



SRGM
Societatea Romana
de Genetica Medicala



THE 7th NATIONAL CONGRESS OF MEDICAL GENETICS

WITH INTERNATIONAL PARTICIPATION

**17-19 SEPTEMBER 2026
ORADEA**

BOOK OF ABSTRACTS



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Congress Venue

Hotel Ramada by Wyndham Oradea

Calea Aradului 9, Oradea, Bihor, 410223, Romania



Dear friends and colleagues,

On behalf of the Organizing Committee, it is our great honor and pleasure to welcome you to ***The 7th National Congress of Medical Genetics with International Participation***, held in **Oradea, Romania**, from **September 17 to 19, 2026**.

Medical genetics is undergoing a stage of profound development, driven by technological and conceptual advances that have significantly influenced medical practice. Modern genomic analysis methods have contributed to a better understanding of the mechanisms of genetic diseases and have opened new perspectives in diagnosis and therapeutic management.

This year's edition holds special significance, marking the Congress's return to Oradea, the city that hosted the First National Congress of Medical Genetics more than two decades ago, in September 2002. The years since then reflect both the remarkable evolution of the field and the consolidation of an academic community dedicated to research and interdisciplinary collaboration.

Thank you all for being part of this Congress!

Congress Presidents

Prof. Dr. Maria Claudia Jurca & Prof. Dr. Florin Burada



THURSDAY, SEPTEMBER 17, 2026

11:00 – 13:30 – REGISTRATION OF PARTICIPANTS

13:30 – 14:00 – OFFICIAL OPENING OF THE CONGRESS

14:00 – 16:05 – PLENARY SESSION I
Moderators: Florin Burada, Claudia Jurca

14:00 – 14:20 – Viorel Jinga – *The Role of Genetic Testing in Urology: Our Experience from Several Projects*

14:20 – 14:35 – Simona Dima – *The ROGEN Project – Strategic Anchor of the National Genomic Research Infrastructure*

14:35 – 14:50 – Florentina Furtunescu – *National Genomic Medicine Strategy – Challenges and Success Factors*

14:50 – 15:05 – Angela Brand – *Personalised Medicine in Europe*

15:05 – 15:20 – Bogdan Feciche – *Current Trends in the Approach to Oncological Urology From Genetic Mutations to Current Surgery*

15:20 – 15:35 – Ovidiu Cristian Frățilă – *The Genetic Landscape of Inflammatory Bowel Disease*

15:35 – 15:45 – Roxana Măciucă – *IL-6 -174 G/C Polymorphism and Torque Teno Virus Infection in Chronic Glomerulonephritis*

15:45 – 16:05 – Partner Sponsor Symposium AstraZeneca

 **Maria Puiu** – *Advances in the Diagnosis and Treatment of Patients with TWO Rare Metabolic Diseases: HPP, LAL-D*

16:05 – 16:25
COFFEE BREAK & EXHIBITION VISIT & POSTERS

THURSDAY, SEPTEMBER 17, 2026

16:25 – 18:45 – PLENARY SESSION II
Moderators: Adela Chiriță-Emandi, Cristina Rusu

16:25 – 16:50 – Eric Legius – *Inheritance Patterns in Genodermatoses*

16:50 – 17:05 – Cristina Rusu – *ORPHA Codes – Practical Importance and Update in the National and International Context*

17:05 – 17:20 – Adela Chiriță-Emandi – *Genetic Characterization and Genotype - Phenotype Correlations in a Cohort of Romanian Patients with Type 1 Neurofibromatosis: Perspectives on a Clinically Unpredictable Disorder*

17:20 – 17:35 – Camelia Alkhzouz – *Early Clinical Manifestations and Diagnostic Possibilities in Lysosomal Diseases*

17:35 – 17:50 – Raluca Teleanu – *From the Diagnostic Odyssey to the Therapeutic Window: Lessons from Pediatric Neurology Practice*

17:50 – 18:05 – Mihaela Amelia Dobrescu – *Driven by Evidence, Not Preference: Therapeutic Decisions in Genetic Disorders*

18:05 – 18:15 – Iulia-Elena Simina – *Challenges in Patient Access to Innovative Treatments for Rare Diseases: Lessons from a Small Angelman Syndrome Cohort*

18:15 – 18:35 – Partner Sponsor Symposium AstraZeneca

 **Adela Chiriță-Emandi** – *Understanding the Process of Transition from Pediatric to Adult Care: In Focuss NF1 with and Without PN*

18:35 – 18:45 – Gold Sponsor Symposium – Blueprint Genetics

 **Thomas Borge** – *Quality Beyond Sequencing – Why Interpretation and the Clinical Report Matter*

19:30

WELCOME COCKTAIL

FRIDAY, SEPTEMBER 18, 2026

08:30 – 10:30 – PLENARY SESSION III
Moderators: Vlad Gorduza, Mariela Militaru

08:30 – 08:45 – Mariela Sanda Militaru – *Male Infertility in the Genomic Era: Guideline Recommendations Versus Clinical Practice*

08:45 – 09:00 – Florin Burada – *Conflicting NIPT Results: From Causes to Clinical Impact and Management – Lessons from Real Cases*

09:00 – 09:15 – Eusebiu Vlad Gorduza – *Jumping Translocation, a Rare Form of Chromosomal Abnormality – Discussion Based on a Clinical Case*

09:15 – 09:30 – Magdalena Budişteanu – *Rare Genomic Imbalances Encompassing Kinase Genes in a Group of Patients with Autism Spectrum Disorders*

09:30 – 09:40 – Mihai Cucu – *Optical Genome Mapping – First Contact in Craiova*

09:40 – 09:50 – Radu-Alexandru Truica – *Diagnostic Challenges in Sex Chromosome Aneuploidies–Case Reports. When Phenotype and Genotype Do Not Agree*

09:50 – 10:10 – Platinum Sponsor Symposium Novartis

 **NOVARTIS Claudia Jurca** – *The Role of Early Diagnosis and the Importance of Genetic Testing in Spinal Muscular Atrophy*

10:10 – 10:30 – Platinum Sponsor Symposium Sanofi

 **Maria Puiu** – *From Genotype to Treatment: Fabrazyme, the Reference Therapy in Fabry Disease for over Two Decades*

10:30 – 10:40
COFFEE BREAK & EXHIBITION VISIT & POSTERS

FRIDAY, SEPTEMBER 18, 2026

10:40 – 12:40 – PLENARY SESSION IV
Moderators: Andreea Cătană, Dragoș Crețoiu

10:40 – 11:05 – Aleš Maver – *Comprehensive Genomic Testing in the Age of Long - Read Sequencing and Artificial Intelligence*

11:05 – 11:20 – Andreea Cătană – *Oncogenetics in the AI Era*

11:20 – 11:35 – Dragoș Crețoiu – *The Geneticist and the Algorithm: Large Language Models in Clinical Variant Interpretation*

11:35 – 11:50 – Vasilica Plăiașu – *Beyond the 'Rigid Textbook Phenotype': AI vs. Human Expertise in Rare Diseases*

11:50 – 12:00 – Gold Sponsor Symposium – Regina Maria

 **Andreea Cătană** – *Beyond the Genetic Code: Genomic Testing in Medical Practice*

12:00 – 12:40 – Partner Sponsor Symposium – Genesis Pharma

 **Moderator: Maria Puiu**
New Insights in the Diagnosis and Management of Rare Diseases

- **Ioana Streață – Vyjuvek (Beremagene Geperpavec)** - *A Topical Gene Therapy Gel for the Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa*
- **Niculina Butoianu – Agamree (Vamorolone)** - *A Dissociative Corticosteroid Designed for the Treatment of Duchenne Muscular Dystrophy (DMD)*
- **Diana Miclea – Givlaari (Givosiran)** - *Diagnosis and Management of Acute Hepatic Porphyria*

12:40 – 14:00
LUNCH

FRIDAY, SEPTEMBER 18, 2026

14:00 – 15:55 – PLENARY SESSION V

Moderators: Claudia Bănescu, Nicoleta Andreescu

14:00 – 14:25 – Oliver Bartsch – *Rubinstein-Taybi Syndrome (RSTS) – Natural History and New Drugs for Treatment*

14:25 – 14:50 – Horia Stănescu – *Evolutionary Shaping of Genomic Architecture: Insights for Human Genetics?*

14:50 – 15:05 – Claudia Bănescu – *Integrated Genomic Profiling in Acute Leukemias: The Experience of the Regional Center of Medical Genetics Mures*

15:05 – 15:20 – Nicoleta Andreescu – *Beyond Diagnosis: 10 Years of CRGMT Experience in the Era of Modern Genetics*

15:20 – 15:35 – Romana Vulturar – *Adult Genetics: Old Roads, New Frontiers in Metabolic Medicine*

15:35 – 15:45 – Gold Sponsor Symposium – Biogenetix

 **BIOgenetiX** **Virgil Valeriu Văjmașu** – *Next Generations Sequencing Laboratory – The Future Was Launched*

15:45 – 15:55 – Gold Sponsor Symposium – Elta 90

 **ELTA'90MR** **Adrian Crețu** – *The Role of WES and WGS in the Diagnosis of Genetic Diseases Using Illumina Sequencing Technology*

15:55 – 16:15

COFFEE BREAK & EXHIBITION VISIT & POSTERS

16:00 – 17:00 - SALA B

WORKSHOP FOR YOUNG GENETICISTS

Eric Legius – *Bayes Theorem in Genetic Counselling*

FRIDAY, SEPTEMBER 18, 2026

16:15 – 17:50 – PLENARY SESSION VI
Moderators: Emilia Severin, Camelia Alkhzouz

16:15 – 16:40 – Orly Luminița Levit – *Beyond Lethal: Contemporary Prenatal Counseling and Neonatal Management in Trisomy 13 and 18*

16:40 – 16:55 – Emilia Severin – *Dental Anomalies in Rare Genetic Diseases: From Clinical Recognition to Molecular Diagnosis*

16:55 – 17:10 – Cristina Gug – *When Alzheimer's Mimics Multiple Sclerosis: Unmasking PSEN1-Linked Disease Present Across Four Generations*

17:10 – 17:25 – Claudia Jurca – *Tall Stature: From Clinical Evaluation to Molecular Diagnosis*

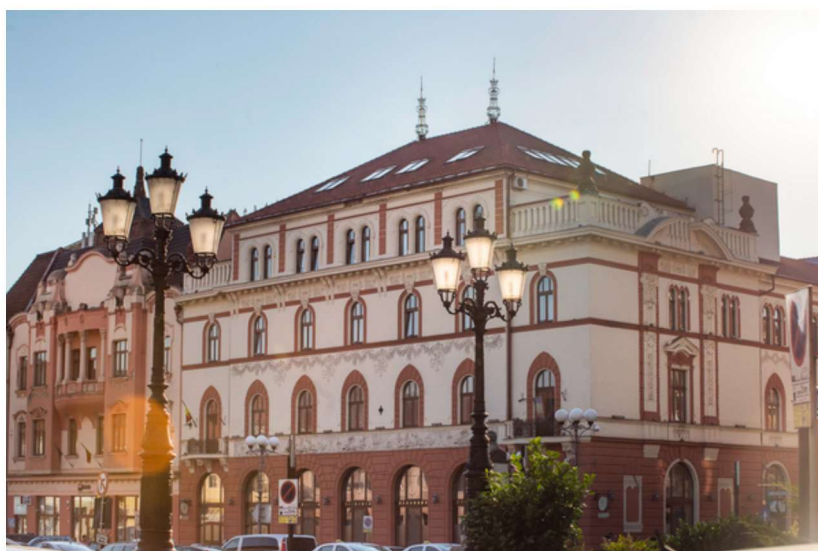
17:25 – 17:40 – Diana Miclea – *Genetic Testing in Short Stature*

17:40 – 17:50 – Gold Sponsor Symposium – Medist

 **MEDIST** **Meral Gavaz** – *Advancing Oncology with GeneMind: Comprehensive Next-Generation Sequencing Technologies*

18:00 – 20:00
SRGM MEMBERS' ASSEMBLY

20:30
GALA DINNER



SATURDAY, SEPTEMBER 19, 2026

09:00 – 11:25 – PLENARY SESSION VII

Moderators: Maria Puiu, Elena Braha

09:00 – 09:15 – Maria Puiu – *ExpertRARE and Equitable Genetics – From National Projects to Changing Clinical Practice in Rare Diseases*

09:15 – 09:30 – Dorica Dan – *Complementarity of Health Policies for Rare Diseases*

09:30 – 09:45 – Tudor Pop – *Pediatric Hepatology in the Genomic Era*

09:45 – 10:00 – Ioana Streață – *Skeletal Dysplasias in 2026: From the Revision of the 2023 Nosology to Precision Genetic Diagnosis, Personalized Therapies and the Development of Local Expertise*

10:00 – 10:15 – Corina Paul – *Clinical and Therapeutic Aspects of Noonan Syndrome*

10:15 – 10:30 – Lavinia Caba – *A Century of Genetics in the Light of the Nobel Prizes: Milestones in the Evolution of Modern Genetics*

10:30 – 10:45 – Elena Emanuela Braha – *Multidisciplinary Approach to MEN2 Syndrome – Personalized Medicine and the Impact of Genetic Family Studies*

10:45 – 11:05 – Platinum Sponsor Symposium Merck

 **Claudia Jurca** – *From Gene to Treatment: Genetics of Desmoid Tumors in Clinical Practice*

11:05 – 11:25 – Platinum Sponsor Laboratorium Life Science

 **Damla Bozkulak** – *Elevating Precision Diagnostics: The Integration of SOPHiA DDM Platform and Advanced NGS Assays*

11:25 – 11:40

COFFEE BREAK & EXHIBITION VISIT & POSTER PRESENTATIONS

SATURDAY, SEPTEMBER 19, 2026

11:40 – 13:10 – PLENARY SESSION VIII
Presentation Session for Young Researchers
Moderators: Romana Vulturar, Ioana Streață

- 11:40 – 11:50 – Teodora Barbarii** – *Harmonizing Genetic Testing for Movement Disorders: A Unified Panel Approach and Reanalysis of 4,046 Unsolved Exomes*
- 11:50 – 12:00 – Lorin-Manuel Pîrlog** – *One Family, Two NF1 Variants, Three Phenotypes: Beyond Targeted Cascade Testing*
- 12:00 – 12:10 – Alexandra Zamfirescu** – *A Recurrent Inflammatory Syndrome: More Than Meets the Eye*
- 12:10 – 12:20 – Miruna Gug** – *Couple-Based Reproductive Genetic Carrier Screening in Western Romania: Reproductive Risk and Public Health Implications*
- 12:20 – 12:30 – Iulia Maria Sabau** – *Linear Reference Versus Personalized Pangenome References for Short-Read Whole-Genome Variant Calling*
- 12:30 – 12:40 – Andreea Ardeleanu** – *Beyond the 'Healthy Carrier: When Genotype Demands Functional Confirmation*
- 12:40 – 12:50 – Catalin Vasile Munteanu** – *Mutations We Almost Missed, Reframed: Diagnostic Blind Spots in Short-Read Data Exemplified*
- 12:50 – 13:00 – Silvia Bleahu** – *Bridging the Gap: The Utility of Expanded Carrier Screening in Couples from Central Romania*
- 13:00 – 13:10 – Vlăduț-Ovidiu Geană** – *Intellectual Disability in Neurofibromatosis Type 1: The Experience of a Romanian Clinical Genetics Center*

13:10 – 13:40
AWARDS
CONCLUSIONS
OFFICIAL CLOSING CEREMONY

13:40 – 14:30
LUNCH

SATURDAY, SEPTEMBER 19, 2026

11:25 – 11:40
POSTER SESSION

1. **Simona Ioana Vicas** – *Integrating Genomics and Metabolic Phenotyping in Rare Diseases: The Role of Exogenous Metabolites in Personalized Medicine*
2. **Gabriel Tudor Indig** – *Complete Androgen Insensitivity Syndrome: A Case Highlighting the Importance of Early Genetic Evaluation and Multidisciplinary Care*
3. **Amoaşii Anastasia** – *Small Stature, Big Picture: Decoding the Ultra-Rare Genetic Syndromes Masked by Prenatal IUGR*
4. **Alexandra Herlaş-Pop** – *CRGM Bihor – Experience of a Pilot Center in Newborn Screening for Spinal Muscular Atrophy*
5. **Maria-Victoria Corbu** – *Integrating Conventional Karyotyping and FISH in the Cytogenetic Characterization of Acute Leukemias: A Tertiary Center Experience*
6. **Adelina-Maria Cormoş** – *A Case Report of Atypical Alport Syndrome Presenting with Acute Abdominal Pain*
7. **Adela-Daria Neacşu** – *Utility and Limitations of LIRICAL and Phenomiser for Phenotype-Driven Disease Prioritization in an Epilepsy Whole-Exome Sequencing Cohort*
8. **Anca-Lelia Riza (Costache)** – *Perinatal Impaired Cytokine Response in at Risk Pregnant Women. The MERSIN Study (Myeloid dERived Suppressor Cells – Role in Severe INfections)*
9. **Mădălina-Diana Rafa** – *Learning from Family History: A Neonatal Death as a Clue to Inherited Metabolic Diseases—Lessons from Argininosuccinic Aciduria*
10. **Alexandra-Aurora Dumitra** – *Genotype-Phenotype Correlations in Patients with Neurodevelopmental Disorders Investigated by Next-Generation Sequencing (NGS) – Experience of a Regional Center and Implications for Personalized Medicine*
11. **Maria-Liana Marica** – *Psychological Impact and Interdisciplinary Management in Achondroplasia: From Genetics to Quality of Life*
12. **Adriana-Stefania Gidea** – *The Dynamic Genome: Somatic Mosaicism Across the Lifespan – From Early Embryonic Mutagenesis to Age-Related Clonal Selection in Human Disease*
13. **Mitut-Veliscu Andreea** – *Marfan Syndrome: Variable Expressivity and Cascade Testing in a Family – Mother and Two Children*

SATURDAY, SEPTEMBER 19, 2026

11:25 – 11:40
POSTER SESSION

14. **Tiberiu-Valentin Pandealea** – *Beyond Common-Mutation Panels: Whole-Gene CFTR Next-Generation Sequencing in a Romanian Cohort Referred for Cystic Fibrosis Suspicion*
15. **Iulia Maria Sabau** – *Temporal Integration of mRNA and lncRNA Expression Identifies Candidate Cis-Regulatory Signatures in Post-Infarction Cardiac Remodeling*
16. **Catalina Muntean-Simona** – *Molecular Spectrum of Polycystic Kidney Disease Diagnosed by NGS Using the TruSight One Panel at the Regional Centre of Medical Genetics Timiș*
17. **Mihai Teodor Barbarii** – *Genetic Counselling in Inherited Cardiomyopathies: Clinical Case Series*
18. **Andrian Fratea** – *Transcriptional Profiling of Immune Cells Reveals a Role for IFN γ /CXCL9/CXCL10 Pathway in Sepsis Patients with Exaggerated Inflammation*
19. **Rebecca-Cristiana Serban** – *Beyond Statural Gain: Evolution of BMI and Anthropometric Profile During Vosoritide Treatment in Patients with Achondroplasia*
20. **Ana-Maria Filip** – *The Immunogenetics of Recurrent Pregnancy Loss: What the Evidence Tells Us*
21. **Lorena-Maria Hanțig** – *Decoding Neonatal Lactic Acidosis: A Biochemical Signature of Mitochondrial Anaplerotic Dysfunction*
22. **Adriana-Stela Crișan** – *MicroRNA Expression in Myeloproliferative Neoplasms*
23. **Raul Andrei Gall** – *Beyond an Adverse Drug Reaction: The Genetic Perspective on Valproate-Induced Hyperammonaemia*
24. **Mihaela-Ștefania Buzdugan** – *Tetrasomy 9p: Phenotypic Correlations and Challenges in Cytogenetic Characterization in a Pediatric Case*
25. **Alina Bogliș** – *From Vascular Phenotype to Molecular Diagnosis: Exome Sequencing Role in Capillary Malformation-Arteriovenous Malformation Syndrome Type 1*
26. **Florica Ramona Dorobantu** – *Severe Delayed Hemolytic Anemia in a Newborn with Maternal–Fetal Rh-c Incompatibility: A Diagnostic Challenge*
27. **Codruta Diana Petchesi** – *Beyond a VUS: A Complex Phenotype*
28. **Olivia Onorica Dumnici** – *Short Stature in Children: A Retrospective Analysis of Cases and Growth Hormone Therapy Outcomes over a 25-Year Period at Regional Center of Medical Genetics Bihor*

ORAL PRESENTATIONS

TALL STATURE: FROM CLINICAL EVALUATION TO MOLECULAR DIAGNOSIS

**Maria Claudia Jurca¹, Alexandra Herlaş-Pop¹, Codruţa Petchesi¹, Kinga Kozma¹,
Oana Iuhas¹, Ana Trandafir¹, Romana Vulturar¹, Aurora Jurca¹, Dan Bembea¹,
Mihaela Buzdugan¹, Dana Carmen Zaha¹, Simona Vicas¹, Alexandru Daniel Jurca¹**

1 University of Oradea, Romania

Background: Tall stature is clinically defined as height exceeding +2 standard deviations above the mean for age and sex, or a discrepancy of more than 2 SD between the child's height and the calculated mid-parental height. While most children present with familial or constitutional tall stature, recognizing cases with an underlying genetic basis is essential for appropriate diagnostic orientation and family counseling.

Methods: This presentation proposes a structured clinical approach to the evaluation of children with tall stature, based on growth velocity, arm span, and associated dysmorphic or systemic features, always interpreted relative to age. Based on these criteria, cases are classified into constitutional/isolated tall stature, endocrine disorders, and genetic syndromes, the latter further structured into three categories: connective tissue disorders, syndromes associated with intellectual disability, and overgrowth syndromes.

Results: Connective tissue disorders (Marfan syndrome and its major phenocopy, homocystinuria, as well as congenital generalized lipodystrophy) frequently present with a marfanoid habitus and metabolic or vascular complications. Syndromes with intellectual disability, illustrated by fragile X syndrome, combine tall stature with characteristic craniofacial features. Overgrowth syndromes driven by epigenetic dysregulation of chromatin (Sotos syndrome, Beckwith–Wiedemann syndrome, and related chromatinopathies) associate tall stature with macrocephaly and minor dysmorphic signs.

Conclusions: Systematic clinical evaluation, dysmorphology, growth pattern, and associated systemic findings, correlated with family history, remains essential for distinguishing benign variants from syndromic tall stature and for guiding targeted genetic testing.

Keywords: *tall stature; connective tissue disorders; overgrowth syndromes; intellectual disability; genetic counseling*

Acknowledgements: This work was supported by the project “Dezvoltarea cercetării genomice în România (ROGEN)”, contract no. 96006/17.12.2024, project code SMIS 324809.

ORPHA Codes - Practical Importance and Update in the National and International Context

Cristina Rusu, Monica Panzaru

Universitatea de Medicina si Farmacie "Grigore T Popa" Iasi

Rare diseases affect approximately 1 in 2,000 individuals and constitute an important public health priority because of the significant challenges they pose in clinical practice, including misdiagnosis, incomplete or delayed diagnosis, and suboptimal allocation of healthcare resources. In Romania, diagnoses are currently reported using ICD-10 codes, which do not provide sufficient specificity for the accurate identification and monitoring of rare diseases. To address these limitations, the European Orphanet initiative developed ORPHA codes, a classification system specifically designed for rare diseases.

ORPHA codes have been implemented in most European countries, although national strategies regarding their adoption, integration, and practical use vary considerably. Selected implementation models will be presented in order to illustrate different approaches to incorporating ORPHA coding into national healthcare systems.

The paper will also examine the broader European context of the continued development of European Reference Networks through the affiliation of new healthcare providers, together with the national framework for the designation and accreditation of new rare disease centres of expertise.

Within this context, the paper aims to emphasize the need for the systematic implementation and routine use of ORPHA codes in Romania. Their integration into clinical and administrative practice may contribute to more accurate identification of rare disease patients, improved epidemiological data collection, better allocation of healthcare resources, and, ultimately, more effective management of patients with rare diseases.

From the Diagnostic Odyssey to the Therapeutic Window: Lessons from Pediatric Neurology Practice

Raluca Ioana Teleanu, Eugenia Roza, Radu Ștefan Perjoc, Oana Aurelia Vladâncenco

Centrul de expertiză pentru boli rare în domeniul neurologiei pediatrice Sp. Clinic de Copii Dr. V Gomoiu București/UMF CAROL DAVILA BUCUREȘTI

Introduction: Rare pediatric neurological diseases are characterized by substantial clinical and genetic heterogeneity, with often nonspecific initial manifestations that may delay diagnosis. With the rapid development of innovative therapies, timely and accurate diagnosis is essential to optimize therapeutic windows and potentially modify disease progression.

Objective: To highlight the importance of early and precise diagnosis and multidisciplinary collaboration in facilitating access to innovative therapies for children with rare neurological diseases.

Methods: Presentation of relevant cases from pediatric neurology practice illustrating the complexity of the diagnostic pathway and the role of multidisciplinary collaboration in diagnosis and therapeutic decision-making.

Results: The integration of clinical, genetic, imaging, and functional data enabled precise diagnosis and identification of appropriate therapeutic opportunities. Access to innovative treatments depends not only on their availability, but also on early disease recognition and effective coordination of the multidisciplinary team.

Conclusions: In the era of innovative therapies, genetic diagnosis is no longer the end of the diagnostic journey, but the beginning of an individualized therapeutic pathway. An integrated multidisciplinary approach can shorten the diagnostic odyssey and transform timely diagnosis into a genuine treatment opportunity.

Keywords: *rare pediatric neurological diseases; early diagnosis; precision diagnosis; innovative therapies; multidisciplinary team; therapeutic window.*

Driven by Evidence, Not Preference: Therapeutic Decisions in Genetic Disorders

Amelia Dobrescu^{1,2}, Alexandru Caramizaru^{3,4}, Anastasia Amoașii¹, Alexandra Bastian⁵, Anca-Lelia Riza^{1,6}, Andreea Dumitrescu¹

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2 Department of Medical Genetics, University of Medicine and Pharmacy of Craiova, Romania

3 MUSKETHER Team, IMRB, Inserm U955, University Paris-Est Créteil, France

4 Reference Center for Neuromuscular Disorders, APHP Henri Mondor, Créteil, France

5 Department of Pathology, Colentina Clinical Hospital, Bucharest, Romania

6 Department of Cellular and Molecular Biology, University of Medicine and Pharmacy of Craiova, Romania

The association of hyperCKemia, severe cardiac impairment, moderate motor deficit, and nonspecific inflammatory pattern on muscle biopsy in a young adult, along with inconclusive variants identified through NGS analysis, is not only a diagnostic challenge, but also a complicated situation to manage from an ethical standpoint. We present the case of a 25-year-old patient evaluated in the genetics department for dilated cardiomyopathy with severe systolic dysfunction – LVEF 30–37%, for whom the clinical examination revealed a proximal motor deficit of the lower limbs and muscle hypertrophy. NGS sequencing in the form of a comprehensive cardiology panel identified the heterozygous pathogenic variant c.1552-3C>G in the GAA (17q25.3) gene, as well as a deletion comprising exons 45-53 of the DMD gene (Xp21.1), classified as a variant of uncertain significance. Since the result does not molecularly confirm any of the pathologies associated with the respective genes, and patients with Pompe disease benefit, in Romania, from treatment for heterozygotes, an urgency for a therapeutic decision arises. A certainty diagnosis will require additional investigations, with possible options including a new muscle biopsy, reevaluation of the DMD VUS, and extended molecular analysis in order to identify a possible second GAA variant. The case highlights once again the importance of rapid and concrete characterization of the genetic status of patients and raises the ethical issue of therapies for which there are still discrepancies between international protocols.

Challenges in Patient Access to Innovative Treatments for Rare Diseases: Lessons from a Small Angelman Syndrome Cohort

Iulia-Elena Simina^{1,2}, Iuliu Stefan Bacos-Cosma³, Alexandra Mihailescu¹, Catalin Vasile Munteanu^{2,4}, Maria Puiu⁵, Nicoleta Ioana Andreescu^{1,2}, Adela Chirita-Emandi^{1,2}

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2. Regional Center of Medical Genetics Timis, Clinical Emergency Hospital for Children "Louis Turcanu", Timisoara, Romania

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5. The Genomics Research and Development Institute, 020021 Bucharest, Romania

"Background: Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by loss of function of the maternally inherited UBE3A allele on chromosome 15q11.2-q13, due to a maternal deletion, a UBE3A variant, paternal uniparental disomy (UPD), or an imprinting defect. AS has entered a new therapeutic era: antisense oligonucleotides reactivating the silenced paternal UBE3A allele (apazunersen/GTX-102, ASPIRE; ION582, REVEAL) are now in global phase 3 trials, alongside early gene therapy programs.

Objective: To describe the genotypic and clinical spectrum of a small Romanian AS cohort and identify practical barriers to accessing innovative disease-modifying therapies.

Methods: We retrospectively reviewed seven patients (age 1-18 years; 4 male) with clinically and/or molecularly confirmed AS, followed at a regional medical genetics center, summarizing genotype, diagnostic pathway, and current treatment.

Results: Genotypes comprised four 15q11-q13 deletions, one UBE3A pathogenic variant, one paternal UPD(15), and one clinical diagnosis without a retrievable molecular report. Confirmatory testing required send-out to three international laboratories (2018-2026); one patient's diagnostic odyssey included an initially negative local epilepsy panel before trio exome sequencing abroad confirmed UPD, eleven years after birth. None of the seven patients meets full genotype-and-age eligibility for ongoing pivotal trials, none has accessed yet an investigational therapy, and all remain on antiepileptic and supportive care alone.

Conclusions: Even as targeted AS therapies approach approval, restrictive trial eligibility windows, absent in-country trial sites, fragmented genetic records, and Romania's documented post-approval reimbursement delays threaten to leave small, dispersed cohorts behind. National patient registries and proactive trial-readiness planning are needed.

Keywords: Angelman syndrome; UBE3A; antisense oligonucleotide; rare disease; patient access"

Acknowledgements: The authors thank the patients and their families for their trust and continued participation in clinical follow-up, and the referring clinicians and laboratories involved in their diagnostic evaluation and care. This work received no dedicated funding. The authors declare no conflicts of interest.

Jumping Translocation, a Rare Form of Chromosomal Abnormality- Discussion Based on a Clinical Case

**Setalia Popa ¹, Mihaela Grănescu ¹, Violeta Martiniuc ², Roxana Popescu ¹,
Andreea Florea ¹, Lavinia Caba ¹, Luminița Păduraru ^{1,2}, Mihaela Guzaganu ²
Eusebiu Vlad Gorduza ^{1,2}**

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(2) Spitalul Clinic de Obstetrică și Ginecologie "Cuza Vodă" Iași

Jumping translocations are extremely rare chromosomal mosaic abnormalities characterized by the translocation of the same chromosomal segment to different recipient chromosomes in distinct cell lines.

We report a boy born prematurely at 35 weeks of gestation with multiple congenital anomalies, including dolichocephaly, a sloping forehead, small nose, micrognathia, low-set posteriorly rotated ears, bilateral cryptorchidism, cardiomegaly with patent ductus arteriosus, cerebral ventriculomegaly, and agenesis of the corpus callosum.

GTG-banded chromosome analysis identified a complex mosaic comprising seven cell lines, all involving the long arm of chromosome 14:

45,X,-14,der(Y)t(14;Y)(q11.2;q12)[76]/45,XY,-14,der(1)t(1;14)(q44;q11.2)[8]/45,XY,-14,der(5)t(5;14)(q15.3;q11.2)[7]/45,XY,-14,der(6)t(6;14)(q27;q11.2)[4]/45,XY,-14,der(21)t(21;14)(q10;q11.2)[3]/45,XY,-14,der(20)t(20;14)(q13.3;q11.2)[1]/45,XY,-14,der(22)t(22;14)(q10;q11.2)[1].

MLPA analysis using subtelomeric probe sets P036 and P070 (MRC-Holland®) identified a 2.21 Mb deletion on chromosome 14. Further analysis with the P358 kit confirmed the deletion of the region spanning positions 19,863,569–22,127,740 on chromosome 14.

This case highlights the value of combining cytogenetic and molecular techniques in the investigation of patients with multiple congenital anomalies.

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The Genetics Laboratory team, "Grigore T. Popa" University of Medicine and Pharmacy, Iași.

Rare Genomic Imbalances Encompassing Kinase Genes in a Group of Patients with Autism Spectrum Disorders

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Background: Autism spectrum disorders (ASDs) are complex and heterogeneous neurodevelopmental conditions. Rare copy number variants (CNVs) and sequence changes have a well-recognized contribution to ASD pathogenesis. Among the involved genes, kinases encode for proteins with important biological roles including brain development and function.

We report the results of array-based genomic comparative hybridization (array-CGH) and triplet primed PCR/MS-MLPA screening for fragile X syndrome, in a group of ASDs patients, with focus on defects involving kinases.

Methods: 300 patients with ASDs were included in this study, after a complex clinical workup including neurological, psychiatric, and psychological evaluations. FMR1 promotor was screened for abnormal methylation (MS-MLPA) and trinucleotide repeat expansion (TP-PCR), for male patients only. Array-CGH was performed in all ASD patients and a similar number of children with no neuropsychiatric diagnosis, using SurePrint G3 Human CGH microarray (Agilent Technologies).

Results: Rare exonic CNVs (< 1% of the total sample) were detected in 200 out of 300 patients and full mutation of the FMR1 in four. Thirty-two kinases were encompassed by rare exonic CNVs. Among these kinases, nine are considered causal for specific conditions and five belong to a larger genomic region associated with known syndromes, such as 1q21.1 duplication, 3q29 deletion, Jacobsen syndrome, 22q11.2 duplication and Xq28 duplication - Lubs type syndrome.

Conclusions: Taking into account the genetic link of kinases with neurodevelopmental disorders, the increasing evidence that kinase dysfunction may play a causative role in these conditions, and the fact that kinases represent promising therapeutic targets, new patient data are needed to enhance the existing knowledge on kinase contribution to ASD pathophysiology.

Acknowledgements: The research leading to these results has received funding from the EEA Grant 2014-2021, under the project contract No 6/2019

Optical Genome Mapping First Contact in Craiova

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We report our initial experience implementing Optical Genome Mapping (OGM) in Craiova, based on four whole-blood (EDTA) samples processed approximately 24 hours after collection. Two samples were maintained at 4°C, while the other two were kept at ambient room temperature under otherwise identical handling conditions. This design allowed a preliminary, direct comparison of short-term storage temperature on sample integrity prior to high-molecular-weight (HMW) DNA isolation, a critical factor for OGM given the method's reliance on ultra-long, intact DNA molecules.

Following the approximately 24-hour pre-isolation interval, HMW DNA extraction was carried out under standard conditions for all four samples. Both the refrigerated and the room-temperature groups showed a measurable quantity of DNA relative to optimally fresh material; nonetheless, all four samples yielded DNA of sufficient quality to proceed to labeling and genome imaging, with no outright analytical failures.

These first-contact results suggest that EDTA whole-blood samples can tolerate up to 24 hours of pre-isolation delay under either refrigerated or room-temperature conditions without precluding successful OGM analysis, although some loss of molecular integrity should be expected regardless of storage temperature. Establishing standardized, expedited transport and cold-chain protocols is nonetheless advisable to minimize degradation and preserve longer DNA fragment lengths, ultimately improving structural variant detection sensitivity in future OGM workflows at our center..

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Diagnostic Challenges in Sex Chromosome Aneuploidies-Case Reports. When Phenotype and Genotype Do Not Agree

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UMFCD, Synevo

"Disorders of sex development (DSD) are a heterogeneous group of conditions that can represent a diagnostic challenge, particularly when clinical findings do not fit the expected chromosomal or gonadal sex. Sex chromosome abnormalities are relatively common, but their clinical presentation can vary considerably, sometimes making the diagnosis difficult. DSD can be diagnosed at different ages. In some patients, the first signs are identified in newborns or children because of atypical or ambiguous genitalia. In others, the condition may remain unrecognized until adolescence or adulthood, when primary amenorrhea, absent or incomplete pubertal development, hypogonadism, or infertility leads to further investigation. Imaging may also reveal abnormalities of the internal reproductive organs or gonads.

The diagnosis can be particularly challenging in patients with a 46,XY karyotype and a female phenotype. Sex reversal and gonadal dysgenesis may be caused by abnormalities involving genes important for sex determination, including SRY. In some cases, however, structural abnormalities of the sex chromosomes, including translocations, may also lead to an apparent discrepancy between genotype and phenotype.

We present a series of DSD cases identified during genetic investigations performed in our laboratory. The patients had different clinical presentations and ages, with some of the genetic findings being unexpected based on the initial clinical picture. These cases illustrate the difficulties that may arise when establishing a diagnosis of DSD and the importance of combining clinical findings with cytogenetic and molecular genetic investigations.

An accurate diagnosis is also important for patient management. In particular, patients with gonadal dysgenesis and Y-chromosomal material may have an increased risk of gonadoblastoma and therefore require appropriate clinical evaluation and follow-up.

Keywords: cytogenetics; disorders of sex development; DSD; sex chromosome abnormalities; genotype–phenotype discordance; sex reversal; 46,XY gonadal dysgenesis; SRY; gonadoblastoma."

Acknowledgements: Synevo; The families of the patients.

Oncogenetics in the AI Era

Cătană Andreea

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Rapid advances in genomics and the development of artificial intelligence (AI) technologies are reshaping modern oncogenetics. The increasing volume of data generated by next-generation sequencing (NGS), transcriptomics, and other omics technologies requires advanced analytical tools capable of translating complex datasets into clinically relevant information.

AI facilitates the identification of genetic variants associated with cancer susceptibility, the classification of somatic and germline mutations, and the integration of molecular data with clinical and imaging information. Through machine learning and deep learning algorithms, AI can improve diagnosis, risk stratification, prognostic assessment, and the selection of personalized therapies. Predictive models may also help anticipate treatment response and identify patients most likely to benefit from targeted therapies or immunotherapy.

The presentation will address both the current applications of AI in oncogenetics and its practical integration into routine clinical care. Relevant clinical examples will include genetic variant interpretation, the use of risk scores, correlation of molecular profiles with therapeutic options, and incorporation of genomic data into multidisciplinary decision-making. Current opportunities and limitations related to the implementation of AI in healthcare systems will also be discussed.

The integration of artificial intelligence into oncogenetics represents an important step toward precision medicine, offering the potential for more effective, predictive, and personalized approaches to cancer prevention, diagnosis, and treatment.

Beyond the 'Rigid Textbook Phenotype': AI vs. Human Expertise in Rare Diseases

Plaiasu Vasilica

INSMC Alessandrescu-Rusescu, Centrul Regional de Genetica Medicala Bucuresti

"Diagnosing rare diseases remains a major clinical challenge because real-world patients rarely present with the definitive, "textbook" phenotypes described in traditional medical literature.

This work reflects on extensive clinical experience in managing rare genetic and metabolic disorders, analyzing cases where patients exhibited highly atypical, multi-systemic manifestations that initially led to prolonged diagnostic odysseys. By evaluating these complex clinical journeys, we contrast traditional human diagnostic workflows with the emerging capabilities of Artificial Intelligence (AI).

AI is fast at reading data, but human doctors are much better at handling rare diseases. While AI processes vast medical datasets at unprecedented speeds, the management of rare diseases remains a fundamentally human challenge. AI is rigid and constrained by its training data. "Medical touch, sight, and hearing" which are the three primary sensory modalities used by healthcare professionals during a physical examination find clues that machines miss them.

When it comes to delivering results a doctor provides true empathy and comfort that a machine can only simulate. Human physicians can read body language in real time, adjust their tone to deliver bad news gently, and build the deep trust that patients need to follow difficult, long-term treatments.

Solving the mystery of rare diseases requires a collaborative, hybrid model where AI serves as a powerful analytical tool, but the clinician validates the clinical reality and transforms mathematical probabilities into personalized medical care."

When Alzheimer's Mimics Multiple Sclerosis: Unmasking PSEN1-Linked Disease Present Across Four Generations

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Background: One family, spanning 3 generations, was clinically diagnosed with multiple sclerosis based on a progressive spastic-ataxic gait disorder with onset around age 35 and death before age 45, in most relatives. The index patient, from the third generation, had an 18-month history of paraparetic gait disorder, ataxia, dysarthria, dysphagia and progressive cognitive decline (MMSE 18/30, GAFS 31), was sent for genetic testing after neurological evaluation and brain MRI.

Methods: Clinical Whole-Exome-Sequencing (WES) was performed, followed by targeted analysis of 2 panels (36 spinocerebellar-ataxia genes and 83 hereditary-spastic-paraplegia genes). Variants were classified using ACMG criteria and correlated with Human Phenotype Ontology (HPO) terms. Targeted testing was used predictively for the children from the IV generation.

Results: The 2 panels were negative. Only uncertain HLA-DRB variants were found, which genetically excluded multiple sclerosis. A heterozygous, probably pathogenic PSEN1 variant, c.1141C>T, p.(Leu381Phe), was identified, associated with early-onset Alzheimer's disease and frontotemporal dementia, phenotypes that may atypically include spastic paraparesis and cerebellar ataxia. This finding reclassified the putative hereditary multiple sclerosis pedigree as early-onset dementia related to PSEN1. Secondary findings included a pathogenic CHEK2 variant (hereditary cancer risk) and uncertain APOB/PCSK9 variants (familial hypercholesterolemia).

Conclusions: Comprehensive molecular testing allowed the correct reclassification of a four-generation neurodegenerative pedigree, previously thought to be multiple sclerosis, as PSEN1-linked early-onset Alzheimer's disease with an atypical spastic-ataxic phenotype. This case highlights the phenotypic overlap between PSEN1-related dementia and hereditary ataxia/spastic paraplegia syndromes, and the value of clinically prioritized WES testing and genetic counseling in atypical, aggressive familial neurodegeneration.

Keywords: PSEN1; early-onset Alzheimer's disease; whole exome sequencing; genetic counselling

Acknowledgements: Thank You, Medical Genetics Team, Neurology Team, Patient and their families

Genetic Testing in Short Stature

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David Ana, Cepoi Marius, Sporis Andrei, Alkhzouz Camelia**

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Short stature is defined as a height more than two standard deviations below the population mean for age and sex. Genetic factors play a major role in determining adult height, accounting for up to 90% of its variation. To date, thousands of genetic variants involving more than 600 genes have been associated with human growth.

Most identified variants have small individual effects, with height resulting from the combined influence of multiple genetic factors. However, some variants have a stronger impact on gene function and may significantly disrupt growth pathways. These effects may occur directly at the growth plate, leading to primary short stature, or indirectly through endocrine and metabolic abnormalities, resulting in secondary short stature.

Diagnosis relies on clinical and radiological assessment, including bone age, together with laboratory investigations. In many cases, the underlying etiology can be confirmed by genetic testing, including karyotyping, gene panels, and exome or genome sequencing. Commonly involved genes include SHOX, FGFR3, NPR2, IHH, PTPN11, COMP, ACAN, COL2A1, GH1, IGF1R, GHRHR, and PROP1.

Recombinant human growth hormone (rhGH) remains an important therapeutic option, while newer treatments are emerging. Vosoritide, currently indicated for achondroplasia, may also have potential in selected other genetic growth disorders. Specific therapies may also be available for associated skeletal, metabolic, or endocrine conditions.

An accurate genetic diagnosis can guide therapeutic decisions by identifying the most appropriate treatment and, in some cases, by helping to avoid therapies that may be ineffective or associated with unnecessary adverse effects.

Complementarity of Health Policies for Rare Diseases

Dorica Dan

Alianța Națională pentru Boli Rare

Although each rare disease affects only a small number of individuals, collectively rare diseases represent a major public health challenge, with profound implications for healthcare, social, and economic systems. Their complexity, predominantly genetic basis, and the need for multidisciplinary expertise mean that the response cannot be exclusively clinical, but must also rely on coherent, coordinated, and evidence-based public policies.

In recent years, national and European policies on rare diseases have evolved significantly, with increasing emphasis on equitable access to genomic diagnosis, the development of registries and biobanks, integration into expert networks, and, importantly, patient- and family-centred care.

This presentation aims to provide an overview of these policies, highlight the progress achieved and the remaining gaps, and emphasize the essential role of all stakeholders in their implementation. Beyond technologies and strategies, the real impact of genomics in rare diseases depends on our ability to translate knowledge into clinical practice and tangible benefits for patients.

Acknowledgements: Eurordis - Rare Diseases Europe

A Century of Genetics in the Light of the Nobel Prizes: Milestones in the Evolution of Modern Genetics

Lavinia Caba, Eusebiu Vlad Gorduza

Universitatea de Medicina si Farmacie "Grigore T. Popa", Iasi, Romania

Nobel Prizes in Physiology or Medicine and Chemistry have played a major role in revolutionizing genetics. This paper presents key milestones in the development of modern genetics.

ORAL PRESENTATIONS

Young Researchers

Harmonizing Genetic Testing for Movement Disorders: A Unified Panel Approach and Reanalysis of 4,046 Unsolved Exomes

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Background: Molecular testing for genetic movement disorders (MD) increasingly relies on exome- or genome-based virtual gene panels. In the absence of consensus guidelines, MD panel design remains heterogeneous across laboratories, with international variation in panel configuration and gene content.

Objectives: To develop a reproducible framework for a unified MD panel design, generate a comprehensive, curated gene-phenotype dataset, and evaluate clinical utility via targeted exome reanalysis.

Methods: Candidate genes were extracted from multiple resources and assessed using predefined criteria for panel inclusion and gene-disease validity. Genes were tiered as Green, Amber, or Red based on evidence strength. Phenotypic spectrum and age-at-onset were assessed for Green genes based on published literature. Newly added Green and Amber genes were interrogated in 4,046 exomes from previously undiagnosed MD cases. **Results:** Among 2,090 extracted genes, 640 were selected. The final panel included 537 Green, 36 Amber and 67 Red genes, expanding the prior panel by 283 genes and removing 42. Across Green genes, only 17% were linked to a single MD feature, whereas the remainder associated up to eight. Age-at-onset data indicated both pediatric and adult presentations in 43% of genes. Targeted exome reanalysis using a 220-gene list identified 37 clinically relevant variants across 28 genes, resolving 16 cases and increasing diagnostic yield by 0.4%.

Conclusions: This study offers a systematic framework for designing a unified MD panel by integrating evidence from multiple sources and accounting for phenotypic and age heterogeneity. Targeted reanalysis yielded actionable diagnoses, confirming its clear benefit in routine clinical practice.

One Family, Two NF1 Variants, Three Phenotypes: Beyond Targeted Cascade Testing

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Background: Neurofibromatosis type 1 (NF1) is an autosomal-dominant tumour-predisposition disorder with near-complete penetrance and variable expression. Rare families in which first-degree relatives carry distinct NF1 pathogenic variants have been reported. In small published series, additional de novo variants were identified in descendants of affected men, generating an unconfirmed hypothesis of increased second-variant risk in their offspring.

Case presentation: A 54-year-old man with clinically and molecularly confirmed NF1 carried the heterozygous pathogenic variant NM_000267.3:c.7926dupT, p.(Lys2643Ter), identified in blood before diagnosis of an FNCLCC grade 2 malignant peripheral nerve sheath tumour of the left radial nerve. Other excised lesions were benign neurofibromas. His sons underwent clinical and molecular evaluation.

Results: Son A carried the paternal c.7926dupT variant heterozygously in blood. At 21 years, he had no clinical NF1 manifestations but met the revised criteria through the molecular criterion in the context of an affected parent. Son B did not carry the familial variant but had three subcutaneous neurofibromas. Therefore, he met NF1 criteria because his father was affected. Comprehensive NF1 sequencing identified a distinct heterozygous pathogenic start-loss variant, NM_001042492.3:c.2T>C, p.(Met1Thr), in blood. The father's full NF1 sequencing did not detect c.2T>C. The mother, aged 54 years, had no clinical features suggestive of NF1 but was not molecularly tested. Given the near-complete adult penetrance, constitutional maternal inheritance was considered unlikely, and c.2T>C was interpreted as presumed de novo. Its de novo status and parent of origin remain molecularly unconfirmed.

Conclusion: A negative familial-variant result excludes the tested allele, not NF1 when clinical findings persist. Discordance should prompt comprehensive NF1 analysis and parental segregation. If maternal testing confirms absence of c.2T>C, this pedigree would extend reports of descendants of affected men carrying a second, independent NF1 pathogenic variant.

A Recurrent Inflammatory Syndrome: More Than Meets the Eye

Alexandra Zamfirescu

Centrul Medical Emerald

Mosaic trisomy 8 is a very rare genetic disorder, classically associated with a multisystem phenotype that may include facial dysmorphism, intellectual disability, and joint, renal, cardiac, and skeletal abnormalities. A distinct autoinflammatory phenotype, known as trisomy 8-associated autoinflammatory disease (TRIAD), has also been described, characterized by recurrent fever and oral, genital, and gastrointestinal ulcerations resembling the clinical manifestations of Behçet disease.

We report the case of a 30-year-old woman with a history of recurrent genital ulcerations since the age of 14, associated with fever, headache, and myalgia. Two years prior to presentation, Behçet disease and familial Mediterranean fever (FMF) were considered in the differential diagnosis. Genetic testing for FMF identified two variants of uncertain significance (VUS) in the MEFV gene. Given the persistent symptoms and inconclusive molecular findings, genetic testing was extended to whole-exome sequencing (WES), which revealed mosaic trisomy 8. This finding was subsequently confirmed by conventional karyotyping of peripheral blood. The patient's clinical presentation was consistent with TRIAD, without the other congenital or multisystem manifestations classically associated with mosaic trisomy 8.

This case highlights the marked heterogeneity of the genetic causes underlying autoinflammatory phenotypes and the broad clinical spectrum of mosaic trisomy 8. It also emphasizes the continued value of conventional genetic testing methods, such as karyotyping, as part of the diagnostic approach to complex and unexplained clinical presentations.

Acknowledgements: The author thanks the patient and all clinicians and laboratory professionals involved in her diagnostic evaluation.

Couple-Based Reproductive Genetic Carrier Screening in Western Romania: Reproductive Risk and Public Health Implications

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Background: Individual carrier status is common, but reproductive risk emerges at the couple level. Reproductive genetic carrier screening (RGCS) can identify couples at increased risk of autosomal recessive (AR) disorders; however, population-specific carrier data remain limited in Romania, even more so at the couple-level.

Methods: We retrospectively analyzed 247 non-consanguineous couples (494 individuals) tested between 2020 and 2024 at a single genetic center in Western Romania using an expanded 302-gene panel, including 300 AR-associated genes, with pre- and post-test genetic counseling.

Results: Shared pathogenic/likely pathogenic (PLP) variants in the same gene were identified in 43/247 couples (17.4%), typically corresponding to a 25% risk of an affected child per pregnancy. Nineteen genes were associated with reproductive risk; HFE, CFTR, and SMN1 accounted for 65.12% of at-risk couples, while 14 additional genes reflected substantial genetic heterogeneity. Notably, three couples shared PLP variants in two genes simultaneously. Among at-risk couples, 60.46% carried identical variants, whereas 39.53% carried different variants within the same gene. Nineteen families had children with AR monogenic disorders; six affected children had died prior to parental carrier testing.

Conclusions: This first couple-based RGCS analysis from Western Romania provides initial data on shared carrier status and reproductive risk and highlights the value of assessing partners jointly. In the context of Romania’s 2026 expansion of neonatal screening from 3 to 22 conditions, these findings support further regionally representative research evaluating how preconception RGCS could complement preventive genetics initiatives and contribute to more equitable access to genetic services.

Keywords: reproductive genetic carrier screening; carrier couples; reproductive risk; preventive genetics; equitable genetic services.

Acknowledgements: All data included in this study belong to Medical Genetics Office Doctor Gug, Timişoara, Romania, and were used with the approval of the institution.

Linear Reference Versus Personalized Pangenome References for Short-Read Whole-Genome Variant Calling

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Linear reference genomes have several limitations such as incompletely representing genetic diversity, collapsing structural variants, and poorly capturing highly polymorphic regions. Personalized pangenome references (PPR) can reduce such biases by providing a more representative reference for read alignment and variant calling. We evaluated PPR approach against conventional GATK pipeline using whole-genome data from 23 Romanian individuals sequenced on both Illumina and Element Aviti platforms. Variant calls were benchmarked against the GIAB HG002 truth set across diverse genomic contexts. We assessed concordance between pipeline-platform combinations and characterized variants detected exclusively by each method. Merfin k-mer support was used for additional variant validation. GenomeScope 2.0 provided reference-free characterization of diploid genome k-mer profiles across sequencing platforms. PPR outperformed GATK for SNVs on both platforms, achieving F1-scores of 0.990-0.993 versus 0.938-0.977, largely driven by higher recall (98.5-98.8% vs. 88.6-96.0%). The advantage was particularly pronounced in challenging regions, including low-mappability regions. Concordance analyses indicated that variant-calling methodology contributed more to detection differences than sequencing platform, while PPR showed greater cross-platform reproducibility. PPR also identified more rare and novel variants reproducibly detected across both platforms. Among pipeline-specific variants evaluated against the GIAB HG002 truth set, PPR achieved a 63.5% true-positive rate versus 24.2% for GATK. Merfin provided additional support for PPR calls. These results demonstrate improved variant detection and cross-platform reproducibility with personalized pangenome-based calling.

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Beyond the 'Healthy Carrier: When Genotype Demands Functional Confirmation

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Introduction:

Hereditary cancer syndromes, such as hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome, are caused by germline pathogenic variants in cancer predisposition genes. In Romania, epidemiological and molecular data on these syndromes remain limited and fragmented.

Background

The label ""carrier"" implies that a patient with a single pathogenic variant remains unaffected because the normal allele provides sufficient function. However, symptomatic heterozygotes are increasingly recognized in hematologic, metabolic, and immunologic disorders. We present two paediatric cases in which the ""healthy carrier"" label proved misleading, and functional testing clarified the genotype–phenotype relationship.

Cases and Results

An 8-year-old boy presented with recurrent epistaxis, later found to have persistent hepatosplenomegaly and hypergammaglobulinemia. Initial genetic testing revealed one pathogenic GBA1 variant and one pathogenic IFIH1 variant, labelling him a carrier for both. Targeted PCR and enzymatic testing detected a second GBA1 variant with deficient enzyme activity, establishing Gaucher disease type 1. IFIH1 gain-of-function is linked to systemic autoimmunity within the type I interferonopathy spectrum and to features overlapping Gaucher disease (hepatosplenomegaly, osteopenia, short stature), reframing this variant as clinically relevant.

A 12-year-old girl presented with recurrent severe allergic reactions (angioedema, allergoderma), pericarditis, and atrial and ventricular septal defects. Genetic testing revealed a pathogenic G6PD variant, labelling her a carrier. Enzymatic testing demonstrated deficient glucose-6-phosphate dehydrogenase activity, reported in association with septal defects and immune dysregulation.

Conclusion

A ""healthy carrier"" result is not synonymous with an unaffected individual. In both patients, functional and molecular testing revealed clinical relevance: enzyme assay confirmed G6PD deficiency in a heterozygous girl, while targeted PCR and enzymatic testing identified biallelic GBA1 disease and helped reframe an IFIH1 variant. Carrier labels warrant functional confirmation rather than reassurance."

Acknowledgements: We sincerely thank the patients and their families for their cooperation and consent to share this case.

Mutations We Almost Missed, Reframed: Diagnostic Blind Spots in Short-Read Data Exemplified

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Background: Reaching the causal genetic variant remains one of the most challenging steps in genomic diagnostics. Clinically relevant findings may be missed because of limited coverage, complex genomic architecture, bioinformatic filtering, variant type, and evolving gene–disease associations. While the field is moving toward long-read sequencing, relevant diagnostic information may still remain hidden within short-read data.

Material and Methods: Over the last year (2025-2026), patients with suspected rare genetic disorders were clinically evaluated at the Regional Center for Medical Genetics Timiș (CRGM Timiș), Romania, and sequencing was performed at the Center for Genomic Medicine, Victor Babeș University of Medicine and Pharmacy Timișoara. Cases were investigated using targeted sequencing and exome sequencing, with phenotype and genotype driven interpretation.

Results: We present multiple cases where causal variants evaded routine pipeline: two challenging TTN variants with low-quality evidence (one false positive and one false negative), apparently missense variants subsequently recognized as indels after visual inspection, two PKD1 cases involving an intronic variant and a gene-conversion event, an NF1 variant detected by genome sequencing and retrospectively visible in a minority of targeted-sequencing reads, a PAX6 variant in a known difficult-to-sequence region, and a C10orf71 likely pathogenic (LP) variant associated with dilated cardiomyopathy, identified by exome-wide analysis but missed by the virtual panel.

Conclusion: Moving from sequencing data to a molecular diagnosis remains a challenging task that requires highly specialized expertise. Systematic visual inspection of sequencing reads, orthogonal validation, and analysis beyond predefined gene lists can uncover clinically relevant variants that would otherwise remain overlooked in short-read data.

Bridging the Gap: The Utility of Expanded Carrier Screening in Couples from Central Romania

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Background. Expanded carrier screening (ECS) has become a key recommendation for reproductive health. However, there are only a few countries across the globe that have national funding in this regard, and most Eastern European countries do not have data pertaining to carrier frequency. While rare diseases impact 150 to 500 million people, genetic testing is scarce and costly. The scope of this prospective observational study was to determine the at-risk couple rates and identify prominent pathogenic or likely pathogenic (PLP) variants in Central Romania.

Materials and Methods. A 172-gene Next Generation Sequencing (NGS) panel, Long-Polymerase Chain Reaction (PCR), Gap-PCR, quick PCR, SANGER sequencing and Fragile X Syndrome screening via Triplet Primed-PCR, and fluorescent capillary electrophoresis were performed during 2024. 91 couples of reproductive age were tested pro bono, all without children and with no known medical history. Pre- and post-genetic test counselling was conducted, and the participants are being monitored for a three-year timeframe.

Results and discussion. The hallmarks of our findings were that 4.4% of couples had PLP variants in the same gene, and 52.7% of participants carried at least one PLP variant. Furthermore, Gap Junction Beta-2 (GJB2) was the most prevalent gene, found amongst 7.7% of the tested individuals.

Conclusion. In light of these findings, further regional research and national policies are needed to establish clear guidelines for ECS panels' contents and beneficiaries. Additionally, national rare disease registers and programs should be implemented to locate and educate the public and medical professionals on carrier screening and reproductive options.

Intellectual Disability in Neurofibromatosis type 1: The experience of a Romanian Clinical Genetics Center

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Background: Neurofibromatosis type 1 (NF1) is caused by heterozygous loss-of-function variants in the NF1 gene, associated with neurodevelopmental disorders (NDDs). Among them, reported intellectual disability (ID) is clinically significant. Romanian data on ID in NF1 patients are lacking. Here, we assessed the frequency of ID and its clinical associations in a Romanian cohort of patients with NF1.

Methods: We performed a retrospective observational study of patients with genetically confirmed pathogenic NF1 variants who were referred to and assessed at the Regional Center of Medical Genetics Timiș. Genetic testing was performed at the Center for Genomic Medicine, "Victor Babeș" University of Medicine and Pharmacy.

Results: 87 patients were included, 76 were eligible. ID information was available for 54 patients; 16 (29.6%) had documented ID. Other NDDs, including ADHD and ASD, were documented in 35. ID was significantly associated with other NDDs (75% vs. 34.8%; $p=0.035$; $OR=5.625$). No significant associations were identified between ID and macrocephaly ($p=0.174$), plexiform neurofibromas (PNFs) ($p=1.000$) or sex ($p=0.770$). Age at diagnosis did not differ significantly between patients with and without ID ($p=0.506$).

Conclusion: ID was documented in approximately one-third of NF1 patients with available clinical information in our cohort, and was significantly associated with other NDDs. The findings also suggest some neurodevelopmental features may remain underrecognized without systematic assessment. These findings highlight the need for standardized neuropsychological assessment in NF1 to improve neurodevelopmental phenotyping and enable more robust future genotype–phenotype analyses.

Keywords: Neurofibromatosis type 1, Neurodevelopmental Disorders, Intellectual Disability, Clinical Phenotyping, Neuropsychological assessment

POSTERS

Integrating Genomics and Metabolic Phenotyping in Rare Diseases: The Role of Exogenous Metabolites in Personalized Medicine

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Rare inherited metabolic diseases are characterized by marked genetic and phenotypic heterogeneity, making early diagnosis and individualized therapeutic management challenging. This narrative review examined recent evidence on the integration of genomic technologies with metabolic phenotyping and the contribution of targeted exogenous metabolic interventions to personalized medicine. This topic is aligned with ROGEN project activities focused on the genomic investigation of unresolved rare disease cases and the functional assessment of genetic variants through complementary omics approaches.

Recent peer-reviewed studies published between 2022 and 2025 were reviewed [1–6]. Integrated approaches combining next-generation sequencing, biochemical testing, transcriptomics, and metabolomics improved diagnostic resolution and supported the functional interpretation of genetic variants, while rapid whole-genome sequencing enabled clinically meaningful decision-making in critically ill patients [1,2]. Metabolomics provided complementary phenotypic information by identifying disease-associated metabolic signatures, supporting patient stratification and linking genetic variation to biochemical consequences [3,4].

From a therapeutic perspective, triheptanoin in long-chain fatty acid oxidation disorders and carnitine in methylmalonic and propionic acidemias illustrate how exogenous compounds can modulate disrupted metabolic pathways and reduce clinically relevant metabolic events [5,6].

Overall, the available evidence supports the concept of precision metabolic medicine, in which genomic diagnosis is complemented by functional metabolic phenotyping to guide targeted interventions. Future integration of genomics, metabolomics, transcriptomics, and computational modelling may further improve diagnosis, therapeutic selection, and individualized management of patients with rare metabolic diseases.

Complete Androgen Insensitivity Syndrome: A Case Highlighting the Importance of Early genetic evaluation and Multidisciplinary Care

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INTRODUCTION : Complete androgen insensitivity syndrome (CAIS) is a rare X-linked disorder in individuals with a 46,XY karyotype, caused by impaired androgen action, most commonly due to pathogenic variants in the androgen receptor (AR) gene, located at Xq12. Early recognition, genetic evaluation, and multidisciplinary care are essential for timely diagnosis and optimal management of individuals with CAIS.

METHODS: We present an 18-year-old female patient referred to the Bihor Regional Center for Medical Genetics for evaluation of primary amenorrhea.

RESULTS: Clinical examination raised suspicion of CAIS based on tall stature above the female reference range, absent axillary and pubic hair (Tanner stage P1), and breast development at Tanner stage B4. Serum testosterone was markedly elevated (>750 ng/dL). Pelvic ultrasound showed a blind-ending vagina, while MRI revealed a small midline structure (18 × 11 mm), interpreted radiologically as a rudimentary uterine structure; ovaries were not visualized. Cytogenetic analysis demonstrated a 46,XY karyotype. Molecular analysis was recommended but declined by the family. Surgical removal of the intra-abdominal gonads was performed. Histopathology demonstrated immature testicular parenchyma with Sertoli cells, rare spermatogonia, and hyperplastic Leydig cells, without neoplastic elements. Following gonadectomy and hormone replacement therapy, testosterone decreased to 78 ng/dL, with LH, FSH, and estradiol levels appropriate for the treatment context. The clinical, hormonal, cytogenetic, imaging, and histopathological findings strongly supported the diagnosis of CAIS.

CONCLUSIONS :CAIS should be considered in phenotypically female individuals presenting with primary amenorrhea, particularly in the presence of markedly elevated testosterone. Early genetic evaluation is important for enabling genetic counselling , and supporting individualized long-term management. Multidisciplinary care is essential for optimal diagnosis, treatment, counselling, and follow-up.

Acknowledgements: We sincerely thank the patient for her cooperation, the CRGM Bihor Committee for their valuable support and all colleagues and health care professionals who contributed to the diagnosis, clinical evaluation and follow-up of the patient.

Small Stature, Big Picture: Decoding the Ultra-Rare Genetic Syndromes Masked by Prenatal IUGR

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Background: Intrauterine growth restriction (IUGR) is often a nonspecific marker of an underlying genetic disorder. Whole exome sequencing (WES) has proven diagnostic value postnatally, and its extension to the prenatal period is increasingly discussed as a way to shorten the diagnostic pathway, since prenatal ultrasound cannot fully capture the postnatal phenotype.

This study illustrates the diagnostic value of postnatal WES in idiopathic prenatal IUGR, supporting its extension prenatally.

Methods: A cohort of 5 patients with isolated prenatal IUGR who underwent postnatal WES, resulting in rare and clinically serious genetic diagnoses, was evaluated through clinical, imaging, and genetic review.

Results: These cases yielded five distinct, ultra-rare diagnoses: Koolen-de Vries syndrome with co-occurring Floating-Harbor syndrome, chromosome 10q26 deletion syndrome, Witteveen-Kolk syndrome with developmental and epileptic encephalopathy type 4, Rubinstein-Taybi syndrome type 1, and autosomal recessive limb-girdle muscular dystrophy type 18. Most patients shared motor and/or language delay, craniofacial dysmorphism, hypotonia, and intellectual disability.

Notably, the muscular dystrophy diagnosis was not suspected clinically even postnatally, as the phenotype mimicked the other neurodevelopmental cases- the diagnosis emerged only through WES.

Conclusions: Isolated prenatal IUGR may mask severe, ultra-rare genetic disorders with neurodevelopmental and/or neuromuscular impact, undetectable by ultrasound alone and, in some cases, not clinically apparent even after birth. These findings support extending WES to the prenatal period to shorten the diagnostic pathway, provided it is accompanied by rigorous genetic counseling addressing the unpredictability of phenotype and the management of VUS.

Keywords: IUGR, WES, prenatal diagnosis, ultra-rare genetic disorders, genetic counseling".

Acknowledgements: We gratefully acknowledge the Regional Center for Medical Genetics Dolj and the clinical and genetic teams involved in the diagnosis and evaluation of these cases.

CRGM BIHOR – EXPERIENCE OF A PILOT CENTER IN NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY

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Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by biallelic pathogenic variants in SMN1. Newborn screening enables presymptomatic diagnosis and timely disease-modifying therapy. In Romania, a pilot SMA newborn screening program was launched in August 2022 at the National Clinical Center for Children's Neuropsychomotor Recovery "Dr. Nicolae Robănescu" in Bucharest. In September 2025, the Regional Center of Medical Genetics Bihor (CRGM Bihor) launched a complementary county-wide program.

Materials and Methods: Newborns from public and private maternity hospitals in Bihor County were screened after parental informed consent. Dried blood spot samples were analyzed using the SALSA® MC002 SMA Newborn Screen (MRC Holland) for homozygous deletion of SMN1 exon 7. Inconclusive results were evaluated by multiplex ligation-dependent probe amplification (MLPA).

Results and Discussion: From September 2025 through August 24, 2026, 4,353 births were recorded, and 4,323 newborns were screened, corresponding to 99.3% coverage. No newborn screened positive for homozygous deletion of SMN1 exon 7. One inconclusive result underwent confirmatory MLPA and was identified as an SMA carrier. The high participation rate indicates strong program uptake.

Conclusions: County-wide SMA newborn screening achieved high coverage and proved feasible in routine practice. The program was funded entirely through donations, highlighting the need for sustainable public funding to ensure continuity and equitable access.

Keywords: spinal muscular atrophy; newborn screening; SMN1; dried blood spot; MLPA

Acknowledgements: The authors gratefully acknowledge all sponsors, donors, and supporting organizations whose support made the Bihor County SMA newborn screening program possible.

INTEGRATING CONVENTIONAL KARYOTYPING AND FISH IN THE CYTOGENETIC CHARACTERIZATION OF ACUTE LEUKEMIAS: A TERTIARY CENTER EXPERIENCE

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Objective

To illustrate the complementary contribution of conventional karyotyping and fluorescence in situ hybridization (FISH) to the cytogenetic characterization of acute leukaemia through selected cases with complementary or discordant findings.

Materials and Methods

A retrospective descriptive analysis was performed on 26 acute leukaemia cases selected from patients investigated at the Cytogenetics Laboratory of Fundeni Clinical Institute between January 1 and May 31, 2026. Conventional Giemsa–Trypsin–Giemsa (GTG) banding and FISH using disease-oriented probe panels were performed, and findings from both techniques were comparatively analysed.

Results

Among the 26 selected cases, clinically relevant FISH abnormalities were identified in two cases (7.7%) with conclusive normal karyotypes and in nine cases (34.6%) with absent or inconclusive karyotypes. Two additional cases (7.7%) with normal karyotypes showed abnormal FISH signal patterns despite the absence of the targeted rearrangements. In 11 cases (42.3%), abnormal karyotypes and FISH findings provided concordant or complementary information, with karyotyping additionally revealing numerical and structural abnormalities, including complex karyotypes. In two cases (7.7%), complex chromosomal abnormalities were identified by karyotyping despite no targeted abnormality being detected by FISH.

Conclusions

Conventional karyotyping and FISH provide complementary information in acute leukaemia evaluation. Selected cases illustrate the ability of FISH to reveal targeted abnormalities or abnormal signal patterns not apparent by karyotyping, while conventional karyotyping provides genome-wide chromosomal context beyond targeted FISH analysis. Their integrated use enables a more comprehensive cytogenetic characterization relevant to disease classification and prognostic stratification.

Acknowledgements: We acknowledge the entire team of the Cytogenetics Laboratory, Fundeni Clinical Institute, for their contribution to this study.

A case report of atypical Alport syndrome presenting with acute abdominal pain

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Background

Alport syndrome is a clinical and genetical heterogenous disorder which affects the type IV collagen networks in basement membranes involving the kidneys, the eyes and the ears.

Acute intermittent porphyria is a genetically disorder resulting from mutations that disrupt heme metabolism. Most common clinical manifestation is severe abdominal pain in young patients. Other important findings are gastrointestinal disturbances, peripheral neuropathy and neuropsychiatric manifestations.

Case presentation

We present the case of a 26 years old male with a history of repeated episodes of acute abdominal pain of unexplained cause associated with constipation, rectorragia, weight loss and paresthesia.

The MRI examination showed an area of mucosal and submucosal edema in the middle and inferior rectal wall and an infundibular angulated gallbladder.

Urine dipstick was with small amount of erythrocytes and leukocytes and negative for proteins.

Further investigations including elevated urinary protoporphyrins pointed towards a clinical diagnosis of acute intermittent porphyria.

Genetic testing was done to asses the exact mutation of the disorder and the result was positive for Alport syndrome with autosomal dominant transmission in COL4A3 gene. Further examination are needed to asses the phenotype for Alport syndrome in this case.

Conclusion

This case highlights the importance of genetic testing for rare disorders as the clinical manifestation can be misleading in diseases which present with symptoms that can mimic other medical and psychiatric conditions. Furthermore, the use of next-generation sequencing was definitive for an accurate diagnosis as genetic testing is moving to broad-spectrum tools.

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Utility and limitations of LIRICAL and Phenomiser for phenotype-driven disease prioritization in an epilepsy whole-exome sequencing cohort

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Background and objective: Phenotype-driven tools can support exome interpretation, but a highly ranked disorder is not equivalent to a molecular diagnosis. We assessed the practical utility and limitations of LIRICAL and Phenomiser in an epilepsy cohort.

Methods: We retrospectively studied 60 patients with epilepsy investigated by whole-exome sequencing. Clinical findings were encoded as Human Phenotype Ontology (HPO) terms. Molecular interpretation considered variant classification, gene–disease association, genotype–phenotype correlation, zygosity, inheritance, disease mechanism and available segregation data. Cases were classified as solved, candidate, VUS-only or unsolved for research purposes only; these assignments did not represent clinically validated or patient-reported diagnoses. Phenotype-driven prioritization was performed using LIRICAL and JAX Phenomiser v0.2.2, compiled and run locally through its command-line interface using HPO data files. In solved cases, retrieval of the research-level molecular assignment within the top 1, 3, 5 or 10 results was assessed. Outputs were categorized as helpful, supportive, non-informative or unsupported by molecular evidence.

Results: LIRICAL and Phenomiser showed variable concordance with variant-based interpretation. Some outputs supported molecularly favored diseases or genes, whereas others ranked disorders lacking adequate support from variant pathogenicity, inheritance or disease mechanism. Sparse or nonspecific phenotyping reduced discriminatory value.

Conclusions: LIRICAL and Phenomiser can structure disease prioritization, but their outputs require integration with variant pathogenicity, inheritance and molecular disease mechanisms and should not be equated with diagnostic confirmation.

Acknowledgements: We gratefully acknowledge the Broad Institute for whole-exome sequencing and the clinical team at the Dr. Victor Gomoiu Clinical Children's Hospital for clinical phenotyping, HPO annotation, and collection of clinical data.

Perinatal impaired cytokine response in at risk pregnant women. The MERSIN study (Myeloid dERived suppressor cells – Role in Severe INfections)

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Background. Pregnancy requires fine immunological tuning in order to protect mother and fetus, while ensuring antimicrobial protection. The physiological immune response may be altered in high-risk perinatal conditions—chorioamniotitis and pre-eclampsia, with the overall result of marked inflammatory and cytotoxic effects. The MERSIN study aimed to characterize immune response changes in normal and high-risk pregnancies, and to identify immune markers predicting perinatal sepsis in the mother and/or neonate.

Methods. The MERSIN study included 18 pregnant women admitted to the Department of Obstetrics and Gynecology of the County Clinical Emergency Hospital Craiova, classified by either normal or high-risk pregnancies. Clinical data was collected using standardized interview forms. Samples were collected at 3 timepoints of the perinatal timeline. PBMCs were isolated from whole blood, and stimulated with clinically relevant sepsis pathogens or with purified PAMPs (pathogen-associated molecular patterns), for 24 hours and for 7 days. The immune response was quantified using ELISA (Enzyme-Linked Immunosorbent Assay), by measuring relevant pro- and anti-inflammatory cytokines.

Results. Preliminary analysis indicates peak levels of IL-6 in the period before birth, in the presence of bacterial stimuli, for high-risk pregnancies, when compared to those with a normal course. Interestingly, a reverse image is registered for IL-1 β levels. The trend would argue for a more pro-inflammatory status in high-risk pregnancies before and immediately after birth. **Conclusions.** Less physiological immunosuppression for pregnancies at risk was described around the moment of birth. Characterizing these divergent cytokine landscapes may reveal mechanisms driving perinatal complications and identify interventions directed to restore immune equilibrium.

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Learning from Family History: A Neonatal Death as a Clue to Inherited Metabolic Diseases—Lessons from Argininosuccinic Aciduria

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Background: Timely diagnosis of Inherited Metabolic Diseases (IMDs) is critical for patient survival. Amino acids chromatography and proton nuclear magnetic resonance (¹H NMR) spectroscopy serves as an efficient screening tool that prevent delays in the management of small molecules disorders.

Case Report: A newborn boy experienced clinical deterioration three days after starting breastfeeding. He presented axial hypotonia, lethargy, seizures and hiccups. Sepsis was ruled out, raising suspicion of an IMD. Notably, his sister had died three years earlier without a definitive diagnosis; her postmortem tandem mass spectrometry (MS/MS) showed abnormalities that remained inconclusive due to postmortem metabolic artifacts. Blood and urine samples were collected prior to initiating protein restriction. Two-dimensional thin-layer chromatography (2D-TLC) identified elevated urinary argininosuccinic acid (Asa) and an anhydride metabolite, while ¹H NMR spectroscopy identified ASA and orotic acid, both pointing to argininosuccinate lyase (ASL) deficiency, or argininosuccinic aciduria (ASA). Biochemical tests also showed hyperammonemia and low blood urea. With timely treatment, the prognosis was favorable, and further dietary plans are taken into account. Conclusions: A careful family history, particularly a previous unexplained neonatal death, may provide a diagnostic clue to an IMD. In healthcare settings where expanded newborn screening is unavailable, selective screening for amino acid disorders, complemented by NMR spectroscopy, can rapidly identify or narrow the differential diagnosis. Reliable results are particularly valuable in emergency settings for patients with acute metabolic decompensation.

Keywords: hyperammonemia, argininosuccinic aciduria, NMR spectroscopy, Inherited metabolic disease, argininosuccinate lyase.

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Genotype-phenotype correlations in patients with neurodevelopmental disorders investigated by next-generation sequencing (NGS) - experience of a regional center and implications for personalized medicine

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Introduction: Genetic testing in neurodevelopmental disorders (NDD) is increasingly integrated into diagnostic algorithms, with literature shifting focus from raw diagnostic yield toward clinical actionability - whether a genetic result changes patient management. Correct interpretation of NGS results first requires rigorous classification of genotype-phenotype concordance. Objective: To describe genotype-phenotype correlations and classify NGS results by concordance with the referral phenotype in a cohort of NDD patients investigated at a regional genetics center. Material and method: Descriptive, retrospective study of 18 NDD patients (autism spectrum disorder, ADHD, language disorders) tested by NGS. Referral reason and genetic result (sequence variants, CNV analysis, ACMG classification) were analyzed for each patient. Results were classified as: pathogenic/likely pathogenic concordant with phenotype; VUS with literature-supported phenotypic correlation; VUS without established correlation; and negative. Results: 6 patients (33.3%) had a pathogenic/likely pathogenic result concordant with phenotype, 4 (22.2%) had VUS with supported phenotypic correlation, 4 (22.2%) had negative results, and 4 (22.2%) had VUS without established correlation. Illustrative cases include trisomy X (47,XXX) concordant with language delay, and a DDX3X variant associated with syndromic X-linked intellectual developmental disorder, alongside incidental variants unrelated to the testing indication. Conclusions: Systematic classification of genotype-phenotype concordance is essential for clinical interpretation of NGS results, distinct from ACMG categorization alone. Genetic testing is increasingly central to personalized medicine in NDD, guiding therapeutic decisions, comorbidity monitoring, and genetic counseling - underscoring the need for prospective studies correlating genetic results with patient management trajectories.

Psychological Impact and Interdisciplinary Management in Achondroplasia: From Genetics to Quality of Life

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This paper offers a comprehensive view of achondroplasia, from its genetic basis to how related complications affect patients' mental health. It outlines the multidisciplinary care pathway, the mechanisms linking chronic psychosocial stress to gene expression, and the role of physician-patient collaboration in quality of life.

Achondroplasia results from a mutation in the FGFR3 gene (4p16.3), impairing growth-cartilage proliferation and bone development. Early family counseling, started at diagnosis, supports psychological adaptation and reduces isolation.

Pediatrics serves as first contact and coordinator, referring patients to Genetics, Endocrinology, Neurology, and Orthopedics, ensuring continuity of somatic and psychological care. Endocrinology and Nutrition monitor obesity risk from reduced basal metabolism and body disproportion. Neurology and Orthopedics track spinal stenosis, foramen magnum compression, and limb development, preventing deformities and chronic pain. ENT and Sleep Medicine manage adenoid hypertrophy and respiratory issues. Each complication has a psychological counterpart: anxiety, isolation, loss of independence, fatigue, and emotional lability, making management an integrated response, not separate interventions.

Prolonged psychosocial stress triggers HPA axis overactivation, cortisol elevation, and NR3C1 methylation, reducing hippocampal regulation of this response. Methylation of BDNF reduces neuroplasticity. These mechanisms increase vulnerability to anxiety and depression, showing psychological impact both results from and shapes disease progression.

Physician-patient collaboration is the foundation of quality of life, built on open communication, shared decisions, education, and monitoring adjusted to feedback. Mutual trust underpins adherence.

Quality of life in achondroplasia depends on collaboration among specialties and family, psychological support from diagnosis onward, and a trust-based partnership between physician and patient.

"Genes outline our limits, but quality of life goes beyond them."

The Dynamic Genome: Somatic mosaicism across the lifespan - from early embryonic mutagenesis to age-related clonal selection in human disease

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Background: Somatic mosaicism is an intrinsic feature of human biology, arising from post-zygotic mutations accumulating throughout life. Advances in sequencing revealed distinct cellular clones across tissues, whose distribution and abundance are shaped by mutation timing, tissue-specific mutational processes, and cellular selection.

Objective: To examine somatic mosaicism across the lifespan, from embryonic mutagenesis to age-related clonal selection and disease.

Methods: We examined genomic and disease studies, focusing on mutational burden, tissue-specific signatures, variant frequencies, developmental timing, and clonal dynamics.

Results: Somatic mosaicism accumulates throughout life, with clone size shaped by mutation timing, tissue-specific processes, and cellular selection. Age-dependent clonal selection has been demonstrated in haematopoiesis, where specific mutations can promote preferential clonal expansion. In other tissues, these dynamics remain less understood, although inflammation, DNA damage, cellular stress, and telomere attrition may promote mutant clone expansion and increase disease risk.

Discussion: Recent evidence suggests that somatic clone size reflects both the timing of mutational events and subsequent age-dependent selection. This is particularly evident in clonal haematopoiesis, where mutations confer biological advantages through distinct mechanisms: alterations in RNA splicing, such as SRSF2 and SF3B1, are associated with adaptation to telomere attrition, whereas PPM1D mutations can alter DNA-damage responses and TERT mutations may influence telomere maintenance. These findings support a context-dependent model in which age-related changes in the tissue environment alter cellular fitness and promote expansion of mutant clones.

Conclusion: Understanding how clones emerge and undergo selection across life may clarify the transition from physiological to pathological clonal evolution, providing new insights into disease.

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Marfan Syndrome: Variable Expressivity and Cascade Testing in a Family — Mother and Two Children

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Background: Marfan syndrome is an autosomal dominant connective tissue disorder caused by mutations in the *FBN1* gene, encoding fibrillin-1, a structural glycoprotein essential for extracellular matrix microfibril integrity. Estimated prevalence is 1 in 5,000–10,000, with multisystemic involvement primarily affecting the cardiovascular, ocular, and skeletal systems, and marked clinical variability even within the same family.

Case Presentation: We report a familial case of Marfan syndrome involving a mother and her two children. The index cases were the two children (aged 10 and 3 years), initially diagnosed according to the revised Ghent criteria. Given the autosomal dominant inheritance pattern, the mother (37 years old) was subsequently evaluated through cascade genetic testing and confirmed to carry the same *FBN1* mutation (NM_000138.5:c.6872-1G>A). Comparative clinical assessment revealed variable expressivity: the mother presented tall stature, mitral valve prolapse, and ligamentous hyperlaxity without ocular involvement; Child 1 exhibited severe pectus excavatum, kyphoscoliosis, congenital bilateral cataract, strabismus, and mitral insufficiency/prolapse; Child 2 showed scoliosis, pectus carinatum, convergent strabismus, and mitral prolapse with mild aortic root dilation.

Management: An individualized monitoring plan (echocardiography, ophthalmology, orthopedics) was established for each affected member, along with beta-blocker initiation, activity restriction, and genetic counseling for the extended family.

Conclusions: This case highlights the marked clinical variability of Marfan syndrome within a single family and underscores the value of cascade genetic testing for early diagnosis in asymptomatic first-degree relatives. A multidisciplinary approach—cardiology, ophthalmology, medical genetics, and orthopedics—remains essential. A single positive genetic test in a parent should prompt systematic evaluation of all first-degree relatives, as early diagnosis in children can prevent fatal aortic complications. Generalizability is limited by the single-family design; longitudinal follow-up and extended family testing are warranted.

Beyond common-mutation panels: whole-gene CFTR next-generation sequencing in a Romanian cohort referred for cystic fibrosis suspicion

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Background: Cystic fibrosis (CF) and CFTR-related disorders vary geographically in their molecular spectrum. Targeted carrier-screening panels, including the 2023 ACMG minimum set of 100 variants, detect only well-established alleles and may miss rarer variants and single pathogenic alleles relevant to carrier status. The Romanian CFTR landscape remains incompletely characterized. We assessed the diagnostic yield and variant diversity of whole-gene NGS in a cohort referred for CF suspicion and quantified disease alleles falling outside the ACMG-100 panel.

Methods: We retrospectively analyzed 61 unrelated individuals referred for suspected CF, tested in May 2026. The entire CFTR gene was sequenced with the Devyser CFTR CE-IVD kit (Illumina NextSeq 550), covering coding exons, flanking intronic regions, the promoter and deep-intronic targets. Variants were analyzed in Amplicon Suite and classified per ACMG/AMP criteria using ClinVar, CFTR2 and Franklin. Each allele was checked against the 2023 ACMG 100-variant set. Compound genotypes are reported without cis/trans phasing. **Results:** Of 61 individuals, 12 (20%) received molecular confirmation of CF (two pathogenic/likely pathogenic alleles), 12 (20%) carried a single P/LP allele, and 37 (61%) were negative; no variants of uncertain significance were reported. p.Phe508del was the most frequent allele but rarely the sole finding. In 8 of 12 confirmed patients, at least one disease allele lay outside the ACMG-100 panel, so panel-based genotyping would have missed the diagnosis, returning only a carrier result.

Conclusions: Whole-gene CFTR NGS identified disease alleles beyond the ACMG-100 panel in most confirmed patients and detected carriers missed by panel-oriented reporting, supporting it as a first-tier approach and providing a regional CFTR reference for Romanian diagnosis and genetic counseling.

Temporal integration of mRNA and lncRNA expression identifies candidate cis-regulatory signatures in post-infarction cardiac remodeling

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Background: Myocardial infarction (MI) induces transcriptional changes that persists beyond the acute phase, whose modulation by mesenchymal stem cell (MSC) treatment and lncRNAs remains unclear. We integrated mRNA and lncRNA profiles in a murine MI model to identify post-MI transcriptional signatures and candidate regulatory interactions associated with MSC.

Methods: RNA-seq data from 36 cardiac tissue samples (Sham, MI, and MI+MSC) across four timepoints (days 3, 7, 14, 28 post-MI) were analyzed with DESeq2 with an interaction model estimating total group effects per timepoint. Differentially expressed mRNAs and lncRNAs were identified using adjusted $p < 0.05$ and predefined fold-change thresholds, followed by KEGG/GO enrichment. Transcripts persistently dysregulated across all timepoints were cross-referenced with genomic co-localization data to prioritize candidate cis-regulatory pairs.

Results: Compared to sham, MI induced a marked transcriptional response, with enrichment shifting from acute inflammation at day 3 toward extracellular matrix organization, and integrin/collagen pathways at days 14-28. A persistent core of 111 mRNAs and 61 lncRNAs was dysregulated across all four timepoints. Genomic co-localization identified 21 candidate cis-regulatory lncRNA-mRNA pairs, including 13 concordantly upregulated pairs involving fibrosis genes (Col12a1, Loxl3, Ltbp2 and Adamts16) and eight downregulated pairs involving metabolic genes (Lpl, Fmo2, Xdh and Thrsp). The MSC response peaked at day 7 and was largely absent by day 28.

Conclusion: Temporal integration of mRNA and lncRNA expression revealed a persistent post-infarction transcriptional core and prioritized cis-regulatory pairs potentially involved in cardiac remodeling, offering targets for functional validation. The transient MSC response suggests limited long-term modulation of the post-MI program.

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Molecular Spectrum of Polycystic Kidney Disease Diagnosed by NGS Using the TruSight One Panel at the Regional Centre of Medical Genetics Timiș

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Background: Polycystic kidney disease comprises a genetically heterogeneous group of inherited kidney disorders with overlapping clinical phenotypes. Next-generation sequencing (NGS) enables simultaneous assessment of multiple genes associated with cystic kidney diseases and ciliopathies. Methods: We retrospectively reviewed 33 consecutive patients tested between 2019 and 2025 at the Regional Centre of Medical Genetics Timis using the TruSight One Clinical Exome Panel (Illumina). Variants were classified by ACMG/AMP 2015 criteria; clinical and family-history data were extracted from consultation records; associations with diagnostic yield were assessed by Fisher's exact test. Results: The cohort comprised 19 females and 14 males; median age at diagnosis was 9 years (1 month–50 years), with 26 (78.8%) pediatric patients. Pathogenic or likely pathogenic variants were identified in 20/33 patients (60.6%). Including variants of uncertain significance (VUS), PKD1 was involved in 15 cases, PKD2 in 8 and PKHD1 in 3 — a PKD1:PKD2 ratio of 1.9:1, well below European cohorts. Truncating changes accounted for 15/26 (57.7%). PKD2 c.916C>T p.(Arg306Ter) occurred in seven apparently unrelated patients (87.5% of PKD2 cases); this local enrichment explains the atypical ratio and indicates a region-specific variant distribution. Positive family history was associated with higher diagnostic yield (88% vs 38%; $p=0.016$). VUS were the sole finding in five patients (15.2%), three received an alternative diagnosis (HNF1B, CYP24A1, SLC26A1) and four (12.1%) were negative. Conclusion: The panel established a molecular diagnosis in over half of the patients. Family history was the strongest predictor of diagnostic yield, and the unusually low PKD1:PKD2 ratio, driven by one recurrent PKD2 variant, underlines the regional specificity of the molecular spectrum.

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Genetic Counselling in Inherited Cardiomyopathies: Clinical Case Series

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Background: Inherited cardiomyopathies affect approximately 1 in 250 to 1 in 500 individuals globally, primarily driven by key sarcomeric, desmosomal and cytoskeletal gene variants that alter myocyte structural integrity, contractility and electrical activity. Due to marked genetic heterogeneity and incomplete penetrance, translating molecular findings into patient management requires a close multidisciplinary collaboration between the cardiology specialist and the medical geneticist. This study presents a clinical case series to evaluate genetic counselling protocols, risk communication models, and cascade screening workflows.

Methods: Representative cases were selected from a broad clinical cohort. Pre-test visits involved clinical and paraclinical examination, three-generation pedigree construction and clinical risk assessment. Molecular evaluation utilized next-generation sequencing with the TarCET Cardiac Comprehensive Panel on the Illumina NextSeq 550 platform. Bioinformatic analysis was performed using Medicover TarCET Sirius, followed by variant classification via VarSome Clinical. Post-test management included genotype disclosure, clinical actionability planning and predictive testing coordination for at-risk relatives.

Results: Pre-test visits established precise phenotype characterization alongside pedigree mapping to refine diagnostic suspicion and identify unflagged familial risk. Post-test visits communicated complex concepts of variable expressivity and age-dependent penetrance, enabling informed decision-making regarding clinical surveillance and lifestyle modifications. Structured cascade screening enabled the identification of asymptomatic carriers for longitudinal surveillance.

Conclusions: Integrating structured genetic counselling into routine clinical practice ensures that genetic testing results are safely translated into personalized patient management. Active collaboration between cardiologists and medical geneticists is essential for bridging genomic findings with bedside care and establishing standardized pathways in precision cardiology.

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Transcriptional profiling of immune cells reveals a role for IFN γ /CXCL9/CXCL10 pathway in sepsis patients with exaggerated inflammation

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Background: Sepsis is a life-threatening condition marked by immune dysregulation. Rather than treating sepsis as a homogeneous entity, contemporary approaches aim to identify distinct patient endotypes to facilitate personalized medicine. This study investigates immune dysregulation in sepsis patients characterized by exaggerated inflammation.

Methods: Peripheral blood mononuclear cells (PBMCs) from 124 sepsis patients and 299 healthy volunteers (FUSE project) were analyzed using RNA sequencing, and inflammatory profiles by proximity extension assay technology. Patients were classified into "High Inflammatory" and "Low Inflammatory" endotypes based on proteomic status. Differential gene expression was assessed with DESeq2, controlling for age and gender; adjusted p-value < 0.05 was considered significant. Pathway enrichment used Over-Representation Analysis.

Results: Sepsis patients exhibited transcriptional upregulation of innate immune pathways, including 'antimicrobial peptides' (S100A8, S100A9, TLR2), 'regulation of Toll-like Receptors' (TLR4, CD14), and 'interferon-alpha/beta signaling' (ISG15, IFI27). Adaptive immunity pathways, such as 'T cell activation and differentiation' (BCL11B, GATA3, CD247), were downregulated. No significant transcriptomic differences were found between pneumosepsis and urosepsis, suggesting that disease severity rather than etiology influenced the immune response. Comparing endotypes, transcriptomic analysis revealed significant upregulation of the interferon-gamma-driven chemokines CXCL9 and CXCL10 in the "High Inflammatory" group. These chemokines recruit activated T cells and modulate inflammatory responses, indicating a potential interferonopathy in this subgroup.

Conclusion: Immune dysregulation in sepsis is primarily driven by disease severity. Upregulation of the interferon-gamma-CXCL9-CXCL10 pathway in the "High Inflammatory" endotype underscores the importance of identifying patient endotypes to advance personalized medicine in sepsis management and may guide targeted therapeutic strategies.

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Beyond Statural Gain: Evolution of BMI and Anthropometric Profile During Vosoritide Treatment in Patients with Achondroplasia

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Background: Achondroplasia is characterized by disproportionate short stature and a distinct anthropometric profile, which limits the isolated interpretation of body mass index (BMI). Although the effect of vosoritide on linear growth is well documented, the evolution of other anthropometric parameters during treatment requires further characterization.

Materials and Methods: We performed a retrospective longitudinal analysis of a cohort of 20 patients with molecularly confirmed achondroplasia (FGFR3 p.Gly380Arg), comprising 170 clinical evaluations. Vosoritide treatment was documented in 19 patients, 18 of whom had longitudinal post-treatment evaluations. Linear growth, weight status, waist circumference, waist-to-height ratio, and body proportionality indices were analyzed. Intraindividual baseline-to-last-available-evaluation comparisons used the Wilcoxon test, and exploratory associations used Spearman's coefficient.

Results: Height-SDS improved significantly, from -3.44 to -3.16 ($\Delta=+0.28$; $p=0.030$). Weight increased from 20.48 to 24.36 kg, with no significant change in BMI-SDS (0.69 vs. 0.52; $p=0.347$). Waist-to-height ratio decreased significantly (0.595 vs. 0.549; $p<0.001$), while waist circumference remained statistically stable. Arm span/height and sitting height/height did not change significantly. The statural response was not significantly correlated with changes in BMI-SDS or waist-to-height ratio.

Conclusions: In the cohort analyzed, vosoritide was associated with improved linear growth without deterioration of BMI-SDS. The heterogeneity of individual trajectories supports a multidimensional evaluation of anthropometric response, beyond statural gain alone.

The Immunogenetics of Recurrent Pregnancy Loss: What the Evidence Tells Us

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Recurrent pregnancy loss (RPL) is defined by the American Society for Reproductive Medicine as two or more failed pregnancies, excluding molar/ectopic pregnancies and implantation failure; the European Society of Human Reproduction and Embryology applies a 24-week threshold. It affects 1–2% of women, with up to 50% of cases idiopathic. This narrative review examines the genetic architecture underlying immune dysregulation in RPL.

A PubMed and Google Scholar search targeted human leukocyte antigen (HLA) and killer-cell immunoglobulin-like receptor (KIR) polymorphisms, partner HLA sharing, downstream immune phenotype, and microRNA (miRNA) regulation. Eleven studies (2018–2026) were selected, prioritising meta-analyses and syntheses over primary reports.

Disrupted maternal–fetal tolerance is central to RPL pathogenesis, involving abnormal decidual natural killer (dNK) cell activation, skewed T helper 17/regulatory T cell balance, dysregulated vascular endothelial growth factor A, interferon-gamma and tumour necrosis factor alpha signalling, and altered macrophage polarisation. Emerging evidence indicates miRNA dysregulation, including within dNK cells.

At the genomic level, HLA-G polymorphisms (the 3' untranslated region 14-bp insertion/insertion genotype, miRNA-binding-site single-nucleotide polymorphisms, and 5' upstream regulatory region variants) are associated with increased RPL risk. Concordant risk genotypes in both partners exert a cumulative effect. Evidence on KIR–HLA combinations remains inconsistent, although maternal KIR-AA with fetal HLA-C2 is more frequent in affected cohorts. Excessive HLA-B/HLA-DR sharing was proposed to impair maternal tolerogenic responses to paternal antigens, but this has not been consistently replicated.

Immunogenetic profiling may support personalised diagnostics and targeted immunomodulation, but evidence remains heterogeneous, and genetic biomarkers require validation before clinical integration.

Decoding Neonatal Lactic Acidosis: A Biochemical Signature of Mitochondrial Anaplerotic Dysfunction

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Introduction: Pyruvate carboxylase (PC) is a biotin-dependent mitochondrial enzyme converting pyruvate to oxaloacetate, a critical anaplerotic reaction that replenishes TCA-cycle intermediates. PC therefore links pyruvate metabolism with mitochondrial energy production, gluconeogenesis, aspartate synthesis, and nitrogen metabolism.

Case presentation: A male neonate with antenatally diagnosed ventriculomegaly presented with respiratory distress, hypotonia, and severe metabolic acidosis. Blood lactate was 10.2 mmol/L, while ammonia progressively increased to 233 μ mol/L. Transfontanellar ultrasonography revealed cystic lesions of the periventricular white matter. Plasma amino acid chromatography showed increased alanine, while urinary amino acids revealed increased citrulline, lysine, and ornithine. Urinary ¹H NMR spectroscopy demonstrated massive lactic aciduria (8000 mmol/mol creatinine; reference <285), together with increased 4-hydroxyphenyllactate and 3-hydroxyisovalerate. The integrated clinical and biochemical findings suggested PC deficiency type B.

Discussion: Impaired pyruvate-to-oxaloacetate conversion limits mitochondrial anaplerosis and TCA-cycle replenishment, redirecting pyruvate toward lactate and alanine. Oxaloacetate depletion may also reduce aspartate availability, linking defective mitochondrial carbon metabolism to impaired urea-cycle flux and secondary hyperammonaemia. This profile therefore reflects interconnected disturbances of mitochondrial energy, carbon, and nitrogen metabolism.

Conclusions: In neonates with severe lactic acidosis, massive lactic aciduria, hyperalaninaemia, and hyperammonaemia, associated with increased citrulline and lysine without glutamine elevation, should raise suspicion of defective mitochondrial anaplerosis rather than a primary urea-cycle disorder. Urinary ¹H NMR spectroscopy can rapidly identify this distinctive metabolic profile, guiding targeted investigations and supportive management pending molecular confirmation.

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MicroRNA Expression in Myeloproliferative Neoplasms

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Introduction

Myeloproliferative neoplasms (MPNs) (BCR::ABL1-negative) are clonal hematological diseases characterized by abnormal proliferation of the myeloid lineage. MicroRNAs play a significant role in tumorigenesis and metastatic spread, and their dysregulation has been identified in many hematological malignancies. Our objective was to evaluate the expression levels of miR-223 and miR-125b in a group of patients diagnosed with MPN - essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).

Materials and Methods

We enrolled unrelated subjects with MPN and healthy controls. Blood samples from all participants were collected in EDTA tubes. We extracted total RNA using the mirVana miRNA Isolation Kit with phenol. We also used TaqMan MicroRNA Reverse Transcription Kit and TaqMan miRNA primers, and specific TaqMan™ assays for hsa-miR-223-3p and hsa-miR-125b-5p.

Results

We observed higher miRNA-125b-5p expression in MPN patients. MiRNA-223-3p expression levels are comparable between patients and healthy individuals. MiRNA-223-3p and miRNA-125b-5p expression levels were also comparable between patients with and without thrombotic events, including major, arterial, and venous thrombosis (all $p > 0.05$). No consistent pattern of differential expression was observed in relation to thrombotic status. We observed a statistically significant association between JAK2 status and miR-125b-5p expression in PV.

Conclusion

MiR-125b-5p was significantly overexpressed in MPN patients, suggesting a potential role in MPN pathogenesis, while miR-223-3p showed no significant differences. The association between miR-125b-5p expression and JAK2 status in PV may indicate a link to the disease's molecular background.

Key words:

Myeloproliferative neoplasms, miRNA, miR-125b-5p, miR-223-3p, thrombosis

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Beyond an Adverse Drug Reaction: The Genetic Perspective on Valproate-Induced Hyperammonaemia

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Introduction: Valproic acid is a widely used anticonvulsant associated with several metabolic adverse effects, including hyperammonemic encephalopathy. By interfering with mitochondrial metabolism and urea-cycle function, valproate-induced-hyperammonemia may mimic or unmask an inherited urea-cycle disorder, including carbamoyl phosphate synthetase I deficiency.

Case report: A 12-year-old boy treated with valproate for seizures developed hyperammonemic encephalopathy, presenting with lethargy, somnolence, speech disturbances, and persistent nausea. Blood ammonia was elevated, while plasma and urinary amino acid analyses revealed increased glycine. Urinary ¹H NMR spectroscopy identified increased orotic and α -ketoglutaric acids. Valproate was discontinued and intravenous arginine–sorbitol was administered, followed by a rapid decrease in ammonia levels and clinical improvement. Repeat plasma and urinary amino acid analyses after valproate withdrawal showed normalization of glycine levels, supporting a valproate-related metabolic effect. **Discussion:** Valproate-induced-hyperammonemia may impair the tricarboxylic acid cycle through α -ketoglutarate depletion. Valproate also interferes with carbamoyl phosphate synthetase I activity and N-acetylglutamate availability, potentially mimicking its deficiency. Elevated urinary orotic acid may suggest an underlying ornithine transcarbamylase deficiency. Importantly, valproate-induced mitochondrial toxicity is particularly severe in patients with the more recently recognized involvement of POLG variants (encoding the mitochondrial DNA polymerase γ), who have an increased risk of hepatotoxicity. **Conclusions:** Valproate-induced hyperammonemia illustrates the close interplay between pharmacological effects and genetic susceptibility. Knowledge of underlying metabolic and mitochondrial disorders, particularly urea-cycle defects and POLG-related disease, is essential for interpreting atypical biochemical profiles, selecting appropriate genetic testing, and avoiding potentially harmful therapies.

Acknowledgements: We gratefully acknowledge the patient and his family for their contribution.

Tetrasomy 9p: Phenotypic Correlations and Challenges in Cytogenetic Characterization in a Pediatric Case

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Introduction: Tetrasomy 9p is a rare chromosomal anomaly with highly variable phenotypic expression influenced by mosaicism.

Materials and Methods: We analysed the clinical, cytogenetic, and paraclinical data from a multidisciplinary evaluation of a 2-year-old female patient.

Results: Prenatal microarray at 21 weeks' gestation indicated a ~42.5Mb copy number gain: arr[GRCh38] 9p24.3q21.11(61,210_68,377,760)x4. Postnatal karyotyping initially confirmed mosaic tetrasomy 9p due to a supernumerary pseudoisodicentric chromosome 9 [psu idic(9)(q21.11)] in 93% of analysed cells (28/30). Born at term (2,290 g; Apgar 3/8), she presented at age two with severe growth retardation and severe psychomotor developmental delay. Phenotypic features included microcephaly, brachycephaly, occipital plagiocephaly, microphthalmia with left-sided persistent hyperplastic primary vitreous, bilateral epicanthus, telecanthus, micrognathia, auricular and digital anomalies. Additional findings included feeding difficulties and infantile spasms, Dandy–Walker malformation, bilateral sensorineural hearing loss, bilateral hip/knee dislocations, renal pelvic dilatation, and mild tricuspid regurgitation. Repeated conventional karyotyping at our center revealed a non-mosaic supernumerary marker chromosome across all 70 metaphases, suggesting a cell-line shift over time or tissue-specific mosaicism.

Conclusions: This case underscores the cytogenetic and clinical complexity of tetrasomy 9p. Shifting or discordant cell-line proportions demonstrate that peripheral-blood profiles may not fully reflect global tissue distribution, supporting the need for integrated molecular, cytogenetic, and multidisciplinary assessments to guide individualised patient care.

Keywords: tetrasomy 9p, mosaicism, conventional karyotyping, genotype–phenotype correlation, genetic counselling.

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From vascular phenotype to molecular diagnosis: exome sequencing role in capillary malformation-arteriovenous malformation syndrome type 1

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Introduction: Capillary malformation-arteriovenous malformation syndrome type 1 (CM-AVM1) is a rare autosomal dominant vascular disorder with high penetrance and variable clinical expressivity even in the same family, caused by pathogenic variants in the RASA1 gene, and it is characterised by a range of vascular malformations. The RASA1 gene encodes a negative regulator, p120-RasGAP, of the RAS/MAPK pathway; heterozygous variants are loss-of-function mutations associated with haploinsufficiency, and recent literature supports the supplementary role of second-hit somatic events in the focal formation of vascular lesions.

Case presentation: We report the case of a child with multiple cutaneous capillary malformations and a complex intramedullary cervical vascular malformation that developed a severe neurological complication, with neurosurgical and endovascular intervention and later with favourable evolution and progressive neurological recuperation. Exome sequencing (ES) detected a heterozygous pathogenic frameshift variant in the RASA1 gene, confirmed by Sanger sequencing. The family history revealed cutaneous vascular lesions in other family members on the maternal line, suggesting familial aggregation. The cascade genetic testing by Sanger sequencing identified the same variant in a heterozygous genotype.

Conclusions: Our case highlights the possibility of severe complications at a young age in the context of limited cutaneous capillary malformations. Because capillary malformations can be discrete and may be the only initial sign, family testing in at-risk relatives is essential for earlier diagnosis, appropriate genetic counselling, and individual clinical surveillance of rare diseases with variable expressivity, to prevent complications. Integrating the phenotype with ES and Sanger validation supports molecular diagnosis of CM-AVM1 and family management..

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Severe Delayed Hemolytic Anemia in a Newborn with Maternal–Fetal Rh-c Incompatibility: A Diagnostic Challenge

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Background: Hemolytic disease of the fetus and newborn (HDFN) caused by non-D Rh antibodies remains an important cause of neonatal hyperbilirubinemia and anemia. Diagnosis may be challenging when initial immunohematological investigations are negative. We present a case of severe delayed neonatal hemolysis associated with maternal–fetal Rh-c incompatibility and evolving direct antiglobulin test (DAT) positivity. **Case presentation:** A term male newborn, delivered by cesarean section at 38–39 weeks of gestation, with a birth weight of 3390 g and Apgar scores of 9/10, was admitted on day 11 of life for marked jaundice. Total serum bilirubin was 24.10 mg/dL, with predominantly unconjugated hyperbilirubinemia, while the initial hemoglobin concentration was 14.0 g/dL. Despite intensive phototherapy and intravenous immunoglobulin administration, progressive hemolytic anemia developed, with venous hemoglobin values decreasing to 11.5, 9.5, and subsequently 7.1 g/dL. The DAT, initially negative, became positive (2+) on repeat testing, whereas the serum irregular red-cell antibody screen remained negative. Extended Rh phenotyping demonstrated a c-negative mother and a c-positive infant, establishing maternal–fetal Rh-c antigen incompatibility. Compatibility testing revealed incompatibility with selected donor red blood cell units in the antihuman-globulin phase. The newborn required two compatible red blood cell transfusions, followed by clinical and hematological improvement. Whole-exome sequencing did not identify a pathogenic or likely pathogenic variant explaining the acute hemolytic phenotype.

Discussion: The combination of severe unconjugated hyperbilirubinemia, rapidly progressive anemia, evolving DAT positivity, and Rh-c antigen incompatibility strongly suggested an immune-mediated mechanism. Maternal anti-c alloimmunization represented the most plausible etiology; however, it could not be definitively demonstrated because specific maternal antibody identification and neonatal erythrocyte elution were not performed. **Conclusion:** Severe immune-mediated neonatal hemolysis should remain a diagnostic consideration despite an initially negative DAT or antibody screen. Serial immunohematological testing, extended Rh phenotyping or genotyping, and timely antibody identification and elution studies may be essential for establishing the diagnosis and guiding appropriate transfusion management.

Keywords: hemolytic disease of the fetus and newborn; Rh-c incompatibility; neonatal hemolytic anemia; hyperbilirubinemia; direct antiglobulin test; alloimmunization.

Beyond a VUS: A Complex Phenotype

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Introduction: Interpretation of variants of uncertain significance (VUS) is particularly challenging in patients with complex phenotypes, where the coexistence of several abnormalities invites a unifying molecular explanation. Familial segregation and longitudinal clinical assessment provide valuable additional information but do not, by themselves, establish causality.

Materials and Methods: We performed clinical evaluation, whole-exome sequencing (WES) and familial segregation analysis by Sanger sequencing in a female infant presenting with severe neonatal respiratory distress, initially attributed to surfactant deficiency, and additional multisystem abnormalities. Familial segregation was assessed in symptomatic relatives. Variants were classified according to ACMG/AMP criteria.

Results: The proband required oxygen therapy for severe neonatal respiratory distress. During the diagnostic work-up, congenital hypothyroidism and bilateral congenital hip dislocation were diagnosed. WES identified a heterozygous COL6A1 variant, NM_001848.3:c.1210G>A, p.(Gly404Arg), classified as VUS. Her sister, who had also experienced neonatal respiratory distress but had no additional manifestations, carried the same variant. In contrast, both the father and brother, who also had a history of neonatal respiratory distress, were non-carriers. The mother was not tested.

Conclusions: Familial segregation did not support a causal relationship between the COL6A1 variant and the respiratory phenotype, as neonatal respiratory distress occurred in both carriers and non-carriers. Therefore, the COL6A1 VUS does not provide a unifying explanation for the phenotype. This case illustrates the importance of familial and longitudinal reassessment in avoiding anchoring bias when interpreting a VUS.

Keywords: COL6A1; variant of uncertain significance; segregation analysis; neonatal respiratory distress; developmental dysplasia of the hip; congenital hypothyroidism; genotype–phenotype correlation.

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Short stature in children: a retrospective analysis of cases and growth hormone therapy outcomes over a 25-year period at Regional Center of Medical Genetics Bihor

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Introduction: Growth disorders represent a significant issue in pediatrics, with growth hormone (GH) deficiency being a major cause of short stature. Early diagnosis and growth hormone replacement therapy can improve growth velocity and help patients reach their height potential.

Objective: To analyze the clinical, genetic, biochemical, imaging, and therapeutic characteristics of patients with severe short stature and GH deficiency registered at the Bihor Regional Center for Medical Genetics over a 25-year period.

Methods: We retrospectively analyzed 93 patients with severe short stature (≤ -3 SDS) who underwent evaluation for GH deficiency. Demographic and perinatal variables, genetic diagnoses, imaging studies, cytogenetic examinations, and auxological progress during growth hormone treatment were assessed.

Results: Of the 93 patients, 59% were male and 41% were female. The majority (57%) originated from rural areas. The predominant age group was 4–8 years (40%). Full-term birth was recorded in 83.9% of patients. Isolated GH deficiency was identified in 78% of patients, panhypopituitarism in 3%, and syndromic forms in 19%, with Turner syndrome being the most frequent. Imaging studies revealed pituitary hypoplasia in 14% and pituitary microadenoma in 2% of patients. Growth hormone treatment was administered in 88% of cases. In the 44 patients with complete monitoring, the growth rate was 7.65 ± 3.04 cm/year during the first year, decreasing progressively to 5.08 ± 2.52 cm/year by the fourth year.

Conclusions: Growth hormone deficiency exhibits significant clinical and genetic heterogeneity. Effective treatment enhances linear growth, with the most pronounced response observed during the first year of therapy.

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