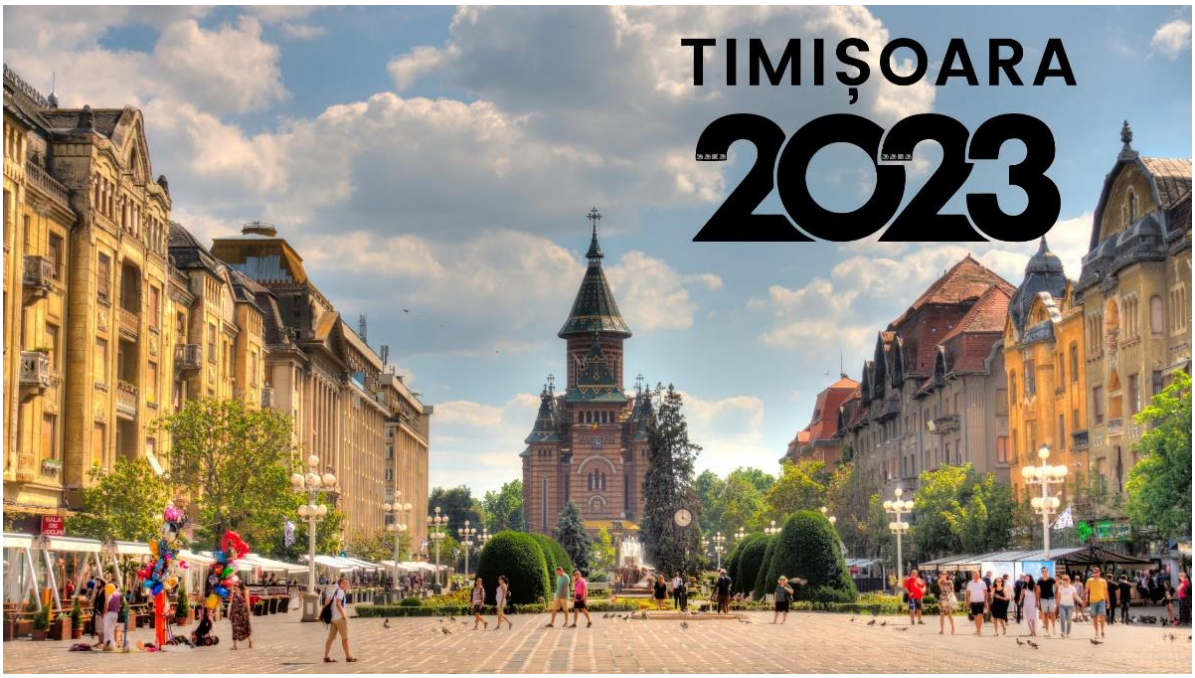
A XIII-A CONFERINȚĂ DE GENETICĂ MEDICALĂ CU PARTICIPARE INTERNAȚIONALĂ

TIMIȘOARA, 28-30 SEPTEMBRIE 2023



Dragi prieteni și colegi,

În numele Comitetului de Organizare ne revine deosebita plăcere de a vă invita la cea de-a XIII-a Conferință de Genetică Medicală cu Participare Internațională, care se va desfășura la Timișoara, capitala culturală a Europei în 2023, în perioada 28-30 Septembrie 2023.

Genetica umană este un domeniu cu dezvoltare rapidă a metodelor de investigație moleculară care pun permanent în evidență noi patologii, dar și strategii de tratament. Conferința de anul acesta ne va oferi ocazia să împărtășim din experiența colegilor, să aflăm informații despre noi direcții științifice și, nu în ultimul rând, să ne bucurăm împreună de zilele de septembrie în capitala culturală a Europei în 2023. Manifestările științifice se adresează deopotrivă profesioniștilor și beneficiarilor domeniului medical interesați de patologia genetică.

Vă așteptăm cu drag să împărtășim acest moment de excelență științifică! Participarea dumneavoastră ne onorează!

Informații suplimentare puteți găsi pe pagina web www.srgm.ro.

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ORAL PRESENTATIONS

CONGENITAL CUTIS LAXA: A COMPLEX DIAGNOSTIC CASE INVOLVING MULTIPLE CLINICAL MANIFESTATIONS

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Congenital cutis laxa encompasses a group of rare disorders characterized by defective connective tissue assembly and metabolism. The inheritance patterns include autosomal dominant, autosomal recessive, and X-linked recessive forms. This condition is attributed to impaired elastogenesis, leading to elastic fiber fragmentation in various tissues and posing a significant diagnostic challenge due to its diverse clinical presentation.

In this case report, we present a 10-month-old female patient who was initially brought in for a routine pediatric check-up, where she exhibited a I/6 cardiac murmur and excessive skin laxity. A genetic consultation was conducted at 11 months old, revealing the presence of prematurely aged face with saggy cheeks and redundant, loose skin throughout her body, a characteristic hallmark of some cutis laxa subtypes. Additionally, she displayed frontal and palpebral hemangiomas, a 7x4cm “cafe au lait” spot on the posterior axillo-scapular region, and a deep, hoarse voice associated with microphtalmia and convergent strabismus. Despite these clinical manifestations, her neurological development was age-appropriate.

Further investigations during her hospitalization unveiled additional anomalies, including a large S-shaped gall bladder, a reduced diameter of the right pulmonary artery, and stenosis at the origin of the right superior lobar artery.

This case underscores the importance of thorough clinical evaluation, a multidisciplinary approach in diagnosing congenital cutis laxa, which can exhibit a myriad of clinical features affecting multiple organ systems. Early recognition and accurate diagnosis are crucial for appropriate management and improved patient outcomes.

CLINICAL AND MOLECULAR FINDINGS IN AUTISM SPECTRUM DISORDERS

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Background: Autism spectrum disorders (ASDs) represent a heterogeneous group of neurodevelopmental conditions associated with lifelong challenges. ASDs have a well-known genetic background, with rare pathogenic CNVs cumulatively accounting as etiologic in ~ 5-10% of patients. Our paper summarizes the clinical and genomic data of 316 children with ASDs.

Methods: The clinical evaluation included neurological, psychiatric, and psychological evaluation. All patients received an ASD diagnosis. Array-based comparative genomic hybridization (array-CGH) using 4x180K SurePrint G3 Human CGH microarray (Agilent Technologies), PCR assays and MS-MLPA for Fragile X syndrome testing were performed for 305 ASD individuals.

Results: Clinical data analysis showed global developmental delay in 96 children and cognitive impairment in 172 cases. Dysmorphic features were noted in 107 patients, neurological problems, such as hypotonia, abnormal gait, dystonic movements, were present in 126 children, and 13 children had epileptic seizures. EEG epileptiform discharges were observed in 33 cases, and 75 children had different brain anomalies (cerebral and/or cerebellar hypotrophy, brain malformations, arachnoid cysts, myelination delay, hypoxic lesions). Different somatic co-morbidities were present in 138 cases and included allergies, digestive problems, eye anomalies, and heart malformations. Our genetic testing approach identified clinically relevant CNVs (pathogenic and likely pathogenic) in 27 out of 305 children with ASD and Fragile X syndrome full mutation in four patients. In addition, 183 variants of uncertain significance (VOUS) were detected in our group.

Conclusions: The clinical and genetic aspects of our cohort were heterogeneous, highlighting once more the wide array of etiopathogenic mechanisms. Comprehensive, new molecular technologies can contribute to a better understanding of the genetic causes of ASD, with important implications on management plan of the patients.

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

NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY IN ROMANIA: 1 YEAR EXPERIENCE OF A PILOT PROJECT AT ROBANESCU CENTER

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Spinal muscular atrophy (SMA), severe neurodegenerative disease in childhood, benefits from three approved treatments, all available for Romanian patients. SMA is considered nowadays a real neurogenetics urgency, children with diagnostic of SMA need to be treated as soon as possible, preferably in presymptomatic state for the best results. This objective can be achieved by newborn screening (NBS), already applied for more than a half of newborn population in European Union. Our pilot project, first NBS genetic screening in our country, covers babies born in eight maternities. More than 12 000 samples were screened in one year time period, from August 2022, for homozygous deletion of exon 7 in SMN1 gene with a validated Melt Assay method, the IVD-CE kit SALSA MC002 SMA Newborn Screen (MRC Holland). Four cases were positive and all were confirmed by second-tier genetic confirmatory test (MLPA). Genetic counseling permitted the diagnostic of two more cases, relatives of one of the positive cases. As 2025 is the year targeted to be the time when NBS for SMA will be available for all newborns in UE, we strongly advocate for including SMA in the National Programm for Newborn Screening.

Acknowledgements: All the patients, their families, all the colleagues in the Robanescu Center and in the eight partner maternities

CLINICAL EFFICACY AND THE DIVERSITY OF GENETIC DIAGNOSIS USING THE TRUSIGHTONE PANEL. THE EXPERIENCE OF THE "C.I.PARHON"NATIONAL INSTITUTE OF ENDOCRINOLOGY

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Background: Compared to WES, large gene panels are used as high-throughput sequencing tests in many clinical centers

Objective: In order to verify the usefulness and diagnostic yield of a gene panel for identifying pathogenic variants in monogenic diseases, the TrueSighOne gene panel was chosen

Materials and methods: Here we report the results of the first 30 selected cases from the "C.I.Parhon" National Institute of Endocrinology referred for genetic evaluation with suspected genetic disorders as assessed by their attending physicians and selected based on signs, symptoms and family history suggestive of a molecular pathology.

Methods: Next-generation sequencing was performed using the TruSight One gene panel (targeting 4813 genes) as a diagnostic test for a variety of clinical indications in our department.

Results: A probable or definite pathogenic finding was reported in 13 of the cases, 6 cases had no mutation detected, 6 cases had a VUS mutation and 5 cases had more than one mutation detected

(heterozygous status for recessive mutations associated with dominant mutations). Gene variants are described in 28 different genes identified in 30 patients.

Conclusion: The clinical utility of large gene panel sequencing in the context of other genetic diagnostic tests can be considered for the benefit of patients

The 13 positive cases compare favorably with similar studies using either this panel or whole-exome sequencing, demonstrating that large gene panels could be a good alternative to whole-exome sequencing for rapid genetic confirmation of mendelian disorders in selected clinical cases in endocrinology.

Acknowledgements: patients, their families, the leadership of the National Institute of Endocrinology, our colleagues.

CURRENT STRATEGIES FOR THE GENETIC DIAGNOSIS OF MITOCHONDRIAL DNA DISORDERS IN REPUBLIC OF MOLDOVA

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Introduction. Mitochondrial DNA disorders are a group of genetic conditions caused by mutations in mitochondrial DNA (mtDNA). Prevalence is estimated around 1 in 5,000-10,000 births, causing diverse clinical symptoms due to impaired cellular energy supply. MtDNA disorders are often complex and heterogeneous due to the variable nature of mitochondrial genetics, making diagnosis and management challenging.

Material and methods. We analyzed mtDNA from 55 patients with common clinical features of mitochondrial disorders. The strategy for the molecular-genetic diagnosis of mitochondrial disorders caused by mtDNA mutations involved performing qPCR-HRM (quantitative PCR-High Resolution Melting) analysis in order to test patients for the most common pathogenic point mutations, followed by mtDNA Sanger sequencing.

Results. After testing 55 patients for 11 common pathogenic mtDNA point mutations associated with mitochondrial diseases by the qPCR-HRM technique, 6 patients (11%) with the pathogenic mutations m.3243 A>G, m.8344 A>G, m.8993 T>G and m.11778 G>A were identified. Our molecular genetic diagnosis strategy provides that if no abnormalities are identified in the mtDNA analyzed by the qPCR-HRM method, the subsequent step involves the analysis of the spectrum of mtDNA genetic variants through Sanger sequencing. The Sanger sequencing technique of 21 mtDNA genes was performed in 29 patients, and as a result, pathogenic or potentially pathogenic mutations associated with mitochondrial pathology were identified in 12 patients (41%).

Conclusion. In the group of 55 investigated patients, it was possible to identify pathogenic and potentially pathogenic variants associated with the patients' phenotype in ~33% of cases.

Acknowledgements: This work was funded by research project „Medicina Genomică și Metabolomică în serviciul profilaxiei maladiilor genetice pentru generații sănătoase în Republica Moldova” [SCREENGEN, Cipher: 20.800009.8007.22]

TRISOMY 12 IN MOSAIC - A CHALLENGE OF PRENATAL DIAGNOSIS. CASE PRESENTATION

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Introduction. Trisomy 12 in mosaicism is a rare condition, and the literature reports only a few cases of live births. The clinical presentation of trisomy 12 mosaicism is highly variable and can include features such as global developmental delay, congenital heart disease, microcephaly, cutaneous spots, dysmorphism, hypotonia, retinopathy, and sensorineural hearing loss. There is only one reported case that also exhibited overgrowth

Case presentation: We report the case of a 31-year-old pregnant woman who performed a non-invasive prenatal blood test at 11 weeks of pregnancy which indicated low risk for trisomy 13, 18, 21, and male fetal sex. The initial three ultrasounds showed a fetus with female genitalia. However, during the fourth consultation at 20 weeks, the genitalia started to exhibit more male characteristics. Subsequently, QF-PCR, SNP array, and a panel for sex development disorders were conducted.

The results of the QF-PCR indicated a normal male fetus. The SNP array analysis revealed that the male fetus had a loss of heterozygosity on chromosome 12. The NGS panel conducted did not show any abnormalities, but there were differences in the coverage of five genes on chromosome 12, suggesting a potential low-grade mosaicism for trisomy 12. Following these findings, a new amniocentesis was conducted, and a G band karyotype analysis was performed. The results of the karyotype analysis was: 47,XY,+12[5]/46,XY[25]. Due to the uncertainty surrounding the phenotypic severity after genetic counseling session the parents decided to terminate the pregnancy.

The particularities of the case: ambiguous external genitalia and the first case of trisomy 12 in mosaic in Romania diagnosed in the prenatal period.

Key words: trisomy 12, karyoptype, SNP array, abnormal ultrasound.

GENETIC PATHOLOGIES UNDER THE MASK OF CONGENITAL GLYCOSYLATION DISORDERS

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Introduction. Congenital Disorders of Glycosylation (CDG) are a group of inherited metabolic disorders caused by defect in the biosynthesis of glycoproteins and other glycoconjugates.

Material and methods. 200 patients under clinical suspicion for CDG at the Institute of Mother and Child were examined by IEFT in collaboration with RadboudUMC, Netherlands, and U.S.A. Criteria for inclusion were children with multisystem impairment predominantly with seizures,

psychomotor retardations, muscular hypotonia, failure to thrive, and dysmorphic features. To differentiate other genetic diseases which mimic CDG, the basic metabolic work-up, IEFT, CGH-array, and WES/WGS have been done.

Results. IEFT was made to all 200 patients. In 197 cases, the profile of tranferrine was normal, but in the other 3 samples, a positive profile on IEFT has been identified,
which allowed suspecting CDG. In all 3 cases was determined secondary abnormalities of glycosylation as Galactosemia and 2 cases of Hereditary Fructose Intolerance. At the same time, following the metabolic work-up, CGH-array, and sequencing tests, other genetic pathologies that phenotypically mimic CDG, were determined. The diagnosed pathologies are Prader-Willi Syndrome, Mitochondrial diseases, Congenital Rett Syndrome, Pontocerebellar hypoplasia type 2A and 4, GNE myopathy, Ethylmalonic encephalopathy, Propionic aciduria, Ureea cycle disorders, and other microdeletion syndromes.

Conclusions. The clinical variability of CDG most often leads to their underdiagnosis. Differential diagnosis of this group of disorders should be very detailed because the phenotype most often mimics other genetic disorders. IEFT and WES/WGS play an important role in the diagnosis of this disorder.

Keywords: CDG, IEFT, multisystem impairment, WES/WGS.

Funding Acknowledgements: research project "Genomic medicine and metabolomic research in the service of the prevention of genetic diseases for healthy generations in the Republic of Moldova" (Acronym: SCREENGEN, code: 20.80009.8007.22)

SURMOUNTING CHALLENGES: IMPLEMENTING NEWBORN GENETIC SCREENING FOR SPINAL MUSCULAR ATROPHY IN REPUBLIC OF MOLDOVA

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Introduction: Spinal muscular atrophy (SMA), resulting from SMN1 gene mutations, stands as a primary contributor to infant mortality. Timely identification through newborn screening (NBS) plays a pivotal role in enabling effective intervention and subsequent monitoring.

Aim: This study endeavors to introduce a pilot newborn genetic screening initiative for SMA.

Methods: The Human Molecular Genetics Lab at the Mother and Child Institute undertook a pilot genetic screening approach of newborns, utilizing an algorithm designed for SMA mutation analysis. Blood samples were obtained from newborns on filter paper cards and subjected to comprehensive analysis involving real-time PCR and MLPA techniques.

Results: Among the challenges encountered in the implementation of the pilot genetic screening for spinal muscular atrophy (SMA), the following can be highlighted: The COVID-19 pandemic imposed constraints on data collection. The lack of and the necessity for developing a real-time based technique with specific primers for SMN1 exon 7 to identify the most frequent mutation leading to SMA. The necessity for validation of the developed technique through a suitable commercial qPCR kit for the same purpose. The lack of an testing method for diagnosis led to integrating the MLPA technique for confirming and evaluating SMN1/SMN2 gene copy numbers.

Successful resolution of these challenges paved the way for the initiation of the screening protocol. Approval was obtained for the research design, protocol, and consent forms, thereby

ensuring the active participation of subjects. A total of 300 blood spot samples were successfully collected from newborns, and 90 of these samples underwent genetic screening. Importantly, none of the analyzed samples exhibited suspicion of SMA.

In conclusion, the Human Molecular Genetics Lab at the Mother and Child Institute effectively surmounted the challenges associated with the SMA screening implementation. This screening methodology holds significant promise for the early detection of SMA cases, enabling timely interventions, and this implementation contribute to the comprehensive assessment of feasibility and cost-effectiveness of this methodology within the context of Moldova.

Acknowledgements: Studiu realizat cu suportul Ministerului Sănătății, Muncii și Protecției Sociale si a proiectului 20.800009.8007.22 „Medicina Genomică și Metabolomică în serviciul profilaxiei maladiilor genetice pentru generații sănătoase în Republica Moldova” [SCREENGEN], din cadrul Programului de Stat (2020-2023), conducător de proiect: dr.med, conf. Cercet. Natalia Ușurelu, autoritatea contractantă: Agenția Națională pentru Cercetare și Dezvoltare

THE UTILITY OF WHOLE GENOME SEQUENCING IN THE DIAGNOSIS OF RETINITIS PIGMENTOSA

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Introduction: Retinitis Pigmentosa (RP) is not a singular pathological entity but rather a group of hereditary retinopathies, affecting 1 in 3745 individuals, making it the most prevalent inherited disease of the retina. Over 100 genetic loci across 50 genes contribute to varied inheritance patterns and expressions in RP. About 20% are autosomal recessive, 10-20% autosomal dominant and 10% X-linked recessive; remaining cases lack family history or known molecular basis.

Materials and Methods: In this clinical case presentation we investigate a 48 years old male that was referred to genetic testing for investigations regarding his progressive vision loss and obesity. Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) from peripheral blood were carried out on the Illumina NGS platform.

Results and Discussion: WES analisis did not find any pathologic mutations in the patient but due to high clinical suspicion of RP a WGS was carried out. Sequencing data was imported in the Varsome Clinical software and gene filters for obesity and retinal dystrophies were applied.

We identified the mutation NM_001375654.1 c.-21_-13+14del in the RP1 gene in heterozygous state. Based on ACMG criteria the variant is likely pathogenic and could cause the pathological phenotype in our patient.

Conclusions: The identified mutation is located in a noncoding region, possibly a regulatory one, underlining the importance of analyzing the genetic material beyond the genic sequences in order to gain useful diagnostic information.

Key words: Retinitis Pigmentosa, WGS, NGS, Mutation

2Q37 MICRODELETION/DELETION SYNDROME -CRGM IASI EXPERIENCE

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2q37 microdeletion/deletion syndrome (2q37 DS) is a contiguous gene deletion syndrome characterized by a highly variable phenotype. The most common clinical features include short stature, obesity, characteristic facial dysmorphism, brachydactyly type E, hypotonia, joint hypermobility/dislocation and scoliosis, mild to moderate developmental delay/intellectual disability, and abnormal behavior with autism spectrum disorder. Congenital heart defects, gastrointestinal and genitourinary anomalies, and brain malformations are also detected in some cases. The molecular explanations of wide phenotypical variability are deletion size, genes involved, mosaicism, and complex chromosomal rearrangements. Diagnosis is confirmed by detection of the 2q37 microdeletion/deletion, using array comparative genomic hybridization (aCGH), or targeted methods such as multiplex ligation-dependent probe amplification (MLPA), or fluorescence in situ hybridization (FISH). Chromosomal analysis may detect large deletions and complex chromosomal rearrangements (e.g. translocations, inversion). We present the Iasi Genetic Center's experience (pure 2q37 microdeletions and complex chromosomal rearrangements) to illustrate the genetic heterogeneity of cytogenetic abnormalities in 2q37 DS, the hallmark features of the syndrome, and to highlight new suggestive elements. Although aCGH is the gold standard diagnosis method, in our experience, MLPA is also a reliable screening method.

Acknowledgements: Medical Genetics Department, "Saint Mary" Emergency Children's Hospital, Iași Romania is part of the European Reference Network ERN ITHACA

This study was made possible by access to the infrastructure, and with the scientific support of the project POC/448/1/1/127606, "Multidisciplinary medical research-development platform in the N-E region" (CENEMED)

DIAGNOSIS OF IMPRINTING DISORDERS USING MS-MLPA

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Imprinting disorders are a group of diseases that disrupt genes expressed in a parent-of-origin manner. Clinical signs can include abnormal growth, abnormal feeding behavior metabolic disturbances, as well as irregular pubertal onset or intellectual disability. MS-MLPA (methylation-specific multiplex ligation-dependent probe amplification), which can detect both copy number variation and epimutations, is the technique most frequently utilized in the diagnosis of these disorders.

Following clinical evaluation, commercially available kits ME028 or ME030 were used to test peripheral blood samples from patients suspected of having one of the following syndromes: Prader-Willi syndrome, Angelman syndrome, Silver-Russell syndrome, or Beckwith-Wiedemann syndrome.

In total, we detected 35 positive cases including 23 cases of Prader-Willi syndrome , 4 cases of Angelman syndrome, 3 cases of Silver-Russell syndrome, and 5 cases of Beckwith-Wiedemann syndrome.

Because it can simultaneously find copy number changes and methylation defects, MS-MLPA is a suitable diagnostic assay. Somatic mosaicism is often present in patients with Silver-Russell syndrome or Beckwith-Widemann syndrome, however, low-grade mosaicism cannot be detected by MS-MLPA, therefore results in these cases should be interpreted with caution. MS-MLPA is unable to distinguish between uniparental disomy and imprinting defects; thus further investigations, such as microsatellite analysis or SNP array, are required.

Acknowledgements: Medical Genetics Department, “Saint Mary” Emergency Children’s Hospital, Iași Romania is part of European Reference Network ERN ITHACA

GENETIC TESTING FOR CYSTIC FIBROSIS IN THE REGIONAL CENTER OF MEDICAL GENETICS CLUJ-NAPOCA

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Introduction: Cystic fibrosis is a complex genetic disorder that primarily affects the lungs and digestive system. The overall incidence in Europe is estimated at 1/3500, with wide variations among countries.

Materials and Methods: We present a retrospective study from the Regional Center for Medical Genetics Cluj-Napoca, Romania that included 286 patients who presented to the hospital between 2018 - June 2023 with clinical suspicion of cystic fibrosis. Three methods were used for genetic testing: strip assays that detect the 34 most common CFTR mutations in the European population, real-time PCR allelic discrimination with TaqMan probes for detecting F508del and recently a PCR multiplex kit designed to genotype the normal and mutant alleles at 33 loci of the CFTR gene.

Results: As expected, the most prevalent mutation found in our cohort was F508del: 14 cases out of 22 positive cases were homozygous for F508del (63,63%), 6 cases were compound heterozygous: F508del + another pathogen variant. We also had a case of a compound heterozygous G542X+27895G>A successfully diagnosed using strip assay. Also, a patient which was F508del heterozygous and none of the 34 most common variants were detected, presented highly suggestive clinical and paraclinical findings (sweat chloride test ~100MEq/l) for cystic fibrosis.

Conclusion: Our findings suggest that detection of F508del with TaqMan probes could be used as the first tier for genetic testing in cystic fibrosis. For patients with high suspicion of cystic fibrosis, but negative for the most common 34 pathogenic variants in the European population, further genetic testing involving CFTR sequencing is required.

Acknowledgements: Thank you to all my wonderful teachers and colleagues from my medical genetics’ residency

GENETIC CAUSES OF EARLY MENOPAUSE

HARADJA Elena Flavia[1]

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Menopause is a major life event that affects all women in a variety of ways, both short-term and long-term.

All women should have access to accurate information, available in all forms and through all recognized sources.

All healthcare professionals should have a basic understanding of menopause and know where to refer women for advice, support and treatment whenever appropriate.

Skilled listening, a closer relationship between health professionals and patients are fundamental tools in this context. Thus, menopause can unfold under a "new face" for many women: a time of rediscovery, of building new dreams and a new beginning.

Acknowledgments: Royal Club of Physicians

THE ROLE OF THE EMBRYOLOGY LABORATORY IN THE PGT PROCEDURE (PRE-IMPLANT GENETIC TESTING) OF EMBRYOS OBTAINED THROUGH IVF

HARADJA Elena Flavia[1]

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Infertility (and subfertility) is a pathology that occupies the 5th place in the list of disabilities globally according to the World Health Organization.

The causes of infertility are 30% due to female factors, 30% to male factors, 30% are mixed, and 10% are unknown.

Among the factors found in both sexes are the genetic factors. We now also have in Romania the possibility of genetic testing of embryos before implantation to help infertile couples get pregnant with the healthiest child possible.

Acknowledgments: Prof. dr Joyce Harper from UCL - UK, Gynera Clinic - Bucharest, Cytogenomic laboratory - Bucharest, Gennet laboratory - Czech Republic, the Future Life group gathers under one umbrella over 40 IVF clinics and 2 genetics laboratories from all over the world Europe.

UPDATES IN RISK-STRATIFICATION IN ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is an aggressive hematological malignancy that primarily affects older individuals (median age of ~65-68 years) and is characterized by uncontrolled proliferation of malignant marrow stem cells and short survival (<20% survive 5 years after diagnosis). AML is characterized by complex pathogenicity that arises as a consequence of the accumulation of chromosomal and molecular abnormalities. In the last year, new updated classification systems of myeloid malignancy were released underlying the integration of molecular analysis into daily clinical practice.

The European Leukemia Net (ELN) 2022 is a risk stratification system applicable for older patients but also for younger cases who undergo intensive treatment. ELN integrates knowledge from novel molecular findings and recent trial results and brings notable updates to risk group assignments. The ELN 2022 guidelines better stratify survival between AML cases with intermediate- or adverse-risk treated with induction chemotherapy. However, it remains difficult to measure a small number of potentially malignant myeloid cells with implications for therapeutic decisions. Furthermore, the latest findings suggest that the AML's clonal architecture has a substantial impact on prognosis. Integrating clinical data, chromosomal aberrations, and gene mutations remains crucial for AML patients. Thus new approaches were proposed, promising more robust prognostic assessments; however, refinements are ongoing to enhance accuracy. We aimed to present the known and new AML risk factors and to discuss the emerging comprehensive approaches to effectively integrate all relevant prognostic data to better stratification and treatment of AML cases.

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

GERMLINE AND SOMATIC MOLECULAR TESTING IN COLORECTAL CANCER

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Colorectal cancer (CRC) is the third most common cause of cancer mortality

worldwide with more than 1.85 million cases and 850 000 deaths annually. Approximately 20% of patients have metastatic disease at presentation and another 25% initially diagnosed with localized disease will later develop metastases. Early-stage CRC is entirely treatable with surgery and adjuvant chemo and radiotherapy. However, recurrence is common, and cancer drug resistance increases the chances of treatment failure.

Mainly driven by the clinical need, molecular genetic testing has been integrated into the standard patient care of cancer management including CRC for various clinical purposes. Molecular findings are often necessary or helpful in screening, diagnosis and prognosis of CRC and related syndromes. New molecular classification may profoundly alter the current understanding and clinical management of CRC. As a powerful sequencing tool, NGS has become the main platform of conducting cancer related molecular diagnostic tests.

In this presentation, we will highlight the importance of germline testing in hereditary cancers and discuss about tumour somatic testing to evaluate the molecular biomarkers widely used in the current clinical practice in CRC treatment.

AGMP THE GENETICS AND PERSONALIZED MEDICINE ASSOCIATION

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The Genetics and Personalized Medicine Association (AGMP), founded in 2019, is the initiative of a Romanian group of Genetics specialists and has emerged as a response to the need for a deeper understanding of the current tremendous advances in genetics and personalized medicine for medical professionals, patients, as well as medical authorities.

We aim

1. To promote personalized and precise medicine in Romania.
2. To expand education in the human genetics field for professionals, patients, and authorities.
3. To stimulate the practical applications of genetic studies for diagnosing and treating patients.
4. To advocate for the social health insurance system's importance of genetic test coverage for medical assistance and public health.

The members of the Association and our partners provide advanced clinical, scientific, and didactic expertise in Genetics for academics, healthcare professionals, the pharmaceutical industry, and also for patient associations and clinical studies.

We have planned to carry out and collaborate in programs, studies, projects, courses, and medical events to disseminate quality scientific information regarding medical Genetics progress and achievements for both medical professionals in other specialties (e.g., pediatrics, oncology, OG, cardiology, neurology, psychiatry, ophthalmology, nutritionist, etc.) and patients.

The Association is involved in education campaigns and humanitarian support actions for vulnerable patients who require urgent genetic investigations and personalized treatments to survive.

Also, the Association aims to bring to the public agenda the solutions offered by genetics and personalized medicine for global and individual health. We are establishing partnerships with all relevant national and international organizations for an integrated plan of action, the development of bilateral programs and scientific activities of interest to achieve common public health objectives at the national and European level.

AGMP is a member of the Ro Health and International Longevity Association.

In recent years, we have initiated a counseling program and online events - AGMP Dialogues, targeting medical staff, patients, journalists, and authorities. Also, we have participated in numerous medical events dedicated to medical professionals (family doctors, students, residents, and different specialties) to promote the new laboratory genetic tests and panels performed in Romania for different medical conditions.

More data about the AGMP www.agmp.ro

AGMP Facebook page – https://www.facebook.com/agmp.romania/.

“EXPERT EYE” FOR “RARE EYES”: INHERITED RETINAL DISEASES (IRDS) – A CASE SERIES

PLAIASU Vasilica

Regional Center of Medical Genetics Bucharest INSMC Alessandrescu-Rusescu

Inherited retinal diseases (IRDs) are genetically highly heterogeneous and exhibits clinical variability. IRDs typically present with severe vision loss that can be progressive, with disease onset ranging from congenital to late adulthood. Genetic testing can help identify the specific variants.

We report the clinical and genetic profile of apparently non-syndromic retinopathies cohort in the Bucharest Regional Center of Medical Genetics. Our strategy was that all patients to be analysed by Whole Exome Sequencing (WES) testing and the results were found to be either homozygous or compound heterozygous for variants in known RD genes, except one who was supplementary analysed by Whole Genome Sequencing (WGS) and a rare heterozygous de novo autosomal dominant variant was identified. The genetic spectrum displayed variants in the following genes: ABCA4, NDP, RPGRIP1, PDE6C, VCAN, TUBB4B, and C2orf71. The suspected clinical diagnoses were represented by rod-cone dystrophy, Stargardt macular degeneration, macular dystrophy or chorioretinitis atrophy, Leber congenital amaurosis.

The clinical and the molecular diagnosis of IRDs are very challenging. WES represented a valuable tool for cost-efficient molecular diagnostics given the large heterogeneity of all cases with IRDs. The genetic testing of IRDs can improve the accuracy of diagnoses and prognoses, the accuracy of genetic counselling and the specific care.

Acknowledgements: Pediatrics Ophtalmology Department - INSMC Alessandrescu-Rusescu Bucharest, Infosan Eye Hospital, Bucharest, Romania, Centogene Laboratory, Rostock, Germany

RLBP1 NOVEL VARIANT IN A PATIENT WITH CONE/ROD RETINOPATHY

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Hereditary retinopathies are a wide spectrum of diseases with multiple etiologies. They require a multimodal and multidisciplinary approach for a complete diagnosis. Here we present the case of a 10 year-old girl who presented to our clinic with poor vision (Snellen 0.4/0.3 with full correction) and an alternating slow recovering exophoria for near and distance. Ocular motility and anterior segment were normal. Eye fundus examination revealed a inhomogeneous retinal background with an uncharacteristic “beaten metal” appearance and some dark spots in the periphery. Electrophysiological examination were as follows: normal dark adapted scotopic rod response amplitude, reduced scotopic combined amplitudes, normal dark adapted oscillatory potentials, reduced amplitudes in photopic examination using light adapted flicker stimulation but normal photopic 3.0 erg response and normal electrooculogram. The clinical diagnosis was cone dominant retinal dystrophy. She was tested at the Regional Medical Genetics Center in Timisoara, Romania, using the Illumina TruSightOne kit and the following heterozygous mutation in the RLBP1 (OMIM

180090) gene was found: NC_000015.9:g.89758388C>G; NM_000326.5:c.428G>C; NP_000317.1:p.(Gly143Ala). The mutation was never before
reported in the literature and was classified as of uncertain significance according to the American College of Medical Genetics guidelines.

This gene encodes a protein expressed in retinal pigment epithelium and Müller glia with transporter role in the visual cycle, also known as CRALBP. Phenotypic findings in a mouse knock-out model and in humans with mutations of this gene (reported in 4 retinopathies), partially overlap with our patient's clinical picture. A clinical trial using AAV8 mediated gene delivery is currently ongoing. Our findings may contribute to a better characterization of the retinitis punctata albescens – fundus albipunctatus spectrum and increased chances for these patients to receive genic therapy in the future.

THE ROMANIAN SOCIETY FOR LYNCH SYNDROME - WHERE DMMR CASES CONTINUE THEIR DIAGNOSTIC, THERAPEUTIC, AND SCREENING JOURNEY

Oana Cristina VOINEA

INCDMM Cantacuzino, UMF Carol Davila

The Romanian Society for Lynch Syndrome is an association of medical professionals, academics and scientists aimed at facilitating the identification of Lynch syndrome patients in Romania. Its primary objectives include optimising the diagnostic, therapeutic, and screening management in accordance with current international guidelines.

The organisation was founded out of pragmatic necessity, by four young determined elite medical professionals, who felt a stringent need for improvement through their own medical practice. Colorectal cancer holds the top position in cancer incidents for both genders in Romania, with Globocan reporting nearly 13,000 new cases. Furthermore, mortality rates earn this disease a number two ranking, with nearly 7,000 deaths. According to Eurostat (2023), Romania records the highest number of mortalities due to preventable causes.

Lynch syndrome constitutes the most prevalent genetically determined pathological condition, which is associated with a predisposition up to 80% higher compared to the general population, for developing cancers of various types.

Among these, colorectal cancer occupies a leading position. Globally, it is estimated that 1 in 273 individuals carries a mutation defining this syndrome; however, Lynch syndrome remains significantly underdiagnosed.

Recognising the importance of understanding this predisposition, numerous Western European countries as well as the United States have established diagnostic and screening protocols aimed at early identification of this condition. Moreover, due to the unique characteristics of cancers attributable to Lynch syndrome, the treatment for these patients involves specific therapies, often yielding high response rates. Furthermore, due to the distinctive biology of cancers associated with Lynch syndrome, the treatment for these patients involves targeted therapies that exhibit high response rates.

In Romania, there is currently no standardised management protocol for this syndrome, and the diagnosis is often made opportunistically. The Romanian Society for Lynch Syndrome aims to enhance the diagnostic rate of this affliction and facilitate the implementation of a national screening and treatment protocol.

A truly cutting-edge initiative is the Romanian Lynch Syndrome Network, established through partnerships between the Romanian Society for Lynch Syndrome and various public institutions, government organisations or private entities that possess the capability to manage these patients.

Centres from different regions of the country are being constantly integrated, with the goal of establishing such centres in every demographic region in the near future. The purpose of these Lynch centres is to implement a standardised procedure for diagnosis, screening, and treatment of these patients, regardless of location, through the creation of the National Lynch Syndrome Registry. Through inter-institutional collaboration, this network paves the way for participating in international project competitions. Its evolutionary perspective envisions the establishment of a national oncogenetics network.

Acknowledgements: This article was published with the support granted by the project entitled "Net4SCIENCE": Applied doctoral and postdoctoral research network in the fields of smart specialization Health and Bioeconomy", project code POCU/993/6/13/154722.

A NEW KAT6A HETEROZYGOUS MUTATION - CASE REPORT

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Background Arboleda-Tham Syndrome (ARTHS) is a rare disorder characterized by developmental delay, dysmorphic facial features and cardiac involvement. To date, KAT6A is the only known ARTHS disease–causing gene, and more than 50 mutations have been identified in approximately 90 cases. KAT6A is an epigenetic modifier and it is involved in numerous biological and developmental processes.

Methods Here, we describe a 5-year-old girl who was referred to us for global developmental delay, intellectual disability, behavioral abnormalities, pulmonary stenosis and dysmorphic facial features (narrow palpebral fissures, epicanthal folds, broad nasal tip, thin upper lip). The history of the pregnancy was unremarkable; she was born at term, having a low birth weight.

Results A conventional karyotype and microarray analysis showed no abnormalities. Then, a whole exome sequencing (WES) test was performed, revealing a new heterozygous mutation in the KAT6A gene corresponding to the diagnosis of ARTHS (OMIM 616268). The variant (NM_006766.5:c.1996+1G>C) was classified as likely pathogenic.

Conclusions The features of this syndrome are non-specific, making it difficult to have a suspicion for this condition based on the clinical symptoms alone. Also, as this variant has never been reported before, we emphasize the importance of WES in the early diagnosis of patients with this type of manifestations.

Acknowledgements: The WES analysis was performed through the Mega grant program for Pediatric Genetic Disorders coordinated by Professor Homa Tajsharghi from the School of Health Sciences, University of Skovde, Sweden

PRENATAL WES IN A CASE WITH A FAMILY HISTORY OF LISSENCEPHALY

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Introduction: Fetal whole-exome sequencing (WES) has been performed more frequently in fetuses presenting malformations or severe fetal hydrops or when no specific diagnosis was obtained by chromosomal microarray.

Case presentation: We present a family that benefited from WES in prenatal diagnosis during the second pregnancy because they have a child with lissencephaly with a known mutation. The first child has the following abnormalities: microcephaly, supernumerary nipple and hypotonia. He was genetically tested after birth using the WES method at UMF Timișoara. A pathogenic mutation c.1205G>A (p.R402H), missense variant in heterozygous status in the TUBA1A gene associated with lissencephaly was identified. During the next pregnancy parents insisted to perform fetal WES to detect whether this pathogenic mutation was present in the fetus.

Material and method: Ultrasounds during pregnancy revealed normal data. Amniocentesis was performed during the 16th week of pregnancy, fetal DNA was extracted using the PureLinkTM Genomic DNA Mini Kit, obtaining 85.3 microg/ml DNA. BGI-XOME Express sequencing prioritizes searched variants using an integrated algorithm developed by BGI. Considering the first child's signs and symptoms, 13 HPs were considered and all genes that could be involved were sequenced.

Results: The HP corresponding to the clinical signs of the affected sibling generated a list of 382 variants, the first 20 considered important being included in the report. The first observation was that the known mutation was not found in the fetus, so TUBA1-associated lissencephaly was excluded. Since we had at our disposal the complete list of the variants present in the first child and in the fetus, we made a comparison and noticed that there were 6 VUS that the prediction software considered possibly harmful. Three of them (HEPACAM, RPL15, ANKRD11) with autosomal dominant inheritance could manifest. Two of them were identified in the first child (HEPACAM, ANKRD11). It remains to be seen how these variants will be reclassified in the future. The 20-week ultrasound scan looked for the signs of diseases associated with these genes, but they were not found and the pregnancy went well. Complete blood count should be monitored after birth because of the risk of Diamond-Blackfan Anemia type 12 associated with the RPL15 gene.

Conclusions: We present data on the first case of fetal WES reported in Romania. For the main suspicion of lissencephaly, we specify that no mutations were identified in the TUBA1A gene, so this disease is excluded. In each case, the benefits of WES testing during pregnancy, the limits of the investigation as well as the costs and perspectives of the family must be weighed. We believe that WES will lead to improvements in prenatal and perinatal care.

Acknowledgements: We express our gratitude to the family that participated in this study and to the partner laboratory BGI Laboratory.

HEREDITARY OPTIC ATROPHY ASSOCIATED WITH OPA1 GENE - NGS GENETIC TESTING FOR 7 MEMBERS OF A FAMILY

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Introduction: Hereditary optic neuropathy refers to a group of inherited diseases that cause optic nerve atrophy, a major cause of visual impairment.

Materials and Methods: A 15-year-old male patient was recently diagnosed with optic atrophy. Sequence analysis and deletion/duplication testing of the 772 genes associated with hereditary ophthalmic disease were performed by Next Generation Sequencing (NGS) was used.

Results: A novel variant, likely pathogenic, in the OPA1 gene was identified in this case. Mutations in this gene have been associated with optic atrophy type 1, an autosomal dominant inherited condition. Six more autosomal recessive genes have been identified in heterozygosity. The pathogen variant of the OPA1 gene (3q28-q29, OMIM:165500) that causes the patient's disease is present in both his mother and the probate's sister. Maternal grandparents do not have the mutation in the OPA1 gene, therefore the mutation occurred de novo in the patient's mother she passed it on to both children. In total, 7 relatives were tested in 3 generations.

Sequencing analysis of OPA1 gene revealed a splicing mutation (c.1589+1dup), in intron 16, in heterozygous state, that is expected to disrupt RNA splicing. This variant is not present in population databases and has not been reported in the literature in individuals affected with OPA1-related conditions.

Conclusions: The genetic cause of hereditary optic atrophy in the proband has been identified. Extensive family testing allowed the diagnosis of 2 other relatives with the same disease, one of them presymptomatic. All this information is especially useful in the post-test genetic counseling and for a prenatal diagnosis in the future.

Acknowledgements: We express our gratitude to the family that participated in this study and to the partner laboratory Invitae Corporation

JOINT ACTION IN RARE GENETIC DISEASES - ROMANIAN MEDICAL GENETICS CENTERS ACTIVITY WITHIN EUROPEAN REFERENCE NETWORKS

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

Ro-NMCA-ID (Romanian Network Multiple Congenital Abnormalities with Intellectual Disability) is member of ERN for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders (ERN ITHACA). As ERN ITHACA member, Ro- NMCA-ID team is actively involved in ILIAD, CPMS, Neurodevelopmental disorders, Clinical guidelines and expert consensus statements and Research workgroups. Ro-NMCA-ID team members are also involved in IRDiRC (International Rare Diseases Research Consortium) Task Force - Framework to assess impacts associated with diagnosis, treatment, support, and community integration.

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

PRENATAL SCREENING AND DIAGNOSIS STRATEGIES - COMPARATIVE STRATEGIES AND POINT OF VIEW

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The field of prenatal screening and diagnosis has undergone enormous changes over the past decades. Many genetic disorders are currently detectable in the prenatal period. Screening and diagnostic algorithms depended on strategy, test availability, performance, cost and turnaround time.

Routine prenatal care has traditionally included common chrosomal aneuplodies (CCA) detection. Traditional screening methods - multiple marker screening (MMS) have been in use. Recently, ACMG strongly recommended NIPS (non-invasive prenatal screening) over MMS for all pregnant patients with singleton and twin gestations for CCA: trisomies 21, 18, and 13. Several cfDNA (cell-free) screening implementation strategies in use: as a secondary test contingent to MMS, Romania included; reflex - combining MMS and NIPS; and primary in some screening programs. As it stands, contingent screening strategies leverage the benefits of NIPT cost-efficiently. NIPS offers many additional applications: fetal sex chromosome aneuploidy (SCA), rare autosomal trisomies (RAT), copy number variants (CNVs) and even micro-deletions and micro-duplications detection; validity and utility are challenging to evaluate for these, as is their current uptake in national programs.

Offering diagnostic testing most often occurs as a follow-up test over MMS/cfDNA. Nonetheless, it can be recommended in inherited mendelian disorders as it additionally enables the diagnosis of other anomalies using complex molecular techniques (array comparative genome hybridization, next generation sequencing).

Any national strategy needs to account for the inequalities in either the offer or the uptake of prenatal screening, genetic counselling and diagnostic testing. The diversity of clinical practice, where NIPS is becoming increasingly prevalent as a first-line tool, factors such as age, socio-economic status, ethnicity and religious beliefs need to be factored in.

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

GENETICS OF CARDIOMYOPATHY: ADVANCES AND PITFALLS OF MOLECULAR DIAGNOSIS

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Cardiomyopathies have age-dependent expression, variable penetrance, overlapping phenotypes, and complex interplay of genes.

Our findings in a case-series referred for genetic testing to CRGM-Dolj in 2023 were based on evaluation by Illumina TruSight Cardio panel on Illumina NextSeq550Dx. Making use these use-cases of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), we are illustrating advances and pitfalls of molecular diagnosis of cardiomyopathies.

In our DCM case series, *TTN* variants were frequent, we are reporting *DSC2* and *MYPN* variants. We report a *TNNT2* variant in a case of CMH – involvement of less known genes is not uncommon. We found a *FBN1* variant in a case referred for CMD testing – genetic syndromes associated with cardiomyopathy may be incidentally identified. Variants of unknown significance in *TTN* were also found in HCM – complex genetics and pleiotropy is challenging in inheritable cardiac disorders.

Only in a minority of cases, a pathogenic/likely pathogenic variant was found. Genetic testing is probabilistic; interpretation of genetic variation may differ and it continues to be refined. Panel sensitivity may be an issue given genes lacking robust evidence are commonly included. In elusive cases, an extensive test (WGS) allows for identification of additional genetic causes, variants situated in deep intronic regions or structural changes that may player a larger than initially anticipated. Common variants may have important roles.

Any genetic result must always be interpreted in the context of the patient's medical and family history; segregation of a putative variant may be useful and actionability as rationale to identify genetic risk is compelling in primary cardiomyopathies.

This work is supported by the National Health Program XIII.2.3. Starting July 2023, the National Insurance House is supporting panel testing in cardiomyopathies.

DATA SHARING AND MINING FOR GENOMICS - EUROPEAN INITIATIVES

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The prospect genomics has to revolutionize healthcare is undeniable. Biomedical data imposes capable infrastructure, careful management, transparent and accountable governance.

Much of existing clinical-genomic data is siloed and inaccessible. International initiatives have come together to tackle interoperability issues – e.g. Global Alliance for Genomics and Health (GA4GH). The GO FAIR initiative aims to implement data principles in order to make it Findable, Accessible, Interoperable and Reusable (FAIR). The federated model is prevalent: within Europe, ELIXIR oversees sub-initiatives including the European Genome Archive (EGA); at a global level, the Common Infrastructure for National Cohorts in Europe, Canada, and Africa (CINECA) project.

Aligned with other large-scale initiatives, the European '1+ Million Genomes' (1MG) and its successor Beyond Million Genomes (B1MG), aim to set up a collaboration mechanism enabling secure access to genomics and corresponding clinical data across Europe. This infrastructure will host Genome of Europe, an ongoing effort to create national genomic reference cohorts.

The project Genomic Data Infrastructure (GDI) is a scale-up and sustainability phase of 1+MG. It aims to establish a federated data infrastructure across Europe. This has many potential use cases, provide a data access governance and a sustainable coordination mechanism, and contribute to improving the inter-operability of genomic and clinical data made available for access.

The Data Governance Act, April 2022, allows for the creation of common **European data spaces** for important areas including health. Negotiations with the Council of Europe will see these digital transformations shape to tackle existing as well as future challenges raised by large-scale health data collection and management in each country.

Beyond generating, finding, accessing and combining disparate datasets, today's systems have not reached maturity.

CHARACTERIZATION OF SEPSIS INFLAMMATORY ENDOTYPES USING CIRCULATORY PROTEINS IN PATIENTS WITH SEVERE INFECTION: THE FUSE STUDY

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Sepsis is a heterogeneous condition due to dysregulated processes in the host immune response. Stratifying patients for personalized immune-based treatments and better prognostic prediction has been attempted using gene expression data, different inflammatory profiles. It has been unexplored whether these endotypes mirror inflammatory proteome profiling. We aimed to identify inflammatory endotypes based on circulating proteins in a prospective study of moderately ill patients with severe infections.

We profiled 92 inflammatory plasma markers using O-link, a targeted proteome platform, In a cohort of 167 patients with severe infection and 192 healthy individuals. We compared between patients with severe infection (Sepsis-2 criteria) and healthy controls. We performed hierarchical clustering based on the differentially expressed proteins, followed by clinical and demographic characterization of the observed endotypes.

We found 62 differentially expressed proteins: TNFSF14, OSM, CCL23, IL-6, and HGF were upregulated, while TRANCE, DNER and SCF were downregulated in patients. Unsupervised clustering identified two different inflammatory profiles. One endotype showed significantly higher inflammatory protein abundance, and patients with this endotype were older and showed lower lymphocyte counts compared to the low inflammatory endotype.

By identifying endotypes based on inflammatory proteins in moderately ill patients with severe infection, our study suggests that inflammatory proteome profiling can be useful for patient stratification.

This study was supported by a Competitiveness Operational Program Grant of the Romanian Ministry of European Funds (FUSE - FUnctional genomics in Severe infections- P_37_745, MySmis 103454).

CONGENITAL ABNORMALITIES AND GENETIC ASSOCIATIONS. WHEN SHOULD WE START AND STOP COUNSELING?

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At times, ethics principles are suboptimal applied in busy prenatal units. Worldwide, they are on the verge of changing, due to advanced prenatal ultrasound diagnosis.

Obstetricians and perinatologists are increasingly involved in performing high-quality anomaly and genetic scans, especially early in pregnancy. We face a wider range of diagnosable diseases throughout the pregnancy, either never reported before or rarely described in prenatal life. Despite that, establishing accurately prenatally the neonatal and childhood outcomes remained a challenge.

We will present and discuss difficult cases, approached in multidisciplinary teams, in which the best collaborative estimates of prognosis turned out to be right and wrong. The postnatal symptoms/evolution may be less severe or more severe than anticipated based on the prenatal assessment. Nevertheless, the complex work-up and the long-term follow-up should be maintained and enhanced. The prenatal US features, non-invasive prenatal testing, conventional karyotyping and/or results on molecular genetics are described in selected cases. We emphasize the usefulness of so-called minor ultrasound markers. At times they were important and meaningful, in some cases they were nothing but an unnecessary source of parental anxiety.

Counselors and obstetricians should exercise caution and carefulness. They should be specifically and continuously trained in this field. Our case series underlines the parental psychological impact and the completely different responses triggered. Also, we highlight the importance of prenatal referral to the genetic department. This ensures better, non-directive, and professional prenatal counseling.

This work benefited from administrative and technical support through the Operational Program Human Capital (POCU) NATALCARE ”Complex Programme Information and Care for Mother and Child” Project Code 142081 (the European Social Fund)

GENETIC COUNSELLING AFTER DISCORDANT NON-INVASIVE PRENATAL TEST RESULTS

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Non-invasive prenatal testing (NIPT) is a screening test with the primary aim of detecting fetal trisomy 21, 13 and 18 by analyzing cell-free DNA (cfDNA) circulating in maternal plasma. cfDNA is derived from both placental and maternal origin, and in cancer patients, part of the cfDNA

pool originates from the tumor. Genome-wide sequencing NIPT platforms can detect aneuploidies and copy number variations of considerable size affecting all chromosomes without clear yes or no answers as in invasive procedures. Therefore, a positive test results need to be confirmed by a definitive diagnostic genetic test from chorionic villus sampling or amniocentesis. In some cases, a discordant result between NIPT and fetal karyotype may occur, which can be attributed to various factors, such as confined placental mosaics, vanishing twin or co-twin demise, low fetal fraction, maternal chromosomal abnormalities, and maternal malignancy. We present several cases with discordant results between NIPT and fetal karyotype and discuss their possible causes mainly focusing on an occult maternal malignancy. Counselling women with unexplained false-positive and false-negative results of NIPT can be challenging. All women should be counselled that NIPT is a screening test and the limitations of cfDNA-based NIPT should be well explained in terms of potential discordant results before women undertake the test. Understanding the causes of discordant NIPT results is essential to enable more comprehensive and appropriate genetic counselling.

THE ROAD BETWEEN GERMLINE AND SOMATIC VARIANTS: A CRGM DOLJ UPDATE IN ONCOGENETICS TESTING AND COUNSELING

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Background/Objectives: By the year 2020, the biggest number of new cases of cancer in Romania was reported in the South-Western Oltenia region- 367.8‰ inhabitants. Moreover, the projection of cancer incidence until the year 2025 shows a trend of continuous growth of new cancer cases in Romania. At the moment, in our country there are no national programs for genetic screening or diagnosis of malignant diseases.

Methods: Testing options for patients consist of next generation sequencing (NGS) panels for both germline and somatic variants on an Illumina NextSeq550 IVD sequencer, in-house capillary sequencing and fragment analysis on a Thermo Fisher 3730xl DNA Analyzer and qRT-PCR on an Applied Biosystems™ QuantStudio™ 7 Flex. Moreover, patients receive both free pre- and post-testing genetic counseling.

Results: We are reporting more than 100 patients with a diagnosis of cancer, referred to CRGM-Dolj between 2019 and 2023. While NGS identified pathogenic, likely pathogenic and variants of uncertain significance (VUS) in genes associated with the phenotype of patients, capillary sequencing was offered to screen the extended family for the identified variants.

Conclusion: Genetic testing is quickly becoming a „Gold Standard" when screening for both germline and somatic variants in patients with either hereditary tumor syndromes or patients in need of personalized approaches to their management. The inclusion and government financing of genetic testing in the routine management of oncological patients represents one of the vital means to stabilize and decrease the ever-alarming numbers of both cancer incidence and mortality not only regionally but on a nation-wide level.

POSTER PRESENTATION

THE CUTIS LAXA TRAP

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Background: Lenz-Majewski hyperostotic dwarfism is a genetic disorder characterized by cutis laxa, brachydactyly, facial dysmorphism, intellectual disability and hyperostotic skeletal dysplasia with severe dwarfism. Skeletal dysplasia and growth retardation usually evolve with age. Consistent features are low weight, microcephaly, developmental delay, delayed fontanelle closure, dysmorphic features including broad forehead, hypertelorism and large ears, sparse hair, cutis laxa, prominent cutaneous veins and joint laxity.

Case presentation: We present the case of a 4-year-old male patient who is under our care since 2019, with multiple and recurrent knee, hip and elbow dislocations, undescended testes, cutis laxa, failure to thrive and dysmorphic features (microcephaly, delayed fontanelle closure, broad forehead, hypertelorism, large ears). A karyotype and genetic testing for subtelomeric MLPA were performed with normal results. In the light of hyperlaxity of the skin and joints, a comprehensive skeletal dysplasias and disorders panel was performed, which identified a variant of PTDSS1 gene, which is associated with Lenz-Majewski hyperostotic dwarfism.

Conclusions: The Lenz-Majewski hyperostotic dwarfism is an extremely rare disorder (to date, approximately 20 cases have been reported), which was associated with pathogenic variants of PTDSS1 gene.

RARE CASE OF STERILITY COUPLE AS A RESULT OF TWO BALANCED ANOMALIES

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We present a case of a couple who consulted our clinic for sterility issues, after experiencing 4 spontaneous abortions. Both members had a normal phenotype, therefore it was suggested that blood samples be taken for chromosome analysis. The examination showed that the 46,XX karyotype was normal for the woman, but, the man's karyograme indicated an unexpected result. The karyotype showed the presence of two different balanced chromosomal anomalies: a reciprocal balanced translocation -46,XY,t(7;8)(q32;q24.1), respectively a balanced pericentric inversion - inv(9)(p12q21.32). Such association between two balanced anomalies is rare. The presence of a balanced reciprocal translocations determines a genetic predisposition to miscarriage, with a risk ranging between 1% and 50% depending on the size of chromosomal fragments implied, the chromosomes engaged in anomaly, the quantity of euchromatin of chromosomal segments and the carrier's sex. During meiosis within carriers of balanced translocations, the segregation of chromosomes has the potential to yield unbalanced karyotypes within gametes and to lead to spontaneous miscarriages. On the other hand, the inversion favours the apparition of abnormal

embryos by an irregular meiotic recombination during crossing-over. The most frequent inversion on the chromosome 9 -inv(9)(p12;q13) is not associated with reproductive risk because the breaking points are located in a heterochromatin region. In our case, one breaking point is located in heterochromatin, while the other point is in a region of euchromatin, the inversion contributing itself to the augmentation of reproductive risk. We consider this couple as a good candidate for the artificial reproductive technique with preimplantation diagnosis.

PREVALENCE OF SOME MUTATIONS IN THE TP53 GENE IN PATIENTS WITH SQUAMOUS CARCINOMA OF THE HEAD AND NECK FROM THE REPUBLIC OF MOLDOVA

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Introduction. Head and neck squamous cell carcinoma (HNSCC) is one of the most common types of cancer in the Republic of Moldova, with 971 new cases and 637 deaths recorded in 2020, it is characterized by a variety of genetic mutations that promote its development and progression. The p53 protein encoded by the TP53 gene regulates the expression of genes involved in cell cycle arrest, apoptosis, DNA repair. TP53 mutations are associated with short survival and tumor resistance to radiotherapy and chemotherapy in patients with HNSCC.

The aim. The aim of the study was to test 3 mutations in the TP53 gene in patients with HNSCC from the Republic of Moldova.

Material and Methods. We analyzed 119 fresh tumor tissue and blood samples collected from patients primarily diagnosed with HNSCC. The DNA was tested for 3 mutations in the TP53 gene: c.524G>A, c.818G>A, c.817C>T by the castPCR method.

Results. The prevalence of TP53 mutations in our study group was 32.77% (39/119) of which 25.21% (30/119) were positive for a single mutation, and 7.56% (9/119) presented double mutations. Of these, 19.32% patients were positive for the c.524G>A mutation and 13.44% for the c.818G>A mutation. Three positive patients had germline mutation, one with c.524G>A and two with the c.818G>A mutation.

Conclusion and Discussions. The prevalence of TP53 mutations tested was 32.77%. The presence of these mutations in a large number of patients could be as a potential assessment or stratification biomarker for prognosis and a predictor of clinical response to radiotherapy and chemotherapy in patients with HNSCC.

Key words: head and neck squamous cell carcinoma, mutation, TP53.

ACKNOWLEDGEMENT: The study was carried out within the State Program 2020-2023 with code 20.80009.8007.02 “Comparative study of the genomic, immunological and functional peculiarities of squamous cell carcinomas in five anatomical locations” (ANCD).

IDENTIFICATION OF SOME MUTATIONS IN THE TP53 AND EGFR GENES IN NON-MELANOMA SKIN CANCER

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Introduction: The main types of non-melanoma skin cancer (NMSC) are basal cell carcinoma (BCC) and skin squamous cell carcinoma (SSCC). In this research, we observe the presence of distinct TP53 and EGFR mutations in SSCC compared to other types of NMSC.

Materials and Methods: The study comprised a cohort of 43 individuals primarily diagnosed with NMSC investigated at the Oncological Institute of the Republic of Moldova between 2020 and 2023. Among them, 36 were diagnosed with SSCC, five with BCC, and two with basosquamous carcinoma (BSC). We extracted DNA from fresh-frozen and formalin-fixed paraffin-embedded tumor tissue samples and analyzed for mutations in the TP53 (c.524G>A, c.818G>A, and c.817C>T) and EGFR (ex19Del, c.2573CT>AG, and c.2369C>T) genes by the castPCR method.

Results: Fifteen individuals (34.88%, 15/43) were identified as positive for at least one TP53 mutation, while only one (2.33%, 1/43) sample tested positive for EGFR ex19Del mutation in BCC. Specifically, TP53 mutations in SSCC were found in 13 cases (3/13 - c.524G>A, 6/13 - c.818G>A, 3/13 – both, and 1/13 - c.817C>T), BCC – one positive case for c.524G>A, and BSC – one for c.818G>A. We confirmed that all mutations were somatic by DNA testing of histologically normal tissue adjacent to the tumor or blood samples.

Conclusions: The mutation frequencies in the TP53 and EGFR genes are 34.88% and 2.33%, respectively. Furthermore, SSCC exhibits a considerable incidence (36/43; 83.72%) and a high mutation accumulation rate (13/15; 86.66%).

Keywords: skin squamous cell carcinoma, TP53, EGFR.

Acknowledgements: The study was carried out within the State Program 2020-2023 with code 20.80009.8007.02 “Comparative study of the genomic, immunological and functional peculiarities of squamous cell carcinomas in five anatomical locations” (ANCD).

A NEW CASE OF 8P CHROMOSOME INVERTED DUPLICATION DELETION SYNDROME–CYTOGENETICS IN THE GENOMIC ERA

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The 8p inverted duplication deletion syndrome (invdupdel(8p)) ORPHA 96092 is a rare chromosomal rearrangement with an incidence of approximately 1/10.000 to 1/30.000 newborns. The main characteristics are the global developmental delay (psychomotor delay and language delay associated with a variable intellectual disability), central nervous system malformations (notably agenesis of the corpus callosum), cardiac malformations, skeletal abnormalities, characteristic facial features, gastrointestinal, genitourinary and visual issues. This complex structural rearrangement is due to the presence of 2 highly repetitive regions (ORDRs- olfactory receptor and defensing repeat

gene clusters) on the short arm of chromosome 8 that constitute breakpoints which can lead to unbalanced crossing-over and result in both loss and gain of genetic material.

Here we describe the case of a 2 years old boy without relevant family history, which was referred to us by his pediatric neurologist. The boy presented with global developmental delay with generalized hypotonia and delayed speech. The head MRI revealed a thinning of the corpus callosum. The cardiologic evaluation noted tricuspid regurgitation, patent ductus arteriosus, patent foramen ovale and an atrial septal defect. Dysmorphic facial features included a high, broad forehead, anteverted nostrils, broad nasal bridge, high palate, and smooth philtrum. A Comparative Genomic Hybridization array was carried out on the Agilent platform and resulted in the diagnosis of a duplication and deletion of 8p in our proband.

This case study underlines the importance of molecular karyotyping in patients with intellectual disability and corpus callosum anomalies.

THE IMPORTANCE OF GENETIC TESTING IN RELATIVES OF PATIENTS WITH MEN 2A - CASE PRESENTATION

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Multiple endocrine neoplasia (MEN) type IIA represents an autosomal dominant disorder produced by a missense mutation in the RET protooncogene which is located on chromosome 10 (10q11.21). Mutations in the RET gene are associated with MEN type IIA, MEN type IIB, Hirschsprung disease and medullary thyroid carcinoma. MEN type IIA presents with medullary thyroid carcinoma- a disease originating from the parafollicular C cells that secrete calcitonin, pheochromocytoma and parathyroid adenomas. We present the case of a 44 year-old female with positive family history of MEN type IIA who was genetically tested and confirmed with the heterozygote mutation NM_020975.6:c.1902C>G, NP_0066124.1:p.Cys634Trp in 2010 when she was also diagnosed with medullary thyroid carcinoma and underwent total thyroidectomy. Two years later adrenal gland nodules began to develop but the patient postponed the bilateral adrenalectomy until 2019. In two of the patient's daughters genetic testing was perfomed as recommended under the age of 6, the mutation being also confirmed, so prophylactic thyroidectomy was recommended and we continued with the biochemical screening for pheochromocytoma and hyperparathyroidism. There is another daughter who is also affected but at the time of the genetic testing she was more than 6 years old and developed in time medullary thyroid carcinoma for which she underwent total thyroidectomy with latero-cervical limphadenectomy.

As a conclusion, we highlight the importance of the genetic screening in relatives of patients with MEN IIA syndrome and prophylactic thyroidectomy where a patological variant associated with MEN IIA is found.

ACUTE MYELOID LEUKEMIA – ASSOCIATIONS BETWEEN GENETIC ALTERATIONS, CLINICAL, PARACLINICAL DATA AND PROGNOSIS

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The purpose of this study was to identify associations between genetic alterations, clinical, paraclinical data and acute myeloid leukemia (AML) prognosis using multiple genetic testing approaches.

We analyzed 410 AML patients by using cytogenetics, MLPA technique, LD-RT PCR, NGS sequencing, fragment analysis, capillary sequencing and PCR based techniques. Part of our results was disseminated in the literature by multiple studies.

We will present our results regarding the genetic alterations identified by cytogenetics, CNVs, gene fusions, NGS sequencing variants. Also, we will discuss the significant prognostic impact of somatic mutations such as FLT3-ITD, NPM1 and DNMT3A and the techniques available including those for variant allele frequency (VAF) identification. We will discuss the benefits, challenges and limitations of the techniques used and the importance of genetic complex approaches. Significant results were found between CNVs, somatic mutations and overall survival. Also between age at diagnosis, LDH level, blast percentage, white blood count, molecular prognostic score, performance status scale and overall survival.

By a comprehensive analysis of the DNA of AML patients we were able to suggest that maybe every patient with AML had genetic alterations, the challenge is to identify them. Once this is successfully perfumed the clinical benefits will appear.

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

HEREDITARY BREAST CANCER IN ROMANIA-MOLECULAR PARTICULARITIES AND GENETIC COUNSELING CHALLENGES IN AN EASTERN EUROPEAN COUNTRY

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In Romania, breast cancer (BC) is the most common malignancy in women. However, there is limited data on the prevalence of predisposing germline mutations in the population in the era of precision medicine, where molecular testing has become an indispensable tool in cancer diagnosis,

prognosis, and therapeutics. Therefore, we conducted a retrospective study to determine the prevalence, mutational spectrum, and histopathological prediction factors for hereditary breast cancer (HBC) in Romania. A cohort of 411 women diagnosed with BC selected upon NCCN v.1.2020 guidelines underwent an 84-gene NGS-based panel testing for breast cancer risk assessment during 2018-2022 in the Department of Oncogenetics of the Oncological Institute of Cluj-Napoca, Romania. A total of 135 (33%) patients presented pathogenic mutations in 19 genes. The prevalence of genetic variants was determined, and demographic and clinicopathological characteristics were analyzed. We observed differences among BRCA and non-BRCA carriers regarding family history of cancer, age of onset, and histopathological subtypes. Triple-negative (TN) tumors were more often BRCA1 positive, unlike BRCA2 positive tumors, which were more often the Luminal B subtype. The most frequent non-BRCA mutations were found in CHEK2, ATM, and PALB2, and several recurrent variants were identified for each gene. Unlike other European countries, germline testing for HBC is still limited due to the high costs and is not covered by the National Health System (NSH), thus leading to significant discrepancies related to the screening and prophylaxis of cancer.

A RARE CASE OF NESCAV SYNDROME IN ROMANIA

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NESCAV syndrome (NESCAVS), also known as Intellectual Disability, Autosomal Dominant 9 syndrome, is a neurodegenerative disorder characterized by onset of features in infancy or early childhood. Affected individuals show global developmental delay with delayed walking or difficulty walking due to progressive spasticity mainly affecting the lower limbs. There is variable impaired intellectual development, speech delay, and learning disabilities and/or behavioral abnormalities.

NESCAVS is caused by de novo heterozygous mutations in the Kinesin family member 1A (KIF1A) gene. The KIF1A gene is located on chromosome 2q37.3 and is expressed mainly in the brain and spinal cord. Pathogenic variants in the KIF1A gene are responsible mainly for three phenotypes: autosomal recessive and dominant spastic paraplegia 30 (SPG30, OMIM 610357), autosomal recessive hereditary sensory and autonomic neuropathy type 2 (HSN2C, OMIM 614213), and autosomal dominant neurodegeneration and spasticity with or without cerebellar atrophy or cortical visual impairment syndrome NESCAVS (OMIM 614255). Most identified KIF1A variants associated with NESCAV syndrome are heterozygous and de novo.

Here we present the case of a six-year old female patient, with microcephaly, spastic paraparesis, delayed speech and language development, and spina bifida occulta. The patient had no specific family history and no issues were detected during the pregnancy. Parents were of Caucasian origin and not related. Initial genetic testing showed normal (negative) SNP-array and spatial orientation disorders genetic test.

The whole genome sequencing identified the c.760C>T [p.(Arg254Trp)] heterozygous mutation in the KIF1A gene; this mutation is classified as a missense pathogenic (class 1) mutation. Due to the early onset (in infancy) and clinical/neurological features, it was diagnosed as NESCAV syndrome.

VARIABILITY IN CLINICAL MANIFESTATION OF PATIENTS DIAGNOSED WITH DIGEORGE SYNDROME

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Chromosome 22q11.2 deletion syndrome also known as DiGeorge syndrome or velocardiofacial syndrome is the most common microdeletion disorder. The syndrome is recognized by the well-known triad of immunodeficiency, congenital heart disease and hypoparathyroidism. It is now known that DiGeorge syndrome also has a heterogeneous presentation with more than 180 clinical features including every organ and system, as well as various common psychiatric illness as deficit disorders, bipolar disorders and also schizophrenia. A multidisciplinary approach it is required for an early diagnosis and improved outcomes.

In this study we collected data from 15 patients diagnosed with DiGeorge syndrome, the median age at the diagnosis was 4 years (range 4 months- 27 years). Symptoms that were present most common were congenital heart defect, cranio-facial dimorphism and developmental delay. Hypocalcemia was present in the 20% of the cases. Most of the patients suffered from recurrent infections. Less common clinical features included multiple renal cysts, hyperkinetic disorder, spina bifida, craniosinostosis and dislalia. The patients were tested using multiplex ligation-dependent probe amplification (MPLA) analysis in our laboratory.

We are highlighting that DiGeorge syndromes's typical and uncommon characteristics are important to improve diagnosis, treatment and follow-up.

GENETIC VARIATIONS OF CXCL12/CXCR4 AND SUSCEPTIBILITY TO ACUTE MYELOID LEUKEMIA

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Introduction: C-X-C motif chemokine 12 (CXCL12), known as stromal cell-derived factor-1, is produced in the microenvironment of the bone marrow and activates its dedicated receptors, particularly C-X-C chemokine receptor type 4 (CXCR4). This interaction substantially activates a spectrum of functions, including cell proliferation, survival, maturation, migration, and liberation of hematopoietic stem cells (HSCs). Considering this major role in hematopoiesis, polymorphisms of CXCL12/CXCR4 genes could result in the excessive proliferation of HSCs, a circumstance that

precipitates the onset of acute myeloid leukemia (AML). The aim of this study was to investigate the association of CXCL12 rs1801157 and CXCR4 rs2228014 and susceptibility to AML.

Material and methods: Genotyping was achieved by using 7500 Real-Time PCR System and specific Applied Biosystems TaqMan Genotyping Assay and we included 225 patients with AML and 483 controls.

Results: In the patients group the genotypes for rs1801157 were 60% wild-type, 34% heterozygous, and 6% with variant genotype and for rs2228014 89% wild-type, 10% heterozygous and 1% with variant genotype. In the control group for rs1801157 61.8% wild-type, 33.6% heterozygous, and 4.6% with variant genotype, and for rs2228014 88.2% wild-type, 11.8% heterozygous and 0% with variant genotype. No significant association was observed between investigated SNPS and AML risk. Moreover, the relation between FLT3 gene mutations, copy number variations and variant genotypes of CXCL12 and CXCR4 genes were analyzed

Conclusion: Our results suggest that CXCL12 rs1801157 and CXCR4 rs2228014 is not associated with AML susceptibility.

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

CARDIO-FACIO-CUTANEOUS SYNDROME AND CELL SIGNALING PATHWAY

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Cardio-facio-cutaneous syndrome (CFC, MIM #115150) is a congenital condition characterized by distinctive facial appearance, heart defects and intellectual disability, short stature, and skin abnormalities. It is an autosomal dominant trait, but most cases are due to de novo mutations. It is included in the large group of RAS-opathies, caused by germline mutations in genes that alter the RAS components of the RAS/MAPK signal transduction pathway. The RAS/MAPK pathway plays an important role in intercellular signaling. Intercellular signaling is the essential way in which cells can communicate with each other by exchanging information, no matter how far apart they are. It usually involves the cooperation between two cells; one that sends the signal, the other that receives it and phenomena that take place at the level of the membranes n CFC syndrome there are mutations in various genes of the RAS/MAPK pathways, such as: BRAF, MEK1 and MEK2 genes. The most common mutated gene is the BRAF gene, present in 75% of cases. All these genes may be involved in different successive steps of the RAS/MAPK signaling pathway. Therefore, it is often difficult to make a differential diagnosis based exclusively on the clinical aspect, molecular tests being mandatory for a precise diagnosis. We report this case, observed over a period of 35 years, to illustrate the evolutionary clinical features and difficulties in establishing a positive diagnosis.

Keywords: CFC syndrome, RAS/MAPK pathway, cell signaling.

MOLECULAR INVESTIGATION BY MLPA OF ABCA3 AND SFTPC GENES ASSOCIATED WITH RESPIRATORY SYNDROME DISTRESS IN NEWBORNS

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BACKGROUND: Surfactant deficiency due to pulmonary immaturity is considered the main reason of respiratory distress syndrome (RDS) in premature infants. Mutations in genes involved in surfactant synthesis and metabolism result in the phenotypes of neonatal respiratory failure and interstitial lung disease in children. These include biallelic loss-of-function mutations in the genes encoding ABCA3 (member 3 of subfamily A of the ABC group of adenosine triphosphate-binding proteins) and heterozygous mutations affecting the expression of the SFTPC (surfactant protein C) gene.

MATERIAL AND METHOD: We perform the MLPA analysis (multiplex ligation-dependent probe amplification) to evaluate the CNCs (copy number changes) for 39 patients diagnosed with RDS using SALSA MLPA probemix P314-A1 ABCA3-SFTPC. The kit investigates 33 exons for ABCA3 gene located on chromosome 16p13.3 and 6 exons for SFTPC gene located on chromosome 8p21.3. The probemix was used in combination with SALSA MLPA reagent kit and data was analyzed with Coffalyser.Net software.

RESULTS: Most of the dosage quotient of each individual reference probe in our study had a value between 0.80 and 1.20, required and purported in the product description. The results revealed a decreased signal probe for ABCA3 gene spanning exon 9, 14 and in two patients in exon 15. Moreover, for SPFTC gene a signal abnormality like a decreased final ratio was highlight in exon 1. Most changes in the SFTPC and ABCA3 genes are point mutations, in most populations such that changes should be confirmed by another molecular technique or target sequencing, whenever possible.

CONCLUSIONS: Considering the results obtained, the analysis of MLPA in newborn patients with deficiencies in surfactant components and respiratory distress syndrome continues to be a matter of debate, therefore larger cohort studies are needed for pertinent conclusions.

Acknowledgements: This work was supported by the University of Medicine, Pharmacy, Science and Technology “George Emil Palade” of Targu Mures Research Grant number 10127/20/17.12.2020. Part of this work was performed using the infrastructure of Center for Advanced Medical and Pharmaceutical Research of the “George Emil Palade” University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania.

AUTOSOMAL DOMINANT OPTIC ATROPHY – CASE REPORT

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Introduction A neuro-ophthalmic condition known as autosomal dominant optic atrophy (ADOA) causes gradual loss of vision on both sides, pallor of the optic disc, loss of central vision, and colour vision impairment. A small minority of patients also have hearing loss and ataxia, and recent research indicate that cardiac and neuromuscular functioning may be disrupted.

Case summary This abstract presents a comprehensive case study of a 10-year-old patient diagnosed with optic atrophy related to the presence of a heterozygous pathogenic variant in the OPA1 gene.

The patient reported a history of approximately 2 years of gradual vision loss. Ophthalmologic examination revealed reduced temporal retinal nerve fiber layer, reduced visual acuity, significant reduction of ganglion cells in both eyes . An extensive work-up was performed, including indirect ophthalmoscopy, biomicroscopy, optical coherence tomography, electroretinography, neuroimaging and genetic testing.

Despite the absence of a curative treatment for OPA1 related optic atrophy, patient management focused on visual rehabilitation strategies, permanent wearing of corrective lenses and the possibility of starting idebenone treatment. The patient and his family were offered genetic counseling, emphasizing the hereditary nature of the condition and potential implications for future generations.

Conclusions This case serves as a reminder of the value of genetic testing in supporting the diagnosis of optic atrophy related to OPA1 gene mutation and the necessity of a multidisciplinary approach to patient care. It also emphasises the difficulties of treating a genetically based condition with few effective treatment choices.

X-LINKED RETINOSCHISIS – CASE REPORT

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Introduction X-linked retinoschisis (XLRS) is characterized by splitting of the retinal layers, mild to severe visual impairment, and a decrease in the amplitude of the dark-adapted b-wave on the electroretinogram. Macular and peripheral schisis are typical clinical characteristics.

Case summary This abstract presents a case study of a 7-year-old male patient diagnosed with X-linked juvenile retinoschisis. The patient presented with a history of gradually worsening vision. Hereditary history revealed that the older brother also suffered from ophthalmic pathology.

Ophthalmological examination revealed visual acuity impairment and macular damage. Optical coherence tomography (OCT) confirmed the presence of schisis cavities within the retina. Molecular genetic analysis of the RS1 gene was performed and a hemzygos pathogenic variant was detected.

The patient underwent a thorough ophthalmologic examination, which included testing the patient's best-corrected visual acuity, examining the anterior segment and dilated fundus, ultra-wide-field retinography, spectral-domain optical coherence tomography, performing fluorescein angiography, electroretinography and performing a visual field test.

Conclusions This case underscores the significance of early detection and intervention in managing retinoschisis, particularly in cases with usual presentations or genetic susceptibility. The use of topical dorzolamide in such circumstances has demonstrated variable response, despite the lack of a clear treatment being documented. Here, we present a case of XLRS with a foveal schisis that responded well to topical dorzolamide. Early topical dorzolamide therapy in XLRS can lessen the development of macular schisis and its accompanying problems, such as lamellar and full-thickness macular holes.

A RARE CAUSE OF NEONATAL HYPOGLYCEMIA

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Background Congenital hyperinsulinism (CH) is a genetic disorder characterized by an inappropriate response of insulin secretion to low plasma glucose levels. Several genes could be involved, the most common one being ABCC8, a gene encoding the sulphonlyurea receptor 1 (SUR1) subunits of the KATP channel complex. In infants and young children, repeated episodes of hypoglycemia could lead to breathing difficulties, seizures, intellectual disability, vision loss, brain damage, and coma.

Methods We aim to present the case of a 1month old boy from a consanguineous family, delivered early-term that was referred to us for persistent hypoglycemia. After repeated episodes of hypoglycemia in intensive care and different hormone levels tests, the multidisciplinary team has decided to perform a hypoglycemia and metabolic newborn screening NGS panel.

Results Our first set of endocrinological tests showed a severe hypoglycemia (value could not be determined), normal cortisol and insulin levels, and an elevated C-peptide level.

A second set revealed high growth hormone levels and normal thyroid stimulating hormone. A genetic test was only available a few months later, when we proceeded to a hypoglycemia and metabolic newborn screening NGS analysis which identified a homozygous pathogenic variant in ABCC8 – c.1960dup (p.Glu654Glyfs*22).

Conclusions Prompt diagnosis and management of CH is critical for preventing brain damage and improving outcomes. CH management requires the integration of clinical, biochemical, molecular, and imaging findings to establish the appropriate treatment.

Acknowledgements: The authors would like to thank the neonatology team for support and making the data available for this paper.

GENETIC DIAGNOSIS OF INBORN ERRORS OF IMMUNITY

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Background/Objectives: Primary immunodeficiencies (PID), for which the name inborn errors of immunity (IEI) is now preferred, represent a group that includes more than 485 heterogeneous pathologies with a wide variability of clinical manifestations. The identification of a specific pathogenic variant that explains the patient's phenotype can help to predict the clinical outcome, to provide personalized management with a multidisciplinary team, and to offer genetic counseling for other family members.

We aim to establish the proportion of positive results in the group of patients with signs of IEI.

Methods: We retrospectively evaluated the results of genetic testing of 92 index patients using WES (whole exome sequencing), WGS (whole genome sequencing) or gene panels - a primary immunodeficiency panel (including different number of genes from 274 to 4813 genes).

Results: Of 92 patients who were evaluated and genetically tested, 46% (44 patients) had a positive result, and 25% (23 patients) had variants of uncertain significance. 38 genes with pathogenic variant and 11 likely pathogenic genes were identified. The most frequently encountered genes were: TRNT1, DNAJC21, JAGN1, MSH6 and CFTR.

Conclusion: Due to the pleiotropism of inborn errors of immunity, the establishment of genetic diagnosis has been hampered by the lack of optimized test solutions for maximum diagnostic yield. The complexity and diversity of IEI also lies in the fact that the same clinical picture can be determined by several genes or a single gene can be associated with several diseases/phenotypes.

Acknowledgements: We thank the families of these patients for their trust and cooperation, Regional Center of Medical Genetics Timis, Clinical Emergency Hospital for Children "Louis Turcanu" Timisoara.

GENETIC PROGNOSTIC AND RISK FACTORS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Chronic Lymphocytic Leukemia (CLL) is the most prevalent among adults and constitutes 25% of adult leukemia cases. Patients may remain asymptomatic without needing treatment for extended periods, while others experience rapid progression despite aggressive therapies. Genetic abnormalities like chromosomal aberrations (copy number variations, CNVs), gene mutations, IGHV gene hypermutation, and single nucleotide polymorphisms (SNPs) are widespread in CLL and carry significant prognostic implications. Our study aimed to comprehensively investigate the genetic profile of CLL patients and characterize the diversity of genetic anomalies.

Materials and methods: We analyzed 125 CLL patients and 239 healthy controls for comparative SNP analysis. Genetic investigation included MLPA (Multiplex ligation-dependent

probe amplification) analysis for CNVs across multiple chromosomal regions, identification of somatic mutations (NOTCH1, SF3B1, and MYD88), mutational status testing of the IGHV gene in two regions, and cytokine SNP analysis for IL-10 rs1800896, IL-10 rs1800872, TNF rs361525, and TNF rs1800750.

Results: MLPA analysis revealed CNVs in 39% of patients, somatic mutations in 13.6%, and co-occurrence of somatic mutations and CNVs in 9.3%. Regarding mutational status, 68.8% had unmutated IGHV, while 31.2% had mutated IGHV in one or both studied regions. SNP analysis indicated variant alleles in 64.8% of patients for IL-10 rs1800896, 48.8% for IL-10 rs1800872, 3.2% for TNF rs361525, and 0.8% for TNF rs1800750. All 125 CLL patients exhibited genetic alterations, with 95.2% having multiple genetic risk factors. Survival was significantly influenced by the combination of unmutated IGHV and CNVs and/or gene mutations ($p<0.001$).

Conclusion: Frequent co-occurrence of multiple genetic alterations significantly impacts prognosis in CLL.

Acknowledgements: Grant from the Romanian Ministry of Education and Research, CNCS—UEFISCDI, project number PN-III-P4-ID-PCE-2020-1928, within the PNCDI III, contract no. PCE 72/2021

GENETIC ANALYSIS OF CNVS IN ROMANIAN CHILDREN WITH DEVELOPMENTAL DELAY, INTELLECTUAL DISABILITY AND MULTIPLE CONGENITAL ANOMALIES

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Background: Intellectual disabilities encompass a varied range of neurodevelopmental disorders with a significant genetic component. This underscores the need for adopting effective guidelines and using advanced molecular genetic techniques in screening and diagnosis for patients in Romania. Our study aimed to assess the frequency of copy number variations (CNVs) in pediatric patients with global developmental delay (GDD), intellectual disability (ID) and multiple congenital anomalies (MCA) using Multiplex Ligation-dependent Probe Amplification (MLPA) technique.

Material and methods: We've included in our study 173 children with GDD, ID, and MCA after stricter selection criteria. MLPA analysis was performed using a combination of kits P245, P064, P036, and P070. Several detected rare chromosomal rearrangements were confirmed using MLPA follow-up kits.

Results: A diagnostic rate of 17.34% for CNVs was achieved among 173 cases with GDD, ID and MCA. Among the CNVs identified, the highest frequency of occurrences was observed within the 22q13 chromosomal region, succeeded by the 17p13, 1p36, 15q11, 10q26, and 11q25 regions. Epilepsy showed a significant correlation with detected CNVs and no correlations between the detected CNVs, the demographic characteristics of the subjects, and their clinical manifestations.

Conclusions: The study highlights the utility of MLPA as a cost-effective tool for diagnosing CNVs in patients with GDD, ID and MCA, particularly when advanced microarray techniques are unavailable. A combined approach of molecular techniques improves diagnostic rates and enhances genetic counselling, contributing to better clinical management and prevention strategies.
Keywords: developmental delay, intellectual disability, congenital anomalies, MLPA, CNV

Acknowledgements

1. National Program of Health of Women and Children VI.2. Women's Health Subprogram 3. Prevention of Genetic Diseases by Pre- and Postnatal Diagnosis.

2. Detection of copy number variations located at 3p26.3, 8p23.1 and 9p24 by Real-Time PCR method in children with intellectual disability, contract 615/6/17.01.2019, CIGCS project, UMFST GE Palade of Târgu Mureș

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

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Introduction: The Multiplex Ligation-dependent Probe Amplification technique, or MLPA, is a multi-target PCR based method able to simultaneously detect structural abnormalities for up to 50 different genomic DNA or RNA sequences, in a single PCR-based reaction. MLPA is a quick and reliable technique to identify inherited or acquired DNA copy number changes, as well as to investigate the methylation status of DNA sequences.

Material and Method: At CRGM Dolj we investigate samples coming from patients with known genetic conditions in their families or with clinical features that point towards a genetic disorder. We processed more than 1300 samples from different types of tissue. The investigations were performed using the SALSA MLPA probemixes and SALSA MLPA Reagent kits.

Results: The detection rate for genetic disorders in postnatal diagnosis was 16.5%. Among the diseases diagnosed in our center we name: Williams-Beuren Syndrome, Fragile X Syndrome, Neurofibromatosis Type I, 1p36.32->1p36.33 deletion, Duchenne Muscular Dystrophy, Spinal Muscular Atrophy, Charcot–Marie–Tooth disease, DiGeorge Syndrome, 22q11 duplication, 15q13.3 microdeletion/ microduplication syndrome, 16p11.2 deletion syndrome, GRIN2B-Related Neurodevelopmental Disorder, X-linked Alport syndrome.

Discussions: MLPA is a fast and robust molecular analysis technique that can be used to detect a wide variety of structural abnormalities in genomic DNA. The results, however, should always be confirmed through other methods and not all deletions and duplications detected by MLPA are pathogenic, one needing to consult the latest scientific literature when interpreting them. There are also limitations regarding this technique, namely regarding the inability to determine single nucleotide polymorphisms or mosaicisms.

Key words: DNA, Ligation, Probe.

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

STÜVE-WIEDEMANN SYNDROME - A COMPLICATED PATH TOWARDS A DIAGNOSIS

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Background. With a prevalence lower than 1 in 1,000,000 individuals, Stüve-Wiedemann (SW) syndrome represents a challenging diagnosis. This severe condition is apparent from birth, and it is characterized by bone abnormalities (frequently an abnormal bowing of the long bones in the legs) and dysfunction of the autonomic nervous system. SW syndrome is an autosomal recessive disease caused by mutations in the LIFR gene.

Methods. In this poster, we describe a premature 6-year-old boy who was referred to us at the age of 5 months for motor delay, severe hypotonia, congenital arthrogryposis, abnormal bowing of the upper and lower limbs, ophthalmological problems, recurrent respiratory infections and feeding difficulties. The clinical manifestations evolved progressively, with the patient requiring numerous surgical interventions, especially for the bone and ocular abnormalities.

Results. Multiple genetic tests were performed (karyotype, microarray and TruSight One NGS panel), but all the results were negative. A whole exome sequencing (WES) provided an answer for our patient, identifying a homozygous mutation in LIFR - NM_001127671.1:c.756dup, p.(Lys253fs*).

Conclusions. SW syndrome is a rare and severe genetic disease requiring complex multidisciplinary care. The choice to perform a genetic diagnosis test is based on the clinical patterns, and when patients have an atypical timeline, the diagnosis could be delayed. We hope this case will contribute to a better description of the evolution of SW syndrome and an improved pediatric management.

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

EPILEPSY MICRORNA BIOMARKERS IDENTIFIED USING BIOINFORMATICS TECHNIQUES

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Introduction Epilepsy is a common disorder, having a wide clinical spectrum and large genetic heterogeneity. Although a well-researched disease, there are still unknown pathogenic mechanisms in epilepsy. High-throughput RNA sequencing methods have been widely used in epilepsy studies to identify biomarkers. Many studies looked into the impact of microRNAs in epilepsy.

Methods We used microRNA counts data GSE193842 to look for microRNA biomarkers in epilepsy. Two bioinformatics approaches have been used. Firstly, DeSeq2 Bioconductor R package was used to look for differentially expressed microRNAs. Then, we predicted the target genes and performed gene set enrichment analysis. In the second approach, we performed supervised

classification using algorithms in MLSeq R package: SVM, LR, kNN, RF, PLDA, PLDA2, NBLDA and voomNSC.

Results 9 microRNAs were significantly differentially expressed, out of which 3 were upregulated and 6 were downregulated. Functional analysis revealed enriched terms and pathways: NF kappa B signaling, regulation of mRNA metabolic process, negative regulation of molecular function, lytic vacuole membrane. SVM classifier had the highest mean accuracy, while voomNSC was the sparse classifier, selecting the lowest number of features.

Conclusion Hsa-mir-21-5p was the common microRNA identified as potential biomarker for epilepsy by both bioinformatics approaches we used. Transcriptomic data together with bioinformatics analyses have high potential to identify prognostic and diagnostic biomarkers in diseases.

Acknowledgements: Proiect "Extinderea serviciilor medicale și comunitare pentru persoanele afectate de boli genetice și rare, acronim MEDI.COM-RARE" finantate de Programul "Provocări în sănătatea publică la nivel european" Sursa principală de finanțare: Mecanismul Financiar al Spatiului Economic European 2014-2021"

AT THE INTERSECTION OF CARDIOGENETICS AND EXTRACELLULAR MATRIX PROTEINS, A PRIMER FOR THE COMPLEX WEB OF CARDIOVASCULAR DISEASE ETIOLOGY

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Cardiovascular diseases (CVDs) represent a significant global health burden, with diverse genetic and metabolic factors contributing to their complex etiology. Cardiogenetics has made remarkable strides in identifying mutations associated with inherited cardiac conditions. Metabolic pathways intricately intertwined with cardiac function can be disrupted by genetic mutations, leading to a spectrum of clinical presentations ranging from mild cardiac dysfunction to severe congenital heart anomalies. Through next-generation sequencing technologies and genome-wide association studies, clinicians and researchers have identified key genetic variants linked to arrhythmias, cardiomyopathies, and sudden cardiac death. Thoracic aortic diseases with a hereditary component (HTAD) can be categorized into two groups: syndromic, which encompasses conditions like Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and others, and non-syndromic, where recognizable physical traits are absent.

These conditions are linked to mutations in several genes that impact extracellular matrix proteins, the signaling pathway of transforming growth factor-beta (TGF-β), and the function of smooth muscle contraction. Besides, molecular autopsy have shed light on the intricate interplay between genetic variations, metabolism and cardiac pathologies. This work aims to pinpoint our experience for the convergence of these fields. We will outline several points to consider in the

practice – from diagnostic of syndromes affecting heart and connective tissue, to few aspects of molecular autopsy (including myocardium), an emerging field in medicine, that has transformed our understanding of sudden unexplained deaths, particularly in young individuals. Integrating these findings into clinical practice has enabled personalized risk assessment, early diagnosis, and tailored treatment strategies for affected individuals and their families. This multidisciplinary approach offers a framework for deciphering the complex web of factors contributing to hereditary cardiac conditions. By harnessing the power of advanced genomic technologies and metabolic insights, clinicians and researchers are paving the way for precision medicine strategies that hold promise for early diagnosis, risk stratification, and targeted interventions, steering us closer to a future of improved cardiovascular health.

Acknowledgements: We thank the patients and their families who have shown unwavering strength and resilience in the face of cardiogenetic disorders

ROLE OF CATECHOL O-METHYLTRANSFERASE GENE VAL158MET POLYMORPHISM IN PATHOLOGY AND DISTRIBUTION IN HEALTHY ROMANIAN VOLUNTEERS

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Introduction: During the last years, numerous genetic association studies have attempted to detect functional gene polymorphisms that contribute to behavior or to the susceptibility for the complex diseases. One of the problems of genetic association studies is the variability in results, which can be explained, in part, by population stratification. One of the most studied polymorphisms in relation to diverse phenotypic associations (various cognitive abilities in healthy individuals and/or people with neuropsychiatric disorders) is the Val158/108Met single nucleotide polymorphism (SNP) in the catechol-O-methyltransferase (COMT) gene; while some studies associate this SNP with major depression or panic disorders, other studies have failed to find any association. The objectives of this study were: (1) to discuss the implication of this polymorphism in human pathology and (2) to describe the distribution, for the first time, of COMT Val108/158Met polymorphism in a large sample of Romanian healthy volunteers. Materials and methods: A sample of N=1323 healthy volunteers were genotyped for the above mentioned SNP. DNA was extracted from buccal epithelial cells or blood and the SNP genotyping was performed using polymerase chain reaction-based restriction fragment length polymorphism assay. To evaluate the genotypes distribution, alleles frequencies and Hardy-Weinberg equilibrium we used $\chi 2$ test run in SPSS. Results: The distribution of COMT Val108/158Met genotypes in our sample was: 27.9%Val/Val, 48.3% Val/Met and 23.8% Met/Met. The alleles frequency was 52.04% for the Val allele and 47.96% for the Met allele. The genotypes were in Hardy-Weinberg equilibrium ($\chi 2 = 1.39$, $p = 0.24$). Conclusion: The results from this study extends the efforts to map the allelic distribution of COMT Val158/108Met alleles in populations around the world and emphasizes that population stratification should be controlled for next studies that could report phenotypic associations in DNA samples from different populations.

Acknowledgements: To the dedicated volunteers, students in Psychology at Babeș-Bolyai University, for their invaluable contributions to our genetic studies.

MULTIDISCIPLINARY APPROACH IN FAMILIAL LYMPHOHISTIOCYTOSIS–RETROSPECTIVE STUDY IN IIIRD PEDIATRICS CLINIC

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Introduction.Familiar lymphohistiocytosis (FHL) are defined as genetically dysfunctions which are present in children under one year (70%). They are characterized by hyper-inflammation caused by the proliferation and activation of lymphocytes and macrophages, and depending on the genetic defect, they are classified in various clinical forms. CHS1 / LYST mutation is present in Higashi Chediatric Syndrome (HCS), and RAB27A mutation is present in Griscelli Syndrome (GS). Although the therapeutic indication for allogeneic transplantation for curative purposes is required as close as possible to the time of diagnosis, the unfavorable evolution towards death in phases of disease acceleration motivates the palliative approach to these cases from the beginning.

Objectives .We proposed a retrospective analysis of FHL cases, 7 cases were included in the study, 2 cases of SCH, 1 case of FHL type V, 4 cases of SG. years from the point of view of the complex curative and palliative medical approach analyzing the limits and challenges until the end of life, both for the medical staff and for the family.

Material and methods.These cases were selected from the onco-hematological pathology of the Pediatric Clinic III between 2010-2020. The clinical and para-clinical data were analyzed to allow the diagnostic classification and the evolution until the moment of death, as well as the psycho-emotional aspects and support of the family.

Results.In SCH, the diagnosis was established early at 3 and 2 months of age, respectively, while in SG the diagnosis was established after the age of: 1 month, 3 years, 4 years and 5 years respectively. Splenomegaly, inguinal lymphadenopathy and umbilical fistula, in the first case SCH, and in the second, skin infection of the earlobe, caused by albinism. In the case of SG, in addition to bicitopenia and organomegaly, progressive and rapid neurological degradation required palliative care. The hematological picture and the analysis of the hair guided the diagnosis.

Allogeneic transplantation was performed in a single case of SG with good subsequent evolution and in the second case being preparation. At SCH it was not possible to perform allogeneic transplantation, but curative therapy was attempted in the first case, according to the HLH Protocol, but with partial response. For 6 months, to subsequently present 3 phases of acceleration and finally evolution towards death. In the second case of SCH, only palliative care was performed, the evolution was progressive towards rapid neurological degradation and death at 6 months of follow-up. The presence in the same family of SCH at 8 years and SG at 2 years made the approach of the family more challenging.

Conclusions. FHL are rare diseases with an unfavorable prognosis, and the limits of curative therapy require a palliative approach from the beginning of the disease.

MULTIDISCIPLINARY APPROACH IN FAMILIAL LYMPHOHISTIOCYTOSIS–RETROSPECTIVE STUDY IN IIIRD PEDIATRICS CLINIC

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Introduction. Familiar lymphohistiocytosis (FHL) are defined as genetically dysfunctions which are present in children under one year (70%). They are characterized by hyper-inflammation caused by the proliferation and activation of lymphocytes and macrophages, and depending on the genetic defect, they are classified in various clinical forms. CHS1 / LYST mutation is present in Higashi Chediatric Syndrome (HCS), and RAB27A mutation is present in Griscelli Syndrome (GS). Although the therapeutic indication for allogeneic transplantation for curative purposes is required as close as possible to the time of diagnosis, the unfavorable evolution towards death in phases of disease acceleration motivates the palliative approach to these cases from the beginning.

Objectives. We proposed a retrospective analysis of FHL cases, 7 cases were included in the study, 2 cases of SCH, 1 case of FHL type V, 4 cases of SG. years from the point of view of the complex curative and palliative medical approach analyzing the limits and challenges until the end of life, both for the medical staff and for the family.

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