acknowledgements: None to noticed

CLINICALLY SIGNIFICANT GERMLINE VARIANTS IN HEREDITARY CANCERS IN SOUTH-WEST ROMANIA – A PRELIMINARY STUDY

Răzvan Pleșea[1,2], Ioana Streata[1,2], Anca-Lelia Riza[1,2], Ionuț Gavrilă[1,2], Stefania Andrei[1,2], Alexandru Prică[1], Mihai Cucu[1,2], Florin Burada[1,2]

[1] Regional Centre for Medical Genetics Dolj (CRGMDJ), County Emergency Hospital Craiova, Romania
[2] University of Medicine and Pharmacy of Craiova, Romania

Introduction: In Romania over 95,000 new cases of cancer are diagnosed annually and nearly 54,000 deaths occur. Estimates show a 6% increase in cancer incidence, by 2035, with 8.3% in men and 3.3% in women and by the year 2020, the biggest number of new cases of cancer in Romania was reported in the South-Western Oltenia region- 367.8‰oo inhabitants.

Material and Method: Genetic testing for patients consisted of next generation sequencing (NGS) panels for germline variants on an Illumina NextSeq550 IVD sequencer and in-house capillary sequencing on a Thermo Fisher 3730xl DNA Analyzer for variant confirmation and family screening. Moreover, patients received free both pre- and post-testing genetic counseling.

Results and discussion: We are reporting more than 120 patients with a diagnosis of cancer, referred to CRGM-Dolj between 2019 and 2024 and more than 20 pathogenic and likely pathogenic germline variants. While NGS identified these variants in genes associated with the phenotype of patients, capillary sequencing was offered to screen the extended family for the identified variants.

Conclusions: Coverage with genetic testing services for early detection of breast cancer, cervical cancer and colorectal cancer is low and marked by inequalities between urban and rural areas and between population categories according to income. The inclusion and government financing of genetic testing in the routine management of oncological patients represents one of the vital means to stabilize and decrease the ever-alarming numbers of both cancer incidence and mortality not only regionally but on a nation-wide level.

Keywords: hereditary cancer, screening, genetic testing

Acknowledgements: Part of the study was supported by the Craiova University of Medicine and Pharmacy, Internal Grant no.23/516/54/16.05.2022. Genetic testing was funded through the National Health Program (XIII Programul national de sanitate a femeii si copilului 2.3. Prevenirea bolilor genetice prin diagostic pre-si postnatal) and POCU ProGeneRare-SMIS code 108073

APPLICATIONS OF GENOMICS IN POPULATION GENETICS

Marius Bembea[1], Ramona Hodișan[1], Irina Streba[2], Kinga Kozma[1], Claudia Jurca[1]

[1] Faculty of Medicine and Pharmacy University of Oradea, Romania
[2] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Introduction: As in other areas of medicine, genomics has also made significant contributions to population genetics, revolutionizing the way we now understand genetic diversity, population structure and evolution. The aim of this study is to present the current state of innovative means of genomics in approaching population genetics studies.

Material and Method: Based on current data from the literature and personal experience, the practical applications and technologies of genomics in population genetics are presented.

Results and discussion: The most used applications are**:** detailed mapping of genetic variations, forensic medicine, population structure studies, reconstruction of evolutionary history, adaptation and natural selection. The results of a second study conducted by the Oradea team, regarding the diversity of haplotype Y in two populations from the Apuseni Mountains region, are briefly presented. The differences in genetic structure between the 2 populations, one with high population stability, the other with significant population fluctuation are relevant. Once with these advances, new dilemmas and challenges have arisen in terms of bioethics, as well as accessibility and genetic counselling. Public health services and policies in our country cannot postpone and, even more, cannot ignore the new guidelines in knowing the genetic structure of the population in our country.

Conclusions: Genomics represents a new frontier in population genetics, with great potential to revolutionize the way diseases are diagnosed, treated and prevented, their origin, spread and evolution, as well as anthropological studies, environmental adaptation and natural selection in human and non-human beings.

Keywords: genomics, population genetics, genetic variability, sequencing, genetic counseling

Acknowledgements: The Doctoral School of Biomedical Sciences, University of Oradea.

HEREDITY AND GENETICS IN ROMANIAN MEDICINE: A JOURNEY FROM CANTEMIR TO DNA

Richard Constantinescu[1]

[1] "Grigore T. Popa" University of Medicine and Pharmacy

Introduction: The history of medical genetics in Romania reflects a long-standing search for understanding how biological traits are transmitted across generations. This paper aims to highlight the evolution of these concepts, from early pre-modern theories to the establishment of genetics as an essential discipline in modern medicine.

Material and Method: The analysis focused on historical sources, such as the works of the scholar Dimitrie Cantemir and the medical studies of prominent figures like Victor Babeș. Both medical texts and specialized literature articles were used to trace the progress in understanding heredity. Additionally, archives and documents related to the development of medical genetics laboratories in Romania during the 20th century were consulted.

Results and discussion: The study reveals that the early conceptions of heredity, although rudimentary, paved the way for a clearer scientific approach. Victor Babeș, through his research in microbiology and pathology, made a significant contribution to the understanding of how traits and vulnerabilities to diseases are inherited. In the latter half of the 20th century, medical genetics became an applied field, with specialized laboratories focusing on the diagnosis and prevention of hereditary diseases. In Romania, the evolution of medical genetics was influenced by both local research and major international scientific discoveries, such as the identification of DNA structure. This integration of new knowledge facilitated improved diagnosis and treatment of genetic diseases, reflecting the global impact of scientific progress on public health in Romania.

Conclusions: Romanian medical genetics has evolved from speculative theories to a well-established scientific discipline, essential for public health. Understanding this historical evolution not only sheds light on the past but also offers valuable insight for future research in medical genetics.

Keywords: heredity, medical genetics, Dimitrie Cantemir, Victor Babeș, history of medicine

Acknowledgements: None

LANDSCAPE OF DISEASE CAUSING VARIANTS IN ROMANIAN CHILDREN WITH INBORN ERRORS OF IMMUNITY

Adela Chirita-Emandi[1,2], Cristina-Loredana Pantea[1,3], Catalin Munteanu[1,3], Cristian G. Zimbru[4], Dragulescu Bogdan[5], Mihaela Bataneant[6,7]

[1] Regional Center of Medical Genetics Timis, Clinical Emergency Hospital for Children "Louis Turcanu", part of ERN ITHACA, Timisoara, Timis, Romania
[2] Department of Microscopic Morphology, Genetics Discipline, Center of Genomic Medicine, University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania
[3] "Victor Babes" University of Medicine and Pharmacy Timisoara, Timisoara, Romania
[4] Department of Automation and Applied Informatics, Politehnica University of Timisoara, Timisoara, Romania
[5] Communications Department, Politehnica University Timisoara, Romania
[6] Second Pediatric Clinic, Clinical Emergency Hospital for Children "Louis Țurcanu" Timișoara, Romania
[7] Third Pediatrics Clinic, "Victor Babes" University of Medicine and Pharmacy Timisoara, Timisoara, Romania

Introduction: Inborn errors of immunity (IEI) are monogenic disorders with a wide spectrum of clinical phenotypes including immune dysregulation, autoimmunity, autoinflammation, and malignancy. IEI may have life-threatening consequences, thus precise and timely genetic diagnosis genetic is crucial in order to improve access to treatment, genetic counselling and prevention. We aimed to investigate the genotypic findings in a cohort of children with IEI from Romania, in order to understand the diagnostic yield of genetic testing and genetic characterization of IEI.

Material and Method: Clinical and genetic investigations were performed in 87 children suspicion of IEI evaluated between 2018-2024. Genetic analysis used next generation sequencing panels that included genes associated with IEI (ranging between 1-760 genes), Whole Exome Sequencing (WES) and Whole-Genome Sequencing (WGS).

Results and discussion: Disease causing variants for IEI (pathogenic or likely pathogenic) were identified in 34/87 (39.1%) participants, in 25 genes. 16/87 (18.4%) participants had variants of uncertain significance. Mean age at IEI clinical diagnosis was 7,2 (±5.6) years. 4/34 (11,7 %) of patients with positive finding had a family history of IEI. NGS panels were used in 41/87(47.1%) patients, WES in 26/87(29.8%) patients, while WGS in 20/87(22.9%) patients. Four patients had more than one test performed. Most frequent genes with disease causing variants identified were**:** *JAGN1*(5 patients), *ATM*(2), *CFTR*(2), *CYBB*(2), *FAS*(2), and *TRNT1*(2).

Conclusions: Several genes were identified as causative for IEI in this cohort. Considering the highly variable and unspecific phenotype, no family history in most cases, a genotyping-first approach constitutes the best option for timely diagnosis and treatment.

Keywords: inborn errors of immunity, Romania, molecular testing, genetic testing, NGS

Acknowledgements: The study was supported by a research grant from the University of Medicine and Pharmacy "Victor Babes" Timisoara, Postdoctoral Internal competition contract no. 5 POSTDOC/2020, Title**:** Role of Genome sequencing in diagnostics of primary immunodeficiency and rare cancers (02.2020-02.2022). Additionally, funding was received from patient association Asociatia Romana a Pacientilor cu Imunodeficiente Primare -ARPID.

WOLFRAM SYNDROME: A JOURNEY FROM GENE TO PHENOTYPE

Maria Claudia Jurca[1,2], Codruta Petchesi[1,2], Sanziana Jurca[3], Alexandru Daniel Jurca[1], Cristina Buzle[2], Mihaela Buzdugan[2], Marius Bembea[1]

[1] Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy University of Oradea
[2] Regional Center of Medical Genetics Bihor, Clinical County Emergency Hospital Oradea
[3] Student, Faculty of Medicine and Pharmacy University of Oradea

Introduction: Wolfram syndrome type 1 (MIM# 222300) is an extremely rare autosomal recessive disorder with an incidence of 1 in 770,000 live births. It is characterized by juvenile-onset diabetes mellitus (DM), progressive optic atrophy (OA), diabetes insipidus (DI), and deafness (D. In addition to these major signs, urinary, neurological, and psychiatric manifestations may also occur. A positive diagnosis requires the presence of diabetes mellitus and optic nerve atrophy. WS1 is caused by mutations in the *WFS1* gene located on chromosome 4p16, which encodes a transmembrane protein called wolframin. They lead to endoplasmic reticulum (ER) stress, impaired calcium homeostasis, and increased cellular apoptosis.

Material and Method: The authors present the case of a 28-year-old patient diagnosed with type 1 DM at the age of 6 and progressive optic atrophy at the age of 26.

Results and discussion: Whole Exome Sequencing Plus (WES) revealed that the patient is a compound heterozygote, carrying a heterozygous nonsense variant c.1943G>A, p.(Trp648*) and a heterozygous missense variant *WFS1* c.1675G>C, p.(Ala559Pro). WES analysis for the entire family showed that the patient's father is heterozygous for the first mutational variant, the mother is heterozygous for the second variant, and the patient's brother and wife do not carry either of the identified mutational variants.

Conclusions: Wolfram Syndrome represents a complex disorder with significant clinical and genetic heterogeneity. Ongoing research into its molecular mechanisms and potential treatments offers hope for improved management and prognosis. Early diagnosis and a multidisciplinary approach are critical to addressing the diverse clinical challenges posed by WS.

Keywords: Wolfram syndrome, juvenile diabetus mellitus, optic atrophy

Acknowledgements: None

AUTISM SPECTRUM DISORDERS IN KLEEFSTRA SYNDROME: CLINICAL CASE REPORT

Mariana Sprincean[1,2,4], Svetlana Hadjiu[1,2,4], Cornelia Călcâi[1,2,4], Aliona Dumitraș[1], Olga Tihai[1], Viorica Galbur[1], Stela Racoviță[1,5], Natalia Balica[1,2], Ninel Revenco[1,2], Groppa Stanislav[1,3,4,5]

[1] State University of Medicine and Pharmacy "Nicolae Testemitanu"
[2] IMSP Institute of Mother and Child
[3] National Epileptology Center, Chisinau, Republic of Moldova
[4] Laboratory of Neurobiology and Medical Genetics of the Brain Health Center, USMF "Nicolae Testemitanu"
[5] Genetics Laboratory of the Center for Personalized Medicine, USMF "Nicolae Testemitanu"

Introduction: Autism spectrum disorders (ASDs) are pervasive developmental disorders of neurobiological origin, involving dysregulated interaction and communication skills, reduced and repetitive interests and actions. The aim of the study is to analyze the genetic aspects, clinical polymorphism and developmental peculiarities of Kleefstra syndrome in children through the lens of a clinical case.

Material and Method: At IMSP Mother and Child Institute in 2024, a clinical case with clinical symptoms suggestive of a genetic pathology was evaluated. The examinations included brain MRI, molecular-genetic examination through genomic sequencing. The genetic testing was carried out abroad using the Whole genome sequencing method, the NGS (Next Generation Sequencing) technique.

Results and discussion: The boy, aged 9 years and 3 months, presented with cognitive impairment, particularly in the area of speech and language, and behavioral disturbances. Phenotypic**:** multiple dysembryogenetic stigmata, microcephaly, clinical signs suggestive of ASD (hyper-agitation), cognitive-verbal retardation (IQ test=38 points), and motor incompetence. Genetic testing**:** submicroscopic 9q34.3 deletion, *EHMT1* gene mutations (suggestive of Kleefstra syndrome). One of the symptoms associated with ASD is Kleefstra syndrome, which occurs in less than 500 cases and is characterized by distinct facial features, developmental delay, mental retardation, hypotonia, communication difficulties, behavioral and socialization disorders.

Conclusions: Among the genetic diseases that can be associated with symptoms on the ASD spectrum is Kleefstra syndrome. The case presented by us indicates the need to expand molecular-genetic examinations in children who present with clinical signs suggestive of ASD. Thus, ASD symptoms need to be assessed to rule out associated genetic diseases.

Keywords: Kleefstra syndrome, autism spectrum disorders (ASD), genetic diseases, children

Acknowledgements: USMF Nicolae Testemitanu

AUTISM SPECTRUM DISORDER IN MALES WITH SEX CHROMOSOME ANEUPLOIDY

Magdalena Budisteanu[1,3,4], Soriba Mihaela Papuc[1], Alina Erbescu[1], Gisela Gaina[1], Laura Mateescu[2,3], Maria Dobre[1], Adelina Glangher[3], Florentina Linca[3], Doina Ioana[3], Ina Focsa[2,3], Andreea Ilinca[5], Sorin Riga[3], Aurora Arghir[1]

[1] Victor Babes National Institute of Pathology, Bucharest, Romania
[2] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3] Prof. Dr. Alex. Obregia Clinical Hospital of Psychiatry, Bucharest, Romania
[4] Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania
[5] University of Medicine and Pharmacy, Craiova, Romania

Introduction: Males with sex chromosome aneuploidy can present neurodevelopmental problems, including speech delay, learning difficulties, social immaturity, anxiety, hyperkinetic behavior. Autism spectrum disorder (ASD) was reported in 11-27% of boys with XXY and 20-30% of males with XYY. In this paper we will present three boys with sex chromosome aneuploidy and ASD, comparing their cognitive and behavioral phenotype with data from literature.

Material and Method: The boys were evaluated in the department of child psychiatry for behavioral problem (difficulties in social interactions and communication, stereotypic movements). The evaluation included medical history, clinical, neurological and psychiatric exams, psychological evaluation with cognitive testing, specific tests for ASD; EEG, and brain MRI. Genetic tests included array CGH and MLPA for fragile X in two boys and CNVs analysis and WES in one case.

Results and discussion: Two males were diagnosed with XYY and one boy, with XXY. All patients had a tall stature and mild motor difficulties. One boy with XYY had level 2 ASD associated with severe speech delay and moderate intellectual disability, while the other boy with XYY had Asperger syndrome. The boy with XXY had level 2 ASD with severe speech delay and moderate intellectual disability. ASD can be present in males with sex chromosome aneuploidy as an important feature, with a serious impact on their life quality. The severity of phenotype can vary from mild (Asperger syndrome) to severe, associating severe speech delay and intellectual disability.

Conclusions: ASD should be considered when evaluating cognitive and behavioral problems in boys with sex chromosome aneuploidy.

Keywords: sex chromosome aneuploidy, autism spectrum disorder, speech delay, intellectual disability

Acknowledgements: This work was supported by grants of the Romanian National Authority for Scientific Research Innovation, EEA Grant 2014-2021, under the project contract No 6/2019

NEONATAL SCREENING AND PRESYMPTOMATIC INTERVENTION IN SPINAL MUSCULAR ATROPHY, GENETIC DISORDER WITH MULTISYSTEMIC INVOLVEMENT

Elena Neagu[1], Madalina Leanca[1,2], Ecaterina Bercu[1], Oana Balanescu[1], Alina Nicut[1], Silvia Shelby[1], Georgiana Nicolae[1,2], Florin Grigoras[1], Mihaela Badina[1,2], Cristian Bercu[1], Daniela Vasile[1], Andrada Mirea[1,2]

[1] National Clinical Hospital for Children Neurorehabilitation "Dr. Nicolae Robănescu" Bucharest
[2] University of Medicine and Pharmacy "Carol Davila" Bucharest

Introduction: Spinal Muscular Atrophy (SMA) is a rare autosomal recessive genetic disease characterized by the degeneration of motoneurons, leading to skeletal muscle atrophy and generalized muscle weakness. The disease is caused by pathogenic variants in the ***SMN1*** gene. Following the neuronal degeneration, motor deficit occurs progressively, with loss of motor function with severe multisystemic consequences.

Material and Method: Our work is based on data from Robanescu Center's pilot study for genetic newborn screening (NBS) of SMA, multidisciplinary clinical investigations and patients' survey after administration of modern genetic therapies.

Results and discussion: More than 30000 newborns from 24 maternities were screened in Robanescu Center's Genetics Laboratory for *SMN1* exon 7 deletion starting with August 2022. 5 positive cases were all confirmed by MLPA. These presymptomatic children immediately entered in treatment program or active survey, all with very good results. The children without NBS, diagnosed in symptomatic stage of SMA, were also evaluated and quickly treated, the effect of therapy and standard care depending on symptoms severity at the moment of initiating the treatment. SMA not only affects neuromuscular functions, but also other body systems, including cardiovascular, gastrointestinal, renal, and bone. Current treatments, such as nusinersen, risdiplam, and onasemnogene abeparvovec-xioi, have shown significant improvements in motor function and survival, but close related with the moment of their administration relative to disease history.

Conclusions: Early identification through neonatal screening, multidisciplinary evaluation and rapid intervention are crucial for improving prognosis.

Keywords: spinal muscular atrophy, neonatal screening, multisystemic involvement, presymptomatic intervention, genetic therapies

Acknowledgements: The Associations**:** SMA Family, One More Step, Alma, Together for Victor Andrei Dinescu, SMACare, The Neuromuscular Disease Academy of Romania.

DICER1 SYNDROME: AN UNEXPECTED DIAGNOSIS BASED ON CYSTIC NEPHROMA

Carmen Muntean[1], Mihaela Chincesan[1], Claudia Banescu[2]

[1] 1st Pediatric Department, UMFST GE Palade Tg Mures
[2] Genetic Department, UMFST GE Palade Tg Mures

Introduction: Cystic nephromas are uncommon, multiloculate lesions located at the renal level and typically manifest in early childhood. While some cases are isolated, others may involve a family member connected to other neighborhoods that comprise DICER1 syndrome.

Material and Method: We present the case of a 12.5-year-old girl who had a history of pediatric recurrent surgery (at four years, and nine years respectively), which was linked to the development of multinodular goiter and an apical pulmonary cyst, which ultimately resulted in the emergence of a massive (8.5/14 cm) vaginal tumor with a fast growth and mass effect.

Results and discussion: The histopathological examination revealed the presence of Sertoli-Leydig cells and vaginal rhabdomyosarcoma. The patient's family history indicated an increase in the frequency of neoplasms. Genetic analyses have confirmed the existence of DICER1 syndrome with a previously unidentified ***DICER1*** mutation.

Conclusions: It is crucial to take the DICER1 syndrome into account when diagnosing cystic nephroma, multinodular tumors, and genital tumors in pediatric patients.

Keywords: cystic nephromas, DICER syndrome, child

Acknowledgements: None

PRENATAL IDENTIFICATION OF CHROMOSOMAL ABNORMALITIES: KARYOTYPING IN VARIOUS TISSUE SAMPLES

Vanesa-Larisa Bloaje-Florică[1], Mariela Sanda Militaru[2]

[1] Emergency Clinical Hospital Bagdasar-Arseni, Bucharest, Romania
[2] Department of Molecular Sciences, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania; Regional Laboratory Cluj-Napoca, Department of Medical Genetics, Regina Maria Health Network, Cluj-Napoca, Romania

Introduction: Cytogenetic karyotype testing is the gold standard method to identify fetal chromosomal abnormalities prenatally.

Material and Method: A total of 1358 pregnant women were enrolled between January 2020 and July 2024, of whom 1305 tissue samples were cultured. All patients were divided into 3 groups according to the tissue sample from which karyotyping was performed. The karyotyping was performed on amniotic fluid cells, mesenchymal fetal cells and chorionic villus tissue.

Results and discussion: Our analysis showed normal karyotype results in 78,7% (1028/1305) of fetuses. Totally, 277 abnormal karyotypes were found. Down syndrome was the most frequent aneuploidy identified in amniotic cells group and chorionic villus group in 53,9% and 65%, respectively, whereas Turner syndrome was the most common among mesenchymal fetal cells. The rates of chromosomal anomalies were compared between the 3 groups based on several indicators. In all 3 groups women with an age ranging between 35 and 39 were the most common. A NIPT positive was the most frequently present in amniotic fluid cells group in a percentage of 65,7% followed by 35% in chorionic villus cells and 0,6% in mesenchymal fetal cells samples. The most reported phenotypic anomalies were cardiac abnormalities followed by cystic hygroma. According to our analysis the aneuploidies frequencies were correlated with the current literature. Furthermore, the advanced maternal age was a recurrent indicator for chromosomal anomalies in all 3 groups.

Conclusions: Cytogenetic karyotyping is a useful method for validation of positive non-invasive prenatal testing results.

Keywords: karyotype, prenatal chromosomal abnormalities

Acknowledgements: The authors acknowledge the Regina Maria Private Healthcare System.

CAVEATS IN RARE DISEASE DIAGNOSTICS: ALTERNATIVE TRANSCRIPTS AND ALTERNATIVE HAPLOTYPES

Teodora Barbarii[1], Diana Barca[2], Madalina Leanca[3], Mariana Predescu[4], Georgeta Cardos[4], Florina Nedelea[4]

[1] Department of Medical Genetics, ''Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Pediatric Neurology Clinic "Prof. Dr. Alexandru Obregia" Clinical Hospital, Bucharest, Romania
[3] Dr. Nicolae Robanescu National Clinical Center for Children Neurorehabilitation, Bucharest, Romania
[4] Department of Medical Genetics, "Filantropia" Clinical Hospital, Bucharest, Romania

Introduction: Whole-exome sequencing (WES) and SNP-array analysis are widely used in the diagnosis of pediatric patients presenting global developmental delay (GDD).

Material and Method: Two pediatric patients (one boy and one girl) presenting GDD and other congenital anomalies were referred for WES testing. Previous genetic tests performed for the boy were negative or had inconclusive results. For the girl, a SNP-array analysis revealed a 17q21.31 microdeletion associated with Koolen-De Vries syndrome, however, the phenotype was only partially overlapping with the disorder, therefore, a WES was further recommended.

Results and discussion: A novel heterozygous proximal frameshift variant in the *TET3* gene was identified for the boy, and classified as likely pathogenic. Segregation analysis found the same variant in the unaffected father, thus, it was downgraded as VUS. A heterozygous well known pathogenic variant in the *MECP2* gene was identified for the girl. Inspection of *TET3* transcripts in the UCSC browser revealed an alternative distal transcript in the Ensemble genes tract compared to NCBI/Refseq genes. Therefore, the proximal frameshift mutation might have none or milder phenotypic effects, since not all *TET3* transcripts are disrupted. Inspection of NGS-based CNV analysis in the IGV software showed no 17q21.31 alteration, which was confirmed by MLPA. The structural diversity of 17q21.31 haplotypes most probably altered SNP-array probes hybridization.

Conclusions: Alternative transcripts and haplotypes are major factors that cause pitfalls in rare disease diagnostics. Close inspection of genomic data is always helpful in establishing an accurate genetic diagnostic and therefore, a proper clinical management and recurrence risk assessment.

Keywords: alternative transcripts, alternative haplotypes

Acknowledgements: None

GENETIC TESTING IN ROMANIA THROUGH AN INTERNATIONAL COLLABORATION – EXPANDING THE ACCESSIBILITY TO WHOLE EXOME SEQUENCING

Alexandru Caramizaru[1], Amelia Dobrescu[1,2], Cristina Durac[3], Andreea Dumitrescu[1], Alexandru Calota-Dobrescu[1], Mihai Cucu[1,2], Edoardo Malfatti[4,5], Homa Tajsharghi[6]

[1] Regional Center of Medical Genetics Dolj, Craiova, Romania
[2] Medical Genetics Department, University of Medicine and Pharmacy of Craiova, Romania
[3] National Institute for Mother and Child Health Alessandrescu-Rusescu
[4] Reference Center for Neuromuscular Disorders, APHP Henri Mondor University Hospital, France
[5] University Paris Est Créteil, Inserm, U955, Imrb, F-94010 Créteil, France; 6School of Health Sciences, Division of Biomedicine, University of Skovde, Skovde, Sweden

Introduction: Although genetic testing in Romania has seen considerable progress in recent years in terms of both technique advancement and availability, it still faces several challenges, and access to these services remains limited. Public health infrastructure and funding for genetic testing programs are still developing, which means that many patients must rely on private clinics or seek services abroad.

Material and Method: By taking part in the NEUROMYODredger-3billion Megaproject, an initiative created to provide free access to whole exome sequencing for patients with undiagnosed neurodevelopmental and neuromuscular disorders in seven countries, we have managed to support this investigation for 64 Romanian patients. WES was realised using a NovaSeq 6000 equipment (Illumina) and the xGen Exome Research Panel v2, xGen human mtDNA panel, and xGen Custom Hyb Panel v1 (Integrated DNA Technologies).

Results and discussion: Pathogenic variants, including SNVs, indels, and CNVs, were identified in 26 cases (diagnostic yield 40.62%). Additionally, 15 patients (23.43%) had variants of uncertain significance (VUS), requiring further investigation and validation. There were 23 negative results (35.93%). The raw sequencing data is currently evaluated in order to reclassify VUS, further explore negative results, and study epidemiological or genotype-phenotype correlations, as well as potential new causative genes.

Conclusions: International collaborations could play an important role in improving access to advanced genetic testing and alleviate some of the financial burden for patients and the healthcare system, laying the groundwork for developing official testing strategies that address our country's unique needs in order to ensure equitable access for all patients.

Keywords: genetic testing, WES, accessibility

Acknowledgements: This project was supported by 3billion, End the Diagnostic Odyssey – Prize granted to Prof. Homa Tajsharghi.

GENOMIC LANDSCAPE OF MYELODYSPLASTIC SYNDROME AND ITS CLINICAL IMPLICATION

Claudia Bănescu[1]

[1] George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș

Introduction: Myelodysplastic syndrome (MDS) is a clonal myeloid disease that appears due to the abnormal expansion of hematopoietic stem and progenitor cells. MDS is characterized by ineffective hematopoiesis and is commonly found in the elderly. The proliferation of undifferentiated blasts is the key factor of MDS progression to acute leukemia.

Material and Method: Genetic abnormalities have an important role in risk-stratification, and management of MDS cases. Genetic abnormalities are incorporated in risk stratification systems such as the International Prognostic Scoring System–Revised (IPSS-R) and Molecular International Prognostic Scoring System (IPSS-M) for MDs. The 5 th edition of WHO MDS classification includes MDS with defining genetic abnormalities such as those interesting chromosome 5q, ***SF3B1*** and ***TP53*** mutations.

Results and discussion: Genetic abnormalities are observed in almost all cases with MDS, more than 90% of patients present ≥1 mutation and ~50% have numerical or structural chromosomal abnormalities, most represented by unbalanced aberrations. Unfortunately, about 30-40% of MDS patients progress to leukemia. Some of the gene mutations (such as ***FLT3, IDH1, IDH2, PTPN11, ASXL1, TP53, NRAS, NPM1***, etc) identified in MDS cases are associated with leukemic transformation and are considered adverse prognostic factors.

Conclusions: In conclusion, the genomics of MDSs is complex and has an important role in the prognostic of MDS and management. The integration of genetic aberrations into prognostic systems is critical for precise risk stratification and also for treatment selection in order to prevent leukemic transformation and to improve MDS patient outcomes.

Keywords: myelodysplastic syndrome, gene mutation, chromosomal abnormalities, prognostic, treatment

Acknowledgements: None

AN INTERESTING RENAL PHENOTYPE (DISTAL RENAL TUBULAR ACIDOSIS) – AND A MYSTERIOUS GENE (*WDR72*)

Horia Stănescu[1]

[1] UCL Department of Renal Medicine, London, United Kingdom

Introduction: Distal renal tubular acidosis (dRTA) is marked by the kidneys' impaired ability to excrete acid, resulting in systemic acidosis.

Material and Method: In pediatric cases, dRTA is predominantly inherited, with five genes currently implicated.

Results and discussion: The "classic" dRTA genes—*ATP6V0A4*, *ATP6V1B1*, and *SLC4A1*—encode proteins crucial for acid secretion by intercalated cells in the collecting duct, thereby explaining their involvement in dRTA. The fourth gene, *FOXI1*, encodes a transcription factor that regulates the expression of these classic genes, making its role in the pathophysiology also clear. The fifth gene, *WDR72*, presents a more complex picture. Initially identified as a causative gene for amelogenesis imperfecta (AI), a dental disorder, *WDR72* was later associated with dRTA.

Conclusions: This presentation highlights the enigmatic nature of *WDR72* and underscores the need for careful phenotyping, understanding of the phylogenetic context, and further research to elucidate its function.

Keywords: dRTA, *WDR72*, amelogenesis imperfecta

Acknowledgements: None

GENETIC PREDISPOSITION ASSESSMENT IN HEREDITARY BREAST CANCER – IOCN CLUJ-RPS REGINA MARIA COLLABORATIVE STUDY

Andreea Cătană[1,2], Irina Iordănescu[3], Mariela Sanda Militaru[2,3], Eniko Kutasi[2], Nicoleta Antone[1], Patriciu Cadariu-Achimaș[1,2], Daniela Laura Martin[1], Carmen Lisencu[1], Miruna Grecea[1], Adrian Pavel Trifa[1,4]

[1] IOCN, Cluj (Institute of Oncology Prof. I. Chiricuță Cluj-Napoca)
[2] University of Medicine and Pharmacy Iuliu Hațieganu, Cluj-Napoca)
[3] RSP Regina Maria (Central Laboratory, Regina Maria, București)
[4] University of Medicine and Pharmacy V. Babeș Timișoara)

Introduction: Breast cancer remains a major health problem being the most common neoplasia, being overtaken in terms of mortality only by lung cancer. An upward trend in the incidence of breast cancer has been shown, with an annual increase of 1-4%. estimating that by 2050, it will reach 3.2 million annually. The vast majority of forms of breast cancer (80%) are diagnosed sporadically in women without an oncological family history. Approximately 10-15% of cases appear in the context of a hereditary predisposition, the most common secondary to some germline mutations at the level of some genes involved in breast carcinogenesis.

Material and Method: We will present the results of a retrospective, longitudinal, carried out in IOCN Cluj, which includes a group of 150 patients with criteria of eligibility for germline testing in hereditary breast cancer.

Results and discussion: Molecular analysis (NGS panel 125 genes), performed in within the RSP Regina Maria Central Laboratory, Bucharest, revealed the presence of predisposing defects in 28% of the test patients. There will be a detailed presentation of the characteristics of the identified mutations as well as the associations with the other clinical and paraclinical variables (subtype molecular, oncological AHC, oncological therapy and prophylaxis).

Conclusions: Oncogenetic assessment and germline testing have become an indispensable tool in breast cancer management because they allow correct performance of personalized oncological screening, therapy and prophylaxis recommendations.

Keywords: breast cancer, hereditary, germline mutation

Acknowledgements: IOCN Cluj, RSP Regina Maria

GENETIC TESTING STRATEGY IN EPILEPSY – CRGM DOLJ EXPERIENCE

Ioana Streata[1,2], Stefania Dorobantu[1,2], Andrei Pirvu[1], Adina Dragos[1,2], Alexandru Prica[1], Amelia Dobrescu[1,2], Razvan Plesea[1,2], Mihai Gabriel Cucu[1,2], Simona Serban-Sosoi[1,2], Ana-Maria Buga[1,2], Florin Burada[1,2], Anca-Lelia Riza[1,2]

[1] Regional Center of Medical Genetics Dolj, Emergency Clinical County Hospital Craiova
[2] University of Medicine and Pharmacy from Craiova, Human Genomics Laboratory

Introduction: Approximately 70% of epilepsy cases involve a genetic component, according to heritability estimates. The primary means of genetic diagnosis include**:** comparative genomic hybridization (CGH), multigene panels, whole exome sequencing (WES) and whole genome sequencing (WGS).Thus, we aim to explore and identify at local level the proper genetic testing strategy in epilepsy.

Material and Method: Between 2016 - 2023, 150 children with clinical diagnostic of epilepsy were tested through aCGH and /or NGS - WES at Regional Centre of Medical Genetics Dolj.

Results and discussion: Complex genetic assessment through aCGH and WES identified pathogenic or possible pathogenic CNVs or SNVs in 54 patients (36%).

Conclusions: In genetic epilepsy, comprehensive clinical phenotyping is crucial in both choosing the first step for molecular testing and interpreting results. Genetic postnatal assessment of patients with epilepsy is a powerful diagnostic tool for clinicians, with implications in the management and counseling of patients and their families. Considering our results, as well as the data known from literature, we can confirm that aCGH associated with NGS - WES has a higher chance to identify the genetic etiology of epilepsy.

Keywords: genetic epilepsy, NGS, molecular karyotyping, WES

Acknowledgements: This work is supported by the National Health Programe VI.3.3. and POCU ProGeneRare - SMIS code 108073.

HOW IMPORTANT ARE GENETICS AND EPIGENETICS IN ULCERATIVE COLITIS

Lavinia Caba[1], Andreea Florea[1], Monica-Cristina Panzaru[1], Eusebiu Vlad Gorduza[1]

[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

Introduction: Inflammatory bowel disease (IBD) is a complex and common multifactorial disease. The most important entities in this category are Crohn disease (CD) and ulcerative colitis (UC). Ulcerative colitis is a chronic inflammatory bowel disease whose incidence is steadily growing worldwide. The interactions between host genetic susceptibility, gut microbiota and environmental factors determine the onset and relapsing evolution of ulcerative colitis, making it a multifactorial disorder.

Material and Method: A literature search was performed in core databases and libraries to obtain many relevant studies**:** PubMed, EBSCO, and Embase.

Results and discussion: The most important independent risk factor is the genetic one and the candidate genes are associated with inflammation, immune regulation and epithelial permeability. The genome-wide association studies identified more than 240 loci associated with IBD, some of them involved in both CD and UC. The main epigenetic modifications in UC are DNA methylation changes and microRNA. The roles of the products of the respective genes plays various roles and intervene in**:** innate mucosal defense, autophagy, oxidative stress, epithelial barrier function, immune cell recruitment, T cell regulation, endoplasmic reticulum stress, drug bioavailability. MiRNA shows a promising evolution in the diagnostic and prognosis of patients with IBD because it has been shown that its expression can change before the onset of the symptoms and its expression can change during the natural course of the disease.

Conclusions: Imbalance of these elements, both genetics and epigenetics, can produce inflammatory bowel disease.

Keywords: ulcerative colitis, genetics, epigenetics

Acknowledgements: None

DISCORDANT NON-INVASIVE PRENATAL TESTING – A CASE SERIES

Florin Burada[1,2], Ana-Maria Buga[1,2], Stefania Dorobanțu[1,2], Ioana Streata[1,2], Mihai Gabriel Cucu[1,2], Amelia Dobrescu[1,2], Razvan Plesea[1,2], Andreea Iordache[1,2], Simona Serban-Sosoi[1,2], Andrei Pirvu[1,2], Alexandru Comanescu[3], Maria Comanescu[3], Stefania Tudorache[3], Dominic Iliescu[3], Anca-Lelia Costache[1,2]

[1] Laboratory of Human Genomics, University of Medicine and Pharmacy of Craiova, Romania
[2] Regional Centre of Medical Genetics Dolj, Emergency Clinical County Hospital Craiova, Romania
[3] Department of Obstetrics and Gynecology, Emergency Clinical County Hospital Craiova, Romania

Introduction: Non-invasive prenatal testing (NIPT) has been widely adopted and is now regarded as the most effective screening test for detecting viable fetal aneuploidies due to its high sensitivity and specificity. With the development of whole-genome sequencing, NIPT can also detect small subchromosomal deletions and duplications. Nonetheless, false positive and false negative results can occur. These discrepancies are often attributed to various factors such as sampling errors, vanishing twins, placental or true fetal mosaicism, maternal copy number variations, or maternal cancer.

Material and Method: We retrospectively reviewed discordant NIPT results among pregnant women referred to the Regional Center for Medical Genetics Dolj (CRGMDJ) of the Emergency Clinical County Hospital, Craiova.

Results and discussion: We identified 14 cases with discordant NIPT results**:** 10 false positives and 2 false negatives. The most common false positive results were for trisomy 8 (3 cases) and trisomy 18 (3 cases). In addition, in two cases, NIPT indicated a high false-positive risk for sex chromosome abnormalities, and in four cases for structural abnormalities. The false negative results occurred for trisomy 21 and microdeletion 22q11.2. Details on maternal age, gestational age, fetal fraction, genetic test results, and explanations for their possible causes are also provided. Our results emphasize that NIPT is not equivalent to diagnostic testing, and both pre-test and post-test genetic counseling should be an integral part of screening programs.

Conclusions: There remains a need for clinical validation studies that provide accurate false positive and negative rates in clinical practice.

Keywords: non-invasive prenatal testing, screening test, diagnostic test, genetic counseling

Acknowledgements: None

THE IMPORTANCE OF GENETIC TESTING IN ESTABLISHING THE OPTIMAL TREATMENT METHOD FOR INFERTILE COUPLES

Mariela Sanda Militaru[1,2], Andreea Catana[1,2], Zina Barabas-Cuzmici[2], Cristina Dragomir[2], Diana Elena Voicu[2], Maria Stefanut[2], Anca Hadarean[2], Eleonora Dronca[1,2], Irina Ioana Iordanescu[2,3]

[1] University Of Medicine And Pharmacy “Iuliu Hatieganu”, Cluj-Napoca
[2] Genetics Department Laboratory, Regina Maria
[3] University Of Medicine And Pharmacy “Carol Davila”, Bucharest

Introduction: Infertility is currently a public health problem that affects about 15% of couples. The causes of infertility are multiple and affect both women and men, and often in a couple the causes are mixed (about 30% of cases).

Material and Method: The current work analyzes both the classic methods of genetic testing (karyotype, analysis of Y chromosome microdeletions) and the usefulness of NGS (next generations sequencing) methods in the evaluation of infertile couples (endometrial microbiome testing, FSH receptor testing, immunological compatibility testing between mother and embryo, etc.)

Results and discussion: Some positive genetic results in various couples with infertility are presented. The identified pathogenic and potentially pathogenic variants correlate best with fertility disorders.

Conclusions: NGS technology has opened new horizons regarding the evaluation of infertility in humans.

Keywords: infertility, karyotype, NGS techniques

Acknowledgements: None

THE ROLE OF GENETIC TESTING FOR *IN VITRO* FERTILIZATION

Loredana-Valentina Nemțanu[1]

[1] Origyn Fertility Center, Iași

Introduction: Embryo preimplantation diagnosis revolutionizes the idea of selecting the embryo obtained by ***in vitro*** fertilization (IVF) and involves a biopsy and genetic tests before it is implanted in the mother's uterus. Thus, the criteria for choosing a good embryo are no longer based only on morphological ones, but also on its genetic results.

Material and Method: The study includes all the patients who undergo preimplantation genetic testing (PGT) since 2017 until present in IVF Clinic Origyn Fertility Center, Iasi, Romania. Methods are based on arrayCGH and NGS (next generation sequencing). Embryonic biopsy was performed on day 5 or 6 of the blastocyst stage for all embryos. The amplification of whole genome was realized using the PicoPLEX WGA kit. Using Array Comparative Genomic Hybridization technique we detected euploid and aneuploid embryos. For NGS Illumina platform we used Vitrolife Embryomap kit for library preparation and sequencing on MiSeq.

Results and discussion: More than 150 couples underwent PGT in our IVF clinic. The aneuploidy status of the embryos was correlated with maternal age.

Conclusions: PGT testing is more efficient than performing numerous unsuccessful embryo transfers.

Keywords: IVF, PGT, euploidy, trisomy, NGS

Acknowledgements: None

PREIMPLANTATION GENETIC TESTING: A CHANCE FOR LIFE

Ina-Ofelia Focșa[1,2,3], Luiza Dimos[3], Andreea Țuțulan-Cuniță[3], Petruța Elisabeta Bana[3], Laurențiu Camil Bohîlțea[1], Danae Stambouli[3]

[1] University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
[2] Clinical Hospital of Psychiatry "Prof. Dr. Alexandru Obregia", Bucharest, Romania
[3] Cytogenomic Medical Laboratory, Bucharest, Romania

Introduction: Advance of both, embryo biopsy and genomic technologies, paved the way for a new era in the prevention of genetic disorders. The use of Preimplantation Genetic Testing (PGT), as a part of Assisted Reproductive Technology procedures, has reduced the trauma of multiple failed in vitro fertilization (IVF) cycles, early miscarriages or pregnancy terminations. Although the PGT ability to allow the transfer of euploid embryos, has a positive impact on the liveborn pregnancy outcome, its use on a wide scale is limited and still controversial.

Material and Method: Here we present our experience on PGT technology, applied to a case series of couples at risk. The clinical indication for PGT included infertility, recurrent miscarriages, or familial history of a genetic disorder. After embryos biopsy, specific NGS-based PGT technologies were used. Most couples - those with infertility or recurrent miscarriage and normal karyotype results, undergoing PGT-A (preimplantation genetic testing for aneuploidies), while PGT-M (preimplantation genetic testing for monogenic disorders) was applied to those couples with a known pathogenic variant for a monogenic disorder.

Results and discussion: The euploid embryos, suitable for transfer, were identified and genetic counselling was provided. 37% of them were euploid, while 63% carried miscellaneous aberrations. Our data have demonstrated significant utility for indicating PGT to couples at risk, especially in poor prognosis IVF patients.

Conclusions: Thus, PGT is a great option for couples who struggle with infertility, miscarriages or pathogenic genetic background to have a child of their own and to avoid the birth of an affected offspring.

Keywords: preimplantation genetic testing, infertility, recurrent miscarriages

Acknowledgements: None

EXOME ANALYSIS PITFALLS AND PERSPECTIVES

Anca-Lelia Riza[1,2], Stefania Dorobantu[1], Andrei Pirvu[1], Adina Dragos[1], Alexandru Prica[1], Amelia Dobrescu[1,2], Razvan Plesea[1,2], Mihai Gabriel Cucu[1,2], Simona Serban-Sosoi[1,2], Ana-Maria Buga[1,2], Florin Burada[1,2], Ioana Streata[1,2]

[1] Regional Centre of Medical Genetics Dolj, Emergency County Hospital Craiova, Romania
[2] Laboratory of Human Genomics, University of Medicine and Pharmacy of Craiova, Romania

Introduction: Next-generation sequencing has significantly improved our ability to identify genetic variants in the coding regions, but it has also brought to light several challenges and limitations.

Material and Method: The Regional Centre for Medical Genetics Dolj has an archive of 443 exomes run on the Illumina NextSeq550Dx and analyzed mainly using an inhouse pipeline based on nf-core/sarek and Variant Effect Predictor.

Results and discussion: The diagnostic rate of exome sequencing, while improved compared to traditional methods, still fails to provide a molecular diagnosis for a significant number of cases, in our experience reaching close to 40%. Technical aspects deriving from the short-read sequencing technology include incomplete coverage of certain genomic regions and unbalanced alleles, which can lead to the missed identification of causative variants. Additionally, the presence of regions with high homology can complicate variant calling. Mosaicism can also pose a challenge in accurately identifying disease-causing variants. Interpretation of the vast number of genetic variants identified with exome sequencing, mostly single nucleotide variation, many of which of uncertain significance, is a primary challenge. Exomes can potentially identify copy number variation, though it remains a difficult pipeline to run without reservations. Improved computational tools and algorithms, coupled with a deeper understanding of the human genome are promising.

Conclusions: As genome-wide sequencing has become increasingly prevalent in the diagnosis of rare Mendelian diseases, the role of panel vs exomes vs whole genome sequencing remains to be seen in different clinical scenarios.

Keywords: next generation sequencing, exome, SNV, CNV

Acknowledgements: This work is supported by the National Health Program XIII.2.3 (combined test, NIPS) and the National Insurance House (diagnostic testing through karyotyping/QF-PCR/MLPA).

MATERNALLY INHERITED DIABETES AND DEAFNESS SYNDROME: THE APPLICABILITY OF THE MLPA METHOD IN EARLY DIAGNOSIS

Alina Bogliș[1,2], Monika Szabo[1,2], Anca Tatomir[1], Claudia Bănescu[1, 2]

[1] Emergency County Hospital of Târgu Mureș
[2] George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș

Introduction: Maternally inherited diabetes and deafness syndrome (MIDD) is estimated at 0.5-1% of all cases of diabetes caused by mitochondrial mutations, primarily in the *MT-TL1* gene that encodes tARN for Leucine. In addition to diabetes and hearing loss, clinical manifestations may include myopathy, cardiomyopathy, epilepsy, retinopathy, and, in rare cases, renal and gastrointestinal dysfunctions.

Material and Method: We report the case of a 46-year-old patient diagnosed with type 2 diabetes associated with sensorineural hearing loss. The patient's medical history revealed hearing loss since childhood and type 2 diabetes with adult onset treated with insulin and oral antidiabetics, along with episodes of asymptomatic hypoglycemia. Family history showed hearing loss (mother, twin brother) and type 2 diabetes (sister). Genetic testing was conducted using the Multiplex Ligation-dependent Probe Amplification technique (MLPA) for mitochondrial DNA analysis (frequent point mutations), and genetic counselling was offered to the patient.

Results and discussion: MLPA analysis revealed a pathogenic mutation m.3243A>G in the *MT-TL1* gene, with an estimated mutant allele fraction of about 39% (suggests moderate heteroplasmy) derived from fresh peripheral blood. The m.3243A>G mutation can be associated with genetic diseases such as MIDD, MELAS syndrome, and myopathies. Heteroplasmy levels can vary by tissue in patients with MIDD, which may contribute to the variability of clinical manifestations.

Conclusions: Early diagnosis, a thorough multidisciplinary approach, and appropriate treatment are essential for the patient's favorable prognosis.

Keywords: mitochondrial, diabetes, deafness, MLPA, m.3243A>G

Acknowledgements: The support for genetic testing was provided by the National Health Program of Women and Children PN.VI.2.3

MLPA GENETIC TESTING: AVAILABLE KITS AND POSITIVE CASES, AN UPDATE AT CRGM DOLJ

Mihai Gabriel Cucu[1,2], Alexandru Calota-Dobrescu[1,2], Adela Cucu[1,2], Andrei Pirvu[1,2], Simona Serban-Sosoi[1,2], Ioana Streata[1,2], Anca Lelia Costache[1,2], Razvan Plesea[1,2], Ana Maria Buga[2,3], Amelia-Mihaela Dobrescu[2], Florin Burada[1,2]

[1] Laboratory of Human Genomics (LGU), University of Medicine and Pharmacy of Craiova
[2] Regional Centre of Medical Genetics Dolj, County Clinical Emergency Hospital of Craiova
[3] Biochemistry Department, University of Medicine and Pharmacy of Craiova

Introduction: The Multiplex Ligation-dependent Probe Amplification technique (MLPA) is a method that uses PCR to simultaneously detect structural abnormalities using up to 50 probes, each specific to a different DNA sequence, to evaluate the relative copy number of each DNA sequence. MLPA is used to identify inherited or acquired DNA copy number changes and investigate DNA sequences' methylation status.

Material and Method: At CRGM Dolj, we analyze samples from patients with clinical features indicative of a genetic disorder or with a positive family history of a known genetic condition. We have processed nearly 1600 samples. Our tests were conducted using the SALSA MLPA probemixes and SALSA MLPA Reagent kits.

Results and discussion: The detection rate for genetic disorders in postnatal diagnosis was 17.4% for all the processed samples, meanwhile in the last year, 18% of the samples were confirmed as positive including diseases like Charcot–Marie–Tooth disease, Duchenne Muscular Dystrophy, Neurofibromatosis Type I or Von Hippel-Lindau disease. MLPA is a rapid and reliable molecular analysis method that identifies a wide range of structural abnormalities in genomic DNA. However, it is essential to validate the results using other techniques, as not all deletions and duplications identified by MLPA are necessarily pathogenic. Interpretation of the findings should be informed by the latest scientific literature.

Conclusions: It's important to note that MLPA has its limitations, particularly in its inability to detect single nucleotide polymorphisms or mosaicisms.

Keywords: DNA, ligation, probe

Acknowledgements: Genetic testing was supported through the ongoing National Health Programme PN.XIII.2.3.

THE USE OF MLPA TECHNIQUE IN GENETIC INVESTIGATION OF ROMANIAN CLL PATIENTS

Beáta Balla[1,2], Florin Tripon[1,2], Andrei Crauciuc[2], Erzsébet Lázár[1,3], Marcela Cândea[1,4], Claudia Bănescu[1,2]

[1] George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș
[2] Laboratory of Genetics, Emergency County Hospital of Târgu Mureș
[3] Clinic of Hematology and Bone Marrow Transplantation, Emergency County Hospital of Târgu Mureș
[4] Hematology Clinic, Emergency County Hospital of Târgu Mureș

Introduction: Chronic lymphocytic leukemia (CLL) is a common form of leukemia among adults, presenting clonal expansion of B lymphocytes that are mature, yet functionally incompetent. Approximately 80% of patients present chromosomal abnormalities known as copy number variations (CNVs). Literature has also reported somatic mutations as potential prognostic markers. Objectives**:** To analyze CNVs and somatic mutations in CLL patients.

Material and Method: 110 CLL patients were tested using a MLPA kit containing probes specific to chromosomal regions frequently involved in the development of CLL, as well as probes for the ***SF3B1*** K700E, ***NOTCH1*** 7541-7542delCT, and ***MYD88*** L265P mutations.

Results and discussion: CNVs identified, in order of frequency**:** del(13q14.3), del(11q22.3), trisomy 12, deletion on the short arm of chromosome 17 (containing the ***TP53*** gene), deletion of 14(q32.33) region, duplication of 10(q23.31), del(19p13.2), and one patient with concomitant trisomy of chromosomes 12, 13, and 19. Mutations in ***SF3B1*** and ***NOTCH1*** were identified in 13 patients each, while ***MYD88*** was found in one patient. Survival was longest in patients with deletion of 13q, followed by ***SF3B1*** mutation, the presence of multiple CNVs, and del(17p). The results are consistent with previously published studies, with slightly different order of frequency of the most common genetic abnormalities. Del(14q32.33), rarely described in CLL, was identified in 4 patients. Our study is the first to report the duplication of 10(q23.31) (containing the tumor suppressor ***PTEN*** gene) in CLL.

Conclusions: CNVs, gene mutations, and their coexistence strongly impact survival. MLPA is an efficient molecular cytogenetic method, identifying genetic abnormalities in 62% of our patients.

Keywords: MLPA, LLC, prognosis

Acknowledgements: This work was supported, in part, by a grant from the Romanian Ministry of Education and Research, CNCS—UEFISCDI, project number PN-III-P4-ID-PCE-2020-1928, within the PNCDI III, contract no. PCE 72/2021.

TESTING OPTIONS FOR TARGET AND FAST INVESTIGATION OF MYELOPROLIFERATIVE NEOPLASMS

Adriana-Stela Crișan[1], Florin Tripon[1], Erzsébet Lázár[1], Claudia Bănescu[1]

[1] George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș

Introduction: Chronic myeloproliferative neoplasms represent a group of clonal disorders of hematopoietic stem cells and are defined by increased production of normal mature cells in one or more cell lineages. With the discovery of the somatic driver mutations in the *JAK2, CALR*, and *MPL* genes, new perspectives in the study of myeloproliferative neoplasms have been brought to light. The standard of diagnosis as well as risk stratification for any suspected patient with myeloproliferative neoplasms is represented by molecular testing. Several methods have been developed to establish a rapid diagnosis.

Material and Method: The molecular techniques used to identify *JAK2 V617F, CALR*, and *MPL* mutations for the rapid diagnosis of patients with suspected myeloproliferative neoplasms were real-time PCR, fragment analysis, and MLPA.

Results and discussion: The use of these diagnostic methods clarified some results that were considered uncertain.

Conclusions: It is very important to specify and understand each pitfall of the molecular techniques used in the diagnosis of myeloproliferative neoplasms.

Keywords: driver somatic mutations, myeloproliferative neoplasms, MLPA technique, real-time PCR, fragment analysis

Acknowledgements: None

POSTER PRESENTATIONS

VON HIPPEL-LINDAU SYNDROME – MULTIDISCIPLINARY ASSESSMENT. CASE REPORT

Andreea Ardeleanu[1], Claudia Stefania Bala[2], Elena Emanuela Braha[3]

[1] Emergency Clinic Hospital Bucharest
[2] Elias Emergency University Hospital
[3] National Institute of Endocrinology "C.I. Parhon"

Introduction: Von Hippel-Lindau syndrome is a multisystemic genetic disorder caused by a mutation in the *VHL* gene. The syndrome is characterized by the formation of tumors (pheochromocytomas, hemangioblastomas, paragangliomas etc.) throughout the body and it has an autosomal dominant inheritance pattern.

Material and Method: We present the case of a 17-year-old male initially admitted for hypertension, which led to the discovery of a left adrenal gland pheochromocytoma, which was removed and the patient discharged. Two years later, a follow-up CT scan showed a relapse of the left adrenal gland pheochromocytoma and the appearance of a new tumor in the right adrenal gland. Suspicion of a multiple endocrine neoplasia syndrome was raised, but the mother denied testing due to cost. Post-surgery, the patient was discharged and later presented in our hospital's pediatric endocrinology department for further evaluation, where he was recommended for a genetics consultation. Family history revealed that the patient's mother was diagnosed earlier in life with pheochromocytoma and his maternal aunt had both a pheochromocytoma and a pancreatic tumor. This raised suspicion of von Hippel-Lindau (VHL) syndrome.

Results and discussion: Genetic testing using the Illumina TruSight One panel confirmed a pathogenic missense mutation in the *VHL* gene. Genetic counseling was provided.

Conclusions: This case underscores the importance of early genetic testing in families with a history of hereditary syndromes like VHL. Identifying the *VHL* mutation highlights the need for proactive screening and timely intervention to improve patient outcomes.

Keywords: von Hippel-Lindau, pheochromocytoma

Acknowledgements: To our patients

RARE DELETION AND DUPLICATION OF CHROMOSOME 4: CASE REPORT AND LITERATURE REVIEW

Anca Florentina Mitroi[1,2], Costel Brinzan[1,2], Mariana Aschie[1,2], Georgeta Camelia Cozaru[1,2]

[1] "Sf. Apostol Andrei" Clinical Emergency County Hospital of Constanta, Pathology Department
[2] "Ovidius" University of Constanta, CEDMOG Center

Introduction: Concomitant terminal deletion and duplication of same chromosome 4 or recombinant chromosome 4 syndrome, resulting for a pericentric inversion of a parent is one of the rarest constitutional anomalies of chromosome 4.

Material and Method: We present a clinical case of a 6 years old boy with terminal 4p duplication and 4q deletion cytogenetically investigated by CGH array, subtelomeric FISH and karyotype.

Results and discussion: The boy presents cranio-facial dysmorphism resembling CHARGE like syndrome, intellectual disability, autism spectrum disorder, irian and choroidal coloboma of right eye, partial optic atrophy both eyes and right cryptorchidy. CGH array revealed a 20.81Mb duplication on 4p16.3-15.31 associated with 3Mb deletion on 4q35.1-q35.2, confirmed with subtelomeric FISH. In present, about 18 cases have been well documented, but only 10 there are cases that have lived and presents the same imbalance like our case (duplication of 4p and deletion of 4p). A genotype-phenotype correlation study was accomplished between present case and previously reported rec (4) in order to delineate the association between chromosomal breakpoints and clinical features.

Conclusions: Our findings indicate that the clinical features of patients with rec(4) are relatively consistent and specifically correlated with the regions of duplication or deletion.

Keywords: recombinant chromosome 4, 4p duplication, 4q deletion

Acknowledgements: This work was supported by National Health Program 6.2.3. We thank the parents for signing the informed consent for publication.

GENETICS ROLES IN FINDING PERSONALIZED TREATMENT IN ONCOLOGY

Claudia-Stefania Bala[1], Elena Emanuela Braha[2], Andreea Ardeleanu[3]

[1] Elias Emergency University Hospital
[2] National Institute of Endocrinology "C.I. Parhon"
[3] Emergency Clinic Hospital Bucharest

Introduction: The aim of modern medicine is to specifically tailor the treatment on the patient and not the disease, mostly in the rare oncological affections.

Material and Method: We present a patient, female, 47 y, with consistent personal medical history and heredo-collateral history of oncological diseases, diagnosed with intrahepatic cholangiocarcinoma stage IV, M1 LYM and M1 HEP (multiple) in oct 2023. The first line palliative chemotherapy was initiated (gemcitabine and cisplatinum) and in feb 2024 the partial remission was observed.

Results and discussion: In this case was performed somatic molecular testing using NGS, for finding potentially targeting genetic alterations. The patient was diagnosed with genetic alterations (- *CDK6* amplification, *CHEK2* I157T mutation, *KRAS G12D, MTAP* loss, *CDKN2A/B CDKN2B* loss, *CDKN2A* loss, *EPHB4* amplification – equivocal, *TP53* - Y163C mutation) - some of them potentially germline (as *CHEK2, TP53* mut), some of them without specific approved treatments (as *CDKN2A/B* loss, *EPHB4* and *TP53* mut Y163C) and some of them with unconclusive results in the ongoing phase I and II studies (as *CDK6* amplification). Based on clinical phenotype and familial medical history the suspicion of LI-Fraumeni syndrome was raised. The germline testing was ongoing at the moment.

Conclusions: Peculiarities of the case**:** younger age at diagnostic; probably germline/familial cancer; rare genetic alterations (not the frequent disease relevant genes with potentially targeted treatments); rare cancer -scarce evidence (NCCN and ESMO). And last but not least, the somatic testing could lead to germline testing, as the evidence of germline cancers is raising.

Keywords: somatic, germline NGS, cancer

Acknowledgements: To SRGM for permitting to have a presentation, to Medical Geneticists which whom I discussed the oncological cases from the genetic point of view.

CYTOGENETIC EVALUATION IN MALE INFERTILITY WITH AZOOSPERMIA

Stela Racoviță[1,3], Svetlana Capcelea[1], Elena Chesov[1,3], Viorica Galbur[1], Eusebiu Vlad Gorduza[5], Mariana Sprincean[1,2,4]

[1] Nicolae Testemitanu State University of Medicine and Pharmacy
[2] Institute of Mother and Child
[3] Genetics Laboratory of the Center for Personalized Medicine, Nicolae Testemitanu SUMP
[4] Laboratory of Neurobiology and Medical Genetics of the Brain Health Center, Nicolae Testemitanu SUMP, Chisinau, Republic of Moldova
[5] University of Medicine and Pharmacy "Grigore T. Popa"

Introduction: Male infertility has a complex multifactorial etiology, including environmental and genetic factors. Among the multiple genetic causes, some of the most common are chromosomal

anomalies. The aim of this study is to evaluate the profile of chromosomal variations in male infertility with azoospermia.

Material and Method: Cytogenetic examination where performed on a group of 115 men with azoospermia between 2017 and 2023. Karyotyping where performed according to the International System of Cytogenetic Nomenclature (ISCN) from 2016, using peripheral blood lymphocytes for the standard method of G banding of metaphase chromosomes.

Results and discussion: In 115 men with azoospermia 91 (79,1%) were identified normal karyotype 46,XY, variations in number or structure of chromosomes were found in 24 (20,8%). Gonosomal abnormalities were identified in 16 (16,7%) cases and 8 (8,3%) cases presented autosomal abnormalities. Among the gonosomal chromosomal abnormalities in 11 cases were aneuploidy XXY (Klinefelter Syndrome), mosaic form 45,X/46,XY and 46,XX karyotype - one case. The structural variations of the Y chromosomes were detected in 3 cases (Yqh+) and 2 cases (Yqh-). Infertile men with azoospermia have the highest risk of carrying genetic abnormalities (25%), in this study, the prevalence of chromosomal abnormalities identified in azoospermia was 20,8%. Today, assisted reproduction technologies are widely used, where the natural barriers to fertilization of eggs are removed, and the diagnosis of the genetic cause underlying infertility is of even greater clinical importance.

Conclusions: Genetic counseling and cytogenetic examination should be offered to infertile couples presenting with azoospermic men, this will allow the cytogenetic cause to be identified and allow an etiological diagnosis and correct reproductive treatment.

Keywords: karyotype, chromosomal abnormalities, male, infertility

Acknowledgements: None

PPP2 SYNDROME TYPE R5D - CLINICAL VARIABILITY – 2 CASES

Adelina Glangher[1], Magdalena Budisteanu[1]

[1] Prof. Dr. Alex. Obregia Clinical Hospital of Psychiatry, Bucharest

Introduction: Pathogenic missense variants in ***PPP2R5D***, a β-subunit of the Protein Phosphatase 2A (PP2A) causes a neurodevelopmental disorder named Jordan's syndrome. The clinical aspect of the affected patients includes global developmental delays, seizures, macrocephaly, ophthalmological abnormalities, hypotonia, attention disorder, social and sensory challenges often associated with autism, disordered sleep, and feeding difficulties.

Material and Method: We present the cases of two patients, a boy and a girl with different clinical pictures. The first patient is a 2 years and 8 months old female with macrocephaly, megalencephaly, cognitive deficiency, myoclonic seizures, axial hypotonia and dysmorphic features. The second patient is a 5 years old boy with pervasive developmental disorder of unspecified type, ADHD, slight delay in psychomotor acquisitions, delay in acquisition of expressive language. Both patients underwent genetic testing by WES.

Results and discussion: The girl result showed a autosomal dominant mutation knows as NM_006245.3(PPP2R5D):c.592G>A (p.Glu198Lys). The boy was positive for another autosomal dominant mutation in ***PPP2R5D*** gene**:** NM_006245.4(PPP2R5D):c.598G>A (p.Glu200Lys). When facing a patient with the following clinical signs**:** macrocephaly, hypotonia, different degrees of neurodevelopmental delay, ASD, epilepsy and megalencephaly, we should always take into consideration PPP2R5D-related neurodevelopmental disorder .

Conclusions: Differences in the ***PPP2R5D*** genotype result in a highly variable clinical picture. Although, along time this condition had many names causing confusion, there is only one genetic condition associated with it.

Keywords: PPP2 syndrome type R5D, developmental delay macrocephaly, megalencephaly, autism

Acknowledgements: None

TO KNOW OR NOT TO KNOW? – PREVALENCE OF CARRIER STATUS FOR CYSTIC FIBROSIS AND NON-SYNDROMIC HEARING LOSS IN A ROMANIAN ADULT POPULATION

Vanesa-Larisa Bloaje-Florică[1], Mariela Sanda Militaru[2]

[1] Emergency Clinical Hospital Bagdasar-Arseni, Bucharest, Romania
[2] Department of Molecular Sciences, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania; Regional Laboratory Cluj-Napoca, Department of Medical Genetics, Regina Maria Health Network, Cluj-Napoca, Romania

Introduction: The prevalence of carrier status for Cystic fibrosis (CF) and Non-syndromic hearing loss (NSHL) among adult population worldwide is tightly linked to preconception or prenatal screening.

Material and Method: We describe the carrier status frequencies of c.35delG variant of ***GJB2*** gene for autosomal recessive non-syndromic hearing loss and delta F508 mutation of ***CFTR*** gene for cystic fibrosis in an adult population. In total, 10801 patients both female and male were included for screening between January 2020 and July 2024. 5587 patients were tested for NSHL and 5214 for CF. In case of the female patients the screening was performed predominantly prenatally while male patients voluntarily chose to get tested.

Results and discussion: Out of all 5214 patients tested for CF 1,21% (63/5214) were heterozygous carriers of delta F508 mutation, 12.7% male and 87.3% female, respectively. Screening for NSHL showed 1,08% (5587/160) patients positive carriers of c.35delG mutation with 2 female patients being homozygous. The mean age of positive carriers in both groups was 34 years old and the most numerous cases were between 30 and 39 years of age. The prevalence of adults carrying mutation variants for either NSHL or CF is poorly evaluated globally. There is a growing need to develop more precise estimates of carrier population of mutation variants for CF and NSHL.

Conclusions: Population-based carrier screening in adults may help reduce CF or NSHL cases and also provide adequate reproductive choices to individuals and couples identified as carriers.

Keywords: cystic fibrosis, nonsyndromic hearing loss

Acknowledgements: The authors acknowledge the Regina Maria Private Healthcare System.

COMPREHENSIVE THERAPIES FOR INHERITED METABOLIC DISEASES: MOLECULAR MECHANISMS AND INNOVATIONS IN TREATMENT

Vanesa-Larisa Bloaje-Florică[1,2], Laura Damian[3], Adina Chiș[1], Romana Vulturar[1]

[1] Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2] Clinical Hospital Bagdasar-Arseni, Bucharest, Romania
[3] Department of Rheumatology, Center for Rare Musculoskeletal Autoimmune and Autoinflammatory Diseases, Emergency Clinical County Hospital Cluj, Cluj-Napoca, Romania

Introduction: Inherited metabolic diseases (IMDs) present significant clinical challenges due to their diverse genetic origins and metabolic pathways.

Material and Method: This poster synthesizes the various therapeutic approaches currently employed to treat different classes of IMDs, highlighting the molecular mechanisms underlying these strategies, including traditional therapies, gene therapy, and innovative CRISPR/Cas9 applications.

Results and discussion: Traditional therapies for IMDs often involve dietary management, enzyme replacement therapy (ERT), and substrate reduction therapy (SRT). Patients with phenylketonuria benefit from a low-phenylalanine-diet or use tetrahydrobiopterine as a chaperone; those with Gaucher disease may receive ERT to supply the deficient enzyme. Gene therapy has emerged as a promising strategy, utilizing viral vectors to deliver functional copies of defective genes. This approach has shown success in adenosine deaminase deficiency and certain lysosomal storage disorders. CRISPR/Cas9 technology represents a transformative advancement in the treatment of IMDs by enabling precise genome editing. This technique allows for the correction of pathogenic mutations, disruption of disease-causing genes, and even the introduction of new genes to enhance metabolic functions. Applications include correcting defects addressing urea cycle disorders by editing genes involved in ammonia detoxification. This poster outlines case studies demonstrating the efficacy of these therapies, discuss the implications for clinical practice, and explore future directions in the treatment of IMDs.

Conclusions: By integrating various therapeutic methods, we can enhance patient outcomes and pave the way for personalized medicine in the management of inherited metabolic disorders.

Keywords: inherited metabolic diseases, CRISPR/Cas9 technology, enzyme replacement therapy, BH4, gene therapy

Acknowledgements: None

DE NOVO DELETION RAI1 GENE - FIRST CASE REPORT OF SMITH–MAGENIS SYNDROME IN ROMANIA

Miruna Gug[1], Diana Miclea[2,3], Nicoleta Andreescu[4,5], Monica Vaida[6], Cristina Gug[4]

[1] Department of Microscopic Morphology, Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2] Department of Mother and Child, Discipline of Pediatrics 1, "Iuliu Haţieganu"; University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3] Department of Medical Genetics, Spitalul Clinic de Urgenţă pentru Copii, Cluj-Napoca, Romania;
[4] Department of Microscopic Morphology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[5] Genomic Medicine Centre "Victor Babeș" University of Medicine and Pharmacy, Timisoara, Romania
[6] Departments of Anatomy and Embryology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Introduction: Smith-Magenis syndrome (OMIM#182290) is a rare, genetic, neurodevelopmental disorder.

Material and Method: A genetic consultation was performed with the recording of data from the clinical picture and the genealogical tree of the family was created. Genetic tests performed**:** (1) NGS technique that included Sequencing analysis and deletion/duplication testing for 912 genes, (2) SNP array, (3) Karyotype of the child and parents. Presentation of the case**:** The proband is a 18-month-old child with craniofacial dysmorphia**:** plagiocephaly, prominent viscerocranium, high forehead, large and low implanted ears, bilateral epicant and convergent strabismus, mouth with tent-shaped upper lip, syndactyly for second and third toes bilaterally. Neurologically, the patient presented axial hypotonia, slight hypertonia of the limbs and immature gait. The psychological evaluation revealed hyperactivity, sleep disorders, expressive language development disorder, mental instability, anxiety, developmental delay corresponding to the age of 12 months.

Results and discussion: (1) The NGS identified two pathogenic deletion variants that affected the entire coding sequences of the *RAI1* and *B9D1* genes. (2) The SNP array technique revealed**:** arr[GRCh38]17p11.2(16853302_205304 10)x1, PATHOGENIC variant. (3) Karyotype of the child the parents showing normal results. Deletion of the *RAI1* gene is associated with autosomal dominant Smith-Magenis syndrome. Our patient has a heterozygous deletion spanning 3677 kb in the 17p11.2 region. Most patients have an interstitial genomic deletion of approximately 4 Mb (range 1.5 – 9 Mb). The deletion in the child occurred de novo.

Conclusions: This case of Smith-Magenis syndrome is caused by a deletion of the *RAI1* gene, not previously reported in Romania.

Keywords: *RAI1* gene, Smith–Magenis syndrome, de novo deletion

Acknowledgements: The work was not supported by any grant.

CONGENITAL NEUTROPENIA DUE TO JAGN1 DEFICIENCY IN ROMA ETHNICITY

Cristina-Loredana Pantea[1,2], Mihaela Bataneant[3,4], Cristian G. Zimbru[5], Maria Puiu[1,3], Margit Serban[6], Adela Chirita-Emandi[1,7]

[1] Regional Center of Medical Genetics Timis, Clinical Emergency Hospital for Children "Louis Țurcanu" part of ERN ITHACA, Timisoara, Timis, Romania
[2] "Victor Babeș" University of Medicine and Pharmacy Timisoara, Timisoara, Romania
[3] Second Pediatric Clinic, Clinical Emergency Hospital for Children "Louis Țurcanu" Timișoara, Romania
[4] Third Pediatrics Clinic, "Victor Babeș" University of Medicine and Pharmacy Timisoara, Timisoara, Romania
[5] Department of Automation and Applied Informatics, Politehnica University of Timisoara, Timisoara, Romania
[6] Hematology and oncology department, Clinical Emergency Hospital for Children "Louis Țurcanu"
[7] Department of Microscopic Morphology, Genetics Discipline, Center of Genomic Medicine, University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania.

Introduction: Congenital neutropenia encompasses a group of rare inborn genetic disorders defined as a peripheral absolute neutrophil count of less than than 1000 cells/μL blood in the first year of life and less than 1500 cells/μL blood after this age. Congenital neutropenias have the risk of long-term haematological complications, such as the risk of developing acute myeloid leukemia or myelodysplastic syndrome.

Material and Method: We report four affected related patients (2 girls and 2 boys) and one unrelated patient (male), all of Roma ethnicity. Congenital neutropenia, periodontal disease, and increased levels of IgG, IgM, IgA were consistent features in these related patients. The unrelated boy had recurrent abscess formation. The most affected patient had 800/μL leukocytes with 240/μL neutrophils. We excluded chronic infections, vitamin B12 or folic acid deficiencies. A bone marrow aspiration was performed and it showed hypercellular bone marrow with granulocytc hyperplasia.

Results and discussion: Genome sequencing analysis showed a homozygous pathogenic variant NM_032492.4:c.63G>T(p.Glu21Asp), in the *JAGN1* gene, in all 5 patients. This confirmed the genetic diagnosis of Autosomal recessive severe congenital neutropenia type 6. The two related girls also had a variant of unknown significance in *HAX1* gene that may be additive for the phenotype. Before genetic test results returned, they received granulocyte colony-stimulating factor (G-CSF) treatment, yet patients were non-responsive. Hematopoietic stem cell transplantation is currently the only curative treatment of the immunological problems in JAGN1 related congenital neutropenia.

Conclusions: The genetic diagnosis allows targeted treatment. The *JAGN1* variant is previously reported in several patients in literature and could represent a founder mutation in Roma ethnicity; however, further studies are needed.

Keywords: congenital neutropenia, JAGN1 deficiency, roma ethnicity, NGS

Acknowledgements: The study was supported by a research grant from the University of Medicine and Pharmacy "Victor Babes" Timisoara, Postdoctoral Internal competition contract no. 5 POSTDOC/2020, Title**:** Role of Genome sequencing in diagnostics of primary immunodeficiency and rare cancers (02.2020-02.2022). Additionally, funding was received from patient association Asociatia Romana a Pacientilor cu Imunodeficiente Primare -ARPID.

WHAT IS WRONG WITH POLG GENE? QUICK VIEW UPON MYOCEREBROHEPATHOPATHY

Cristina-Adriana Buzlea-Zaha[1], Maria Claudia Jurca[1], Marius Bembea[1], Kinga Kozma[1], Codruta Diana Petchesi[1], Mihaela Buzdugan[1]

[1] SRGM, ESHG, ERN ITHACA, The Doctoral School of Biomedical Sciences, University of Oradea.

Introduction: The *POLG* gene (polymerase gamma) is an essential gene in the replication of the mitochondrial genome (it encodes mitochondrial DNA polymerase). Mutations in the *POLG* gene cause mitochondrial DNA depletion syndromes, or late-onset mitochondrial DNA deletion syndromes, in early childhood. Currently, 6 forms of the disease are identified**:** 1. Alpers syndrome; 2. Myocerebrohepatopathy spectrum; 3. Myotonic epilepsy, myopathy, sensory ataxia; 4. Spectrum of ataxia neuropathy; 5. Progressive external ophthalmoplegia autosomal dominant form; 6. Progressive external ophthalmoplegia autosomal recessive form.

Results and discussion: Whole Exome Sequencing (WES) identified two pathogenic variants at the level of the *POLG* gene**:** (c.1760C>T, p.(Pro587Leu) respectively c.752C>T, p.(Thr251Ile), interpreted to be in cis (on the same chromosome) and a probably pathogenic variant at the level of the same gene - c.3400C>T, p.(His1134Tyr) probably in trans (on both homologous chromosomes). Corroborating the clinical and paraclinical anamnestic data, we have as a definite diagnosis Myocerebrohepatopathy. The evolution of the case was unfavorable, the patient's condition deteriorated, following a period in Intensive Therapy, later death occurred. The patient is compound heterozygous showing one mutational variant was inherited from one parent, the other mutational variant from the other parent, thus proving that both parents are heterozygous carriers.

Conclusions: The importance of molecular genetic testing is fundamental in evaluating such rare inherited disorders. Early molecular diagnosis will make genetic counseling and medical case management to become more accurate.

Keywords: *POLG* gene, childhood myocerebrohepatopathy

Acknowledgements: I thank to SCJU Bihor/ CRGM Bihor, Dr. Maria Claudia Jurca, Dr. Kinga Cozma for sharing the case report and medical experience related to the chosen topic.

X LINKED INTELECTUALL DISABILITY ASSOCIATED WITH THE CASK GENE

Mihaela-Stefania Buzdugan[1,2,3], Cristina- Adriana Buzlea Zaha[1,2,3], Codruta Diana Petchesi[1,2,3], Kinga Kozma[1,2,3], Aurora Alexandra Jurca[1,2,3], Elena Alexandra Kirner[1,2,3], Corina Mihaela Nagy[1,2,3], Marius Bembea[1,2,3], Claudia Maria Jurca[1,2,3]

[1] Faculty of Medicine and Pharmacy, University of Oradea
[2] Regional Centre for Medical Genetics Bihor (part of ERN ITHACA), Bihor County
[3] Bihor County Clinical Emergency Hospital, Oradea Romania

Introduction: *CASK* Gene (calcium calmodulin dependent serine protein kinase) is located in region p11.4 on chromosome X. The gene is involved in normal brain development and it has a dominant X linked inheritance. The two main disorders associated with the mutations in the *CASK* Gene are Microcephaly with Pontine and Cerebellar Hypoplasia (MIPCH) an X linked Intellectual Disability (XL-ID) with or without nystagmus.

Material and Method: The authors present the case of a girl with X Linked Intellectual Disability associated with the *CASK* gene.

Results and discussion: Testing 320 genes associated with epilepsy showed heterozygous pathogenic deletion of exons 16-21 of *CASK* gene. The parents and also the brother of the index patient are unaffected and so the assumption of a de novo mutation is entitled. The difficulty of diagnosis was the fact that they were no other cases in the family. And so the initial investigations were focused on finding a teratogenic factor to explain the observed developmental disorders.

Conclusions: efficient interdisciplinary collaboration is a necessary for establishing the diagnosis and for the effective management of this pathology.

Keywords: *CASK*, intellectual disability, X-linked, dominant, de novo mutations

Acknowledgements: I would like to express my gratitude to the committee of the Bihor Medical Genetics Center and Prof. Univ. Dr. Habil. Jurca Maria Claudia for their support and professionalism. My sincere appreciation goes to the entire team for their dedication and efforts in the field of medical genetics.

THE ROLE OF TELOMERE BIOLOGY IN EARLY AGING: HOW AN EXTRA COPY OF CHROMOSOME 21 CONTRIBUTES TO EARLY-ONSET ALZHEIMER'S DISEASE

Enikő Kutasi[1,2], Adina Chis[3], Diana Alexandra Văduva[2], Andreea Cătană[1,4,5], Mihaela Adela Vințan[2,6], Camelia AlKhzouz[2,7], Romana Vulturar[3]

[1] Discipline of Medical Genetics, Department of Molecular Sciences, "Iuliu Hațieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania
[2] Emergency Clinical Hospital for Children, Cluj-Napoca, Romania
[3] Discipline of Cell and Molecular Biology, Department of Molecular Sciences, "Iuliu Hațieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania
[4] Regina Maria Health Network, Regional Laboratory Cluj-Napoca, Department of Medical Genetics, Cluj-Napoca, Romania
[5] Department of Oncogenetics, Institute of Oncology "Prof. Dr. I. Chiricuță" Cluj-Napoca, Romania
[6] Department of Neurosciences, "Iuliu Hațieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania
[7] Department Mother and Child, "Iuliu Hațieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania

Introduction: Telomeres are vital for DNA integrity. With each cell division, these protective structures shorten, limiting the number of divisions to prevent errors in the distribution of genetic material in aging cells.

Material and Method: The paper summarizes the latest research about telomere shortening in early aging.

Results and discussion: The accumulation of senescent cells contributes to age-related changes and diminished regenerative capacity. Several genetic disorders are associated with premature aging and early onset of age-related conditions. Down syndrome (DS) is a relatively common aneuploidy, occurring in approximately 1:1100-1:1000 live births, being a leading cause of intellectual disability. DS patients show a higher prevalence and earlier onset of age-related diseases, particularly Alzheimer's disease (AD), due to the accelerated buildup of beta-amyloid plaques. In DS patients, telomere shortening occurs at an accelerated rate due to the overexpression of several genes, influenced by multiple factors such as obesity, inflammation, hormonal imbalances, stressors, elevated levels of reactive oxygen species, and autoimmune conditions. Although telomere length in children with DS is initially greater than in the general population, their telomeres shorten more rapidly. Early-onset AD characterizes DS, even in low-degree trisomy 21 mosaicism. The overexpression of the *APP* gene is highly responsible for AD, as cases of partial trisomy 21 lacking APP triplication showed lower rates of AD-like pathology. Other important chromosome 21 genes contributing to AD in DS are**:** *USP25* - aggravates neuroinflammation and cognitive deficits, and *DYRK1A* - regulates axonal and synaptic vesicle protein networks.

Conclusions: DS is strongly linked to AD.

Keywords: telomeres, Down syndrome, early-onset Alzheimer's disease, premature aging

Acknowledgements: None

CHROMOSOMAL ANOMALIES AND DISORDERS OF THE CORPUS CALLOSUM

Monica-Cristina Panzaru[1], Lavinia Caba[1], Lacramioara-Ionela Butnariu[1], Roxana Popescu[1], Setalia Popa[1], Irina Nuca[1], Oana-Maria Pavaloaia[2], Eva Gavril[1], Cristian Ciobanu[1], Mihaela Gramescu[1], Eusebiu-Vlad Gorduza[1], Cristina Rusu[1]

[1] "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania
[2] County Hospital of Emergency "Saint John the New" Suceava

Introduction: Disorders of the corpus callosum (DCC) – partial or complete agenesis, dysgenesis, and hypoplasia - are some of the most common congenital cerebral anomalies. Chromosomal abnormalities have been identified in up to 20% of DCCs.

Material and Method: We conducted a retrospective study of cases with DCC and chromosomal anomalies, followed up at the Iasi Regional Medical Genetics Centre for 3 years, to highlight the suggestive associated features. All cases were tested using chromosomal analysis and multiplex ligation-dependent probe amplification combined kits.

Results and discussion: Complete and partial chromosomal anomalies have been identified in cases with DCC**:** trisomy 18, deletions (4q35, 5p15, 17q21), duplications (Xq28), and complex rearrangements (invdupdel8p). The most common associated features are central nervous system anomalies, epilepsy, hypotonia, intellectual disability, heart defects, and suggestive facial dysmorphism.

Conclusions: Detection of associated anomalies and genetic testing are essential in developing personalized management in DCC cases, given the variable outcome.

Keywords: corpus callosum, chromosomal anomalies

Acknowledgements: The authors would like to acknowledge the Clinical Emergency Hospital for Children "Sfanta Maria" (Regional Centre for Medical Genetics Iasi), Iasi, part of ERN ITHACA., Romania.

UNRAVELING THE SPECTRUM: CYSTINURIA AND THE CONTIGUOUS GENE DELETION SYNDROME HYPOTONIA-CYSTINURIA SYNDROME – A JOURNEY FROM CASES TO PATHOGENESIS

Romana Vulturar[1], Adina Chiș[1], Bogdan Bulată[2], Andreea Răchișan[2], Dan Delean[2]

[1] Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2] Pediatric Nephrology, Dialysis and Toxicology Clinic, Emergency Clinical Hospital for Children, Cluj-Napoca, Romania

Introduction: Cystinuria is a condition where defective renal tubular reabsorption of dibasic amino acids leads to recurrent cystine stone formation. Symptoms include flank pain, hematuria, renal complications.

Material and Method: We synthesized peculiarities for several pediatric cystinuria cases we diagnosed, including a unique case of Hypotonia-Cystinuria-Syndrome (HCS). The review of the literature (for 2014-2024), using the **Keywords:** Cystinuria pathogenesis, Contiguous Gene Deletion Syndrome, Hypotonia-Cystinuria-Syndrome, helps in highlighting the clinical features, diagnostic challenges, and management strategies.

Results and discussion: In pediatric patients, early diagnosis is crucial, and management typically involves hydration, dietary modifications, and pharmacological treatments; captopril may be used to reduce cystine levels by altering renal handling of amino acids. When first-line-treatments fail, cystine-binding-thiol-drugs like tiopronin and D-penicillamine could lower free cystine in urine, but require careful monitoring due to potential side effects. There are no curative genetic treatments for cystinuria yet, gene therapy and cystine crystal growth inhibitors are promising new approaches being actively researched. Ongoing clinical trials are testing the effects of dapagliflozin, tolvaptan, alpha-lipoic acid in patients. HCS is a rare contiguous gene deletion syndrome involving mutations in the *SLC3A1* and *PREPL* genes located on chromosome 2p21; there are additional neurological symptoms (hypotonia and developmental delays) alongside cystinuria.

Conclusions: HCS underscores the complexities of contiguous gene syndromes where the loss of multiple genes leads to a more severe phenotype. Administering growth hormone will improve overall height in affected children. Continued progress in understanding cystinuria/HCS genetics and pathogenesis will likely lead to more effective targeted therapies in the future.

Keywords: cystinuria, Hypotonia-Cystinuria syndrome, cystine stones, contiguous gene deletion syndrome, alpha-lipoic acid

Acknowledgements: The authors acknowledge the Faculty of Medicine from the University of Medicine and Pharmacy "Iuliu Hatieganu" in Cluj-Napoca.

DECODING THE COMPLEXITY: FROM RASOPATHY GENES TO CLINICAL IMPLICATIONS IN NOONAN AND NOONAN-LIKE SYNDROMES

Florina Nazarie[1], Cecilia Lazea[2,3], Diana Miclea[2,3], Adina Chiș[4], Camelia AlKhzouz[2,3], Romana Vulturar[4]

[1] Discipline of Medical Genetics, Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2] First Pediatric Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3] Clinical Emergency Hospital for Children, Cluj-Napoca, Romania
[4] Discipline of Cell and Molecular Biology, Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

Introduction: Noonan syndrome (NS) and related disorders, known as "RASopathies," are a group of diverse conditions characterized by short stature, congenital heart defects, distinct facial features, and developmental delays. These syndromes are caused by germline mutations in genes involving RAS/MAPK signaling pathway, which is crucial for regulating cell growth, proliferation, and differentiation.

Material and Method: This review synthesizes findings from the past 12 years, utilizing keywords such as 'Noonan Syndrome,' 'RASopathies,' 'genetic mutations,' 'clinical implications,' and 'RAS/MAPK pathway' to identify relevant literature.

Results and discussion: This poster provides an overview regarding molecular basis and clinical implications of NS and Noonan-like syndromes, including Noonan syndrome with multiple lentigines (NSML), cardiofaciocutaneous syndrome, and Costello syndrome. The specific genes involved include**:** ***PTPN11, SOS1, RAF1, KRAS, HRAS***; mutations in these genes lead to dysregulation of the RAS/MAPK pathway and associated phenotypes. Patients with NS have an increased risk of developing certain childhood cancers, particularly juvenile myelomonocytic leukemia, acute lymphoblastic leukemia, neuroblastoma (10.8-fold), and rhabdomyosarcoma (mainly in Costello syndrome). This increased risk is thought to be related to mutations in RAS/MAPK pathway genes like *PTPN11*.

Conclusions: Early recognition of the characteristic features of these syndromes allows for timely specialist referral and intervention, including growth-hormone-therapy, cardiac management, developmental support. Regular cancer screening is essential to manage potential complications. Understanding the molecular underpinnings and clinical spectrum of RASopathies enhances genetic counseling, anticipates complications, and supports the development of personalized treatment strategies. This knowledge also facilitates the pursuit of targeted therapies to modulate the RAS/MAPK pathway and improve patient outcomes.

Keywords: Noonan, RASopathies, *PTPN11*, cardiogenetics, childhood cancers

Acknowledgements: We thanks to the patients and their families for their accept to participate as we embark on a study related to this subject.

GENETIC LINKS: UNCOVERING THE HIDDEN CONNECTION BETWEEN TELOMERES AND METABOLISM

Bogdan Borzei[1], Elena Pirlici[1], Adriana Fodor[2,3], Adina Chiș[4,5], Romana Vulturar[4,5]

[1] Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2] Department of Diabetes and Nutrition Diseases, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[3] Department of Diabetes, Emergency Clinical County Hospital Cluj, Cluj-Napoca, Romania
[4] Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[5] Association for Innovation in Rare Inflammatory, Metabolic, Genetic Diseases INNOROG

Introduction: Telomere shortening has been increasingly recognized as a crucial factor in the development of metabolic dysfunction, particularly in the context of metabolic syndrome (MetS) and type 2 diabetes (T2D). We examine the interplay between telomere biology and metabolic health, emphasizing how telomere length (TL) serves as a biomarker for cellular aging and its implications for metabolic disorders.

Material and Method: We conducted a literature search for publications between 2015 and 2024, using the **Keywords:** "telomere length," "metabolic syndrome," "type 2 diabetes," "telomere shortening," "metabolism," and "oxidative stress."

Results and discussion: MetS, characterized by abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, and is associated with accelerated telomere attrition. Studies indicate that shorter TL correlates with the severity of MetS components, suggesting a bidirectional relationship where metabolic dysregulation exacerbates telomere shortening; diminished TL contributes to insulin resistance and other T2D-related complications. Mechanisms underlying this relationship include inflammation, mitochondrial dysfunction, all of which are prevalent in individuals with MetS. Furthermore, lifestyle modifications such as weight loss and dietary changes may mitigate telomere attrition and improve metabolic outcomes.

Conclusions: We synthesize current research findings on the connections between telomere shortening, MetS, and T2D, highlighting the potential for targeting telomere maintenance as a therapeutic strategy to prevent or manage these conditions. Understanding this relationship is essential for developing innovative approaches to combat T2D and associated metabolic disorders through the lens of telomere biology.

Keywords: telomere shortening, metabolism, metabolic syndrome, type 2 diabetes, mitochondrial dysfunction

Acknowledgements: Programul de granturi pentru cercetare-dezvoltare și inovare "Grantul pentru tineri cercetători REGELE CAROL I"

AXONAL GUARDIANS: NEUROFILAMENTS AS PIONEERING BIOMARKERS IN CELL BIOLOGY AND NEUROMUSCULAR DISEASES

Elena Pîrlici[1], Bogdan Borzei[1], Laura Damian[2,3], Adina Chiș[4,5], Mihaela Vințan[6,7], Romana Vulturar[4,5]

[1] Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2] Department of Rheumatology, Emergency Clinical County Hospital Cluj, Centre for Rare Autoimmune and Autoinflammatory Diseases (ERN-ReCONNET), Cluj-Napoca, Romania
[3] CMI Reumatologie Dr. Damian, Cluj-Napoca, Romania
[4] Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[5] Association for Innovation in Rare Inflammatory, Metabolic, Genetic Diseases INNOROG
[6] Department of Neuroscience, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[7] Emergency Clinical Hospital for Children, Cluj-Napoca, Romania

Introduction: Neurofilaments (NFs) are essential structural components of neurons, crucial for maintaining axonal integrity and function. Recent advancements in neurobiology have positioned neurofilaments, particularly neurofilament light chain (NfL), as promising biomarkers for genetic neuromuscular diseases (NMDs).

Material and Method: We conducted a literature search for publications between 2000 and 2024, utilizing the **Keywords:** "biomarker measurement," "motor neuron disease," "neurofilament light chain," "neurodegeneration," "diagnostic biomarkers," and "treatment response."

Results and discussion: This literature review evaluates the role of NfL and other neurofilament subtypes in the pathophysiology of genetic NMDs, including amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and hereditary neuropathies. Elevated levels of neurofilaments in biofluids such as cerebrospinal fluid (CSF) and blood correlate with neuronal degeneration and disease progression, indicating their potential utility in diagnostic and prognostic applications. Furthermore, the review discusses how neurofilament measurements can be employed to monitor therapeutic responses in clinical trials, enhancing patient management strategies.

Conclusions: By elucidating the mechanisms behind neurofilament alterations in genetic NMDs, this research highlights the potential for developing novel therapeutic strategies aimed at improving patient outcomes. The findings suggest that NFs could serve not only as biomarkers for disease severity but also as indicators of treatment efficacy, paving the way for more personalized approaches to managing these debilitating conditions. Overall, understanding the dynamics of neurofilament changes offers valuable insights into the progression of genetic NMDs and emphasizes their role in advancing clinical practices and therapeutic interventions.

Keywords: neurofilament light chain, neurodegeneration, biomarker measurement, motor neuron disease

Acknowledgements: The research, development, and innovation grant program "King Carol I Young Researchers Grant"

GENERATION AND USE OF SYNTHETIC DATA USING AI, MACHINE LEARNING AND ARTIFICIAL NEURAL NETWORKS IN RARE GENETIC DISEASE RESEARCH: EXPLORATIVE STUDY ON ANKYLOSING SPONDYLITIS PATIENTS FROM ROMANIA

Darius Lotrean[1], Laura Țiburcă[2,3], Claudia Maria Jurca[4,5], Adina Chiș[6], Romana Vulturar[6]

[1] Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania
[2] Oradea County Emergency Clinical Hospital, Rheumatology Outpatient Clinic
[3] Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania
[4] Regional Center of Medical Genetics Bihor, County Emergency Clinical Hospital Oradea
[5] Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Romania
[6] Discipline of Cell and Molecular Biology, Department of Molecular Sciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

Introduction: This paper investigates a machine learning (ML) and artificial intelligence (AI) -based solution for data augmentation, aiming to facilitate statistical analysis based on artificial neural networks.

Material and Method: For 44 patients with ankylosing spondylitis from Oradea, data was extracted from medical records and data obtained by blood DNA genotyping for 4 single nucleotide polymorphisms (SNPs) and 1 multi-nucleotide polymorphism. Based on the collected data, AI (Gretel.AI) generates ML-models that produce synthetic data with statistical properties equal to the data it was trained on. Different configurations of the model were tested and evaluated using the quality report generated by Gretel.AI. Data produced by the best performing model was used, independently and combined with real data, for the development of artificial neural networks (ANNs), and compared with ANNs trained exclusively on real data.

Results and discussion: Twelve models were developed, scoring between 75 and 81 out of 100, with an average of 78.58. While real data conformed to Hardy-Weinberg-equilibrium for four out of five variants, synthetic data did not meet this standard. ANNs trained on synthetic data achieved over 90% accuracy, while those trained on real data reached 80-90%. It should be emphasized that synthetic data serves as an augmentation of real data and doesn't represent fabrication of non-existent data. The results suggest significant potential for AI, ML and deep learning technologies in genetic research, although further validation across different pathologies is necessary.

Conclusions: Data augmentation can greatly enhance research into rare genetic diseases, improving statistical analysis and model training capabilities.

Keywords: machine learning, ankylosing spondylitis, artificial neural networks (ANNs), data augmentation, synthetic data

Acknowledgements: We express our gratitude to all patients with ankylosing spondylitis who have agreed to participate in this genetic association study.

RENAL MICRORNA AS POSSIBLE BIOMARKERS AND THERAPEUTICAL TARGETS IN NUMEROUS KIDNEY CYSTIC DISEASES

Camelia-Maria Chirteș[1], Carmen Muntean[2], Claudia-Violeta Bănescu[1,3]

[1] Laboratory of Genetics, Department of Genetics, Emergency County Hospital, Târgu Mureș, Romania
[2] Department of Pediatrics I, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania
[3] Center for Advanced Medical and Pharmaceutical Research, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Targu Mures, Romania

Introduction: MicroRNAs are small non-coding molecules, composed by 18 and 24 nucleotides in length, microRNAs an important role in regulating and modulating gene expression. Up to this day the importance of microRNAs has been recognized in many studies, as they participate in cell development, differentiation and metabolism. As a matter of fact, microRNAs can influence as well as normal and pathological conditions in numerous biological systems.

Material and Method: In this mini-review we conducted a literature search for publications between 2016 and 2024 using the words**:** "renal cysts", "renal microRNA", "microRNA therapy", "kidney development", kidney physiology".

Results and discussion: The involvement of microRNAs in kidney development and physiological function and also the crucial role that they pay in the pathogenesis of renal cystic diseases it is already well known as it follows; miR17-92 in Polycystic kidney disease and Cystic kidney disease also in Incidental renal cysts, miR192 Diabetic kidney, miR873-5p in Tuberous sclerosis and miR-92 Von-Hippel-Lindau Syndrome. MiR15-a it seems to be a promoter of cystogenesis, first identified in studies on rat models.

Conclusions: Although several microRNAs have been described in kidney until the present moment, there is a necessity of new studies in order to figure out the precise role and utility as therapeutical targets.

Keywords: microRNA, kidney, therapy

Acknowledgements: None

BIOELECTRICAL IMPEDANCE ANALYSIS OF BODY COMPOSITION IN NORMAL AND OVER-WEIGHT/OBESE PARENTS AND THEIR ADULT OFFSPRING

Katalin Csép[1], Boglárka Bancheș[1], Edina Erszény[1]

[1] UMFST G.E. Palade, Department of Genetics

Introduction: Obesity is a complex condition characterized by important heterogeneity. The utility of body mass index (BMI) defining the phenotype is limited and alternatives such as body composition analysis may contribute to a better assessment of the associated morbidity and mortality risk. Studies investigating heredity of body composition parameters are few and reported heritability estimates very variable.

Material and Method: Bioelectrical impedance analysis (BIA) of body composition was carried out in a case-control study of BMI-diagnosed normal and over-weight/obese parents and their adult offspring recruited from Covasna and Harghita counties.

Results and discussion: In the parent-offspring pairs investigated (n=192), the mean age of parents and their offspring was 65.76+/-10.96 and 41.39+/-11.11 years. The risk of obesity and waist-hip-ratio-assessed abdominal obesity in the offsprings was significantly increased in case of parental over-weight/obesity (OR=3.19, 95%CI=1.22-8.36, p=0.01 and OR=4.08, 95%CI:1.46-11.42, p=0.007). In the offspring of affected parents, average fat mass (24.11+/-9.12 vs 21+/-6.6), as well as visceral and subcutaneous fat percentage (11.34+/-4.16 vs 9.12+/-4.4 and 25.3+/-7.48 vs 21.68+/-8.45) were higher, and height, lean body mass, muscle and bone mass showed statistically significant Pearson correlation with parental values (r=0.29, 0.23, 0.28, 0.24, $p<0.05$). Data may be interpreted in the light of observations suggesting that both family studies and BIA underestimate the role of genetics in obesity and body composition, while heritability estimates decrease with age and in less severe forms.

Conclusions: Body composition and adipose tissue distribution analysis may be useful for a better risk assessment and more efficient management of obesity-affected families.

Keywords: obesity, body composition, bioelectrical impedance analysis, family study, heritability

Acknowledgements: None

INDEX OF AUTHORS