



ICORD

We inspire global collaboration
among all rare disease stakeholders



17th Annual ICORD Meeting

14-16 November 2025

DEU Sabanci Cultural Center
Izmir, Türkiye

BOOKS OF ABSTRACT

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“17th Annual ICORD Meeting”

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“17th Annual ICORD Meeting”

Dear Colleagues,

It is our great pleasure to invite you to the 17th ICORD Meeting, which will take place from November 14-16 at the 9 Eylül Sabancı Cultural Center in Izmir, Turkey. This prestigious event will bring together experts, researchers, healthcare professionals, patient advocates, and policymakers from around the world to discuss the importance of rare diseases and strengthen international collaboration in this critical field.

As a global network dedicated to improving the lives of those affected by rare diseases, ICORD (International Meeting on Rare Diseases & Orphan Drugs) fosters international cooperation by bringing together stakeholders to share knowledge, promote research, and advocate for better policies. This meeting will serve as a vital platform to exchange ideas, discuss innovative solutions, and advance global efforts in rare disease diagnosis, treatment, and care.

We look forward to welcoming you to Izmir for an engaging and productive meeting where we can work together to advance the global fight against rare diseases through international collaboration and innovation.

With kind regards,

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“17th Annual ICORD Meeting”

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14 KASIM 2025	
09.00 - 09.20	Açılış Konuşmaları <i>Uğur ÖZBEK, Ali Osman KILIÇ</i>
09.20 - 10.20	PANEL: Türkiye'de Nadir Hastalıkların Yönetimi Oturum Başkanları: Murat GÜLŞEN, Munis DÜNDAR
09.20 - 09.40	Türkiye Nadir Hastalıklar Eylem Planı <i>Hikmet Can ÇUBUKCU, Sağlık Bakanlığı</i>
09.40 - 10.00	TÜSEB - Türk Genom Projesi ve Nadir Hastalıklar Ayağı <i>Tunç TUNCEL, TÜSEB</i>
10.00 - 10.20	Nadir Hastalıklarda Tarama <i>Yüksel Hakan AYDOĞMUŞ, Sağlık Bakanlığı - (Online)</i>
10.20 - 11.00	Kahve Arası
11.00 - 12.00	PANEL: Nadir Hastalıklarda Türkiye Deneyimi Oturum Başkanları: Ercan MIHÇI, Haluk AKIN
11.00 - 11.15	ACURARE ve İstisna Projesi ve Tanısız Hasta Platformu <i>Özden HATIRNAZ NG, Acıbadem Ü.</i>
11.15 - 11.30	RAREBOOST Projesi ve Ege Bölgesi Deneyimi <i>Uğur ÖZBEK, İBG</i>
11.30 - 11.45	Ankara Üniversitesi Nadir <i>Tuba EMİNOĞLU, A.Ü.</i>
11.45 - 12.00	İstanbul Üniversitesi Nadir <i>Güliden GÖKÇAY, İ.Ü.</i>
12.00 - 13.00	PANEL: Tedavi Edilebilir Nadir Hastalıklar Oturum Başkanları: Özgür ÇOĞULU, Semra HIZ, Gökay BOZKURT
12.00 - 12.20	Nadir Hastalıklarda Ex Vivo ve İn Vivo Gen Tedavileri <i>Musa KARAKÜKÇÜ, Erciyes Ün.</i>
12.20 - 12.40	Nörolojik Hastalıklar <i>Uluç YIŞ, DEÜ</i>
12.40 - 13.00	Hereditör Anjioödem <i>Nihal METE GÖKMEN, Ege Ün.</i>
13.00 - 14.00	Öğle Yemeği
14.00 - 14.30	UYDU SEMPOZYUMU - PHARMİNAL Olgu örnekleri ile hedefe yönelik tedavilerle immün yetmezlikler: Gerçekten nadir mi? <i>Ceyda TUNAKAN DALGIÇ, Ege Ün.</i> Oturum Başkanı: Ayça AYKUT
14.30 - 16.00	Panel: Nadir Hastalıklar İçin Klinik Araştırmalar: Bakış Açıları ve Değerlendirmeler Oturum Başkanları: Hamdi AKAN, Okay ÇAĞLAYAN, Erdener ÖZER
14.30 - 15.00	Nadir Hastalıklar İçin Klinik Araştırmalardaki Fırsatlar ve Zorluklar <i>Yeşim TUNÇOK, DEÜ</i>
15.00 - 15.30	Türkiye'de Nadir Hastalıklar İçin Yapılan Klinik Araştırmalara Araştırmacıların Bakış Açısı <i>Fatih EZGÜ, Gazi Ün.</i>
15.30 - 16.00	Türkiye'de Nadir Hastalıklar İçin Klinik Araştırmalara İlaç Endüstrisinin Bakış Açısı <i>Umut MÜREN, Sanofi Türkiye ve Orta Doğu Ülkeleri Klinik Araştırmalar Ünitesi Direktörü</i>
16.00 - 16.10	Tartışma
16.10 - 16.30	Kahve Arası

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14 NOVEMBER 2025	
09:00 - 16:30	3. Ulusal Nadir Hastalıklar Sempozyumu
16:30 - 17:00	Opening Ceremony and Welcome Address <i>Uğur ÖZBEK, Rumen STEFANOV, Bayram YILMAZ, Rector</i>
17:00 - 18:30	Keynote lecture by ICORD representatives, Turkish health officials, and global rare disease advocates. Chair: <i>Uğur Özbek, Rumen Stefanov</i> <i>A Global Approach to Rare and Undiagnosed Diseases - David PEARCE - International Rare Diseases Research Consortium</i> <i>"ERDERA As a Strategic Backbone for Europe's Rare Disease Ecosystem - Başak UYSAL - ERDERA</i>
15 NOVEMBER 2025	
Day 1: Innovations in Rare Diseases	
08:30 - 10:00	Session 1: Advances in Genomic Medicine Chair: <i>Neşe ATABEY, Munis DÜNDAR, Mehmet ÖZTÜRK</i>
08:30 - 09:00	Understanding human genome: Latest technologies to functionally characterize human genes and model genetic diseases <i>Mazhar ADLI - Northwestern University</i>
09:00 - 09:30	International Collaborations: Genome studies from the Middle East. <i>Khalid FAKHRO - Sidra Medicine, Qatar</i>
09:30 - 10:00	Sustainable Genomics in Rare Disease Diagnosis <i>A. Zeynep TUMER, Kopenhagen-DK - (ONLINE)</i>
10:00 - 10:30	Coffee Break
10:30 - 12:00	Session 2: Newborn Screening and Early Intervention Chair: <i>Beyhan TÜYSÜZ, Funda TÜZÜN ERDOĞAN, Özlem GİRAY BOZKAYA</i>
10:30 - 11:00	Expanding Newborn Screening: Regional experiences and lessons learned. <i>Dr. Peter SCHIELEN - International Society for Neonatal Screening (ISNS) (ONLINE)</i>
11:00 - 11:30	Preventive Strategies: The role of early diagnosis in reducing disease burden. <i>Ahmad N. Abou TAYOUN - Al Jalila Children's Specialty Hospital, UAE</i>
11:30 - 12:00	One Health Approach: Integrating human, animal, and environmental health for rare disease prevention. <i>Alberto MANTOVANI - Italy</i>
12:00 - 13:00	Lunch Break
13:00 - 13:30	How To Combine Genomics, Deep Phenotyping, and AI to Diagnose Patients with Rare Diseases  Speaker: Dr. Tolga ASLAN Chair: Berk ÖZYILMAZ, Ozan ÇETİN
13:30 - 15:00	Session 3: Gene Therapy and Innovative Treatments Chair: <i>Ferda ÖZKINAY, Fatih EZGÜ</i>
13:30 - 14:00	Gene and Cell Therapies for Inborn Metabolic Disorders: State of the Art and Future Directions <i>Fatih EZGÜ - Gazi Univ</i>
14:00 - 14:30	Challenges in Delivery and Access: Logistical and regulatory hurdles in the region. <i>Bilge Esin ÖZTÜRK - MeiraGTx, UK</i>
14:30 - 15:00	Platform Therapies: Progress in vector-based gene therapies and their scalability. <i>Afroz RASHNONEJAD - Ohio State Univ (ONLINE)</i>
15:00 - 15:30	Coffee Break
15:30 - 16:30	Session 4: Patient-Centered Care and Advocacy Chair: <i>David PEARCE - International Rare Diseases Research Consortium, Oleg KVLIVIDZE - Georgia</i>
15:30 - 15:50	The Role of Advocacy Groups: Highlighting the work of patient advocacy organizations. <i>Mikk and Helene CEDEROTH - Wilhelm Foundation (ONLINE)</i>
15:50 - 16:30	Panel Discussion: Bridging gaps between patients, healthcare providers, and policymakers. Debaters: <i>Çağdaş CANBOLAT, ISMRD</i> <i>Zeynep ÇAKIR</i> <i>Şeyda Nur HALİTOĞLU</i>
16:30 - 18:00	Networking and Poster / ORAL Presentations Session Chairs: Tahir ATİK, Ferda PERÇİN, Aslı Ece SOLMAZ, Aslı SUBAŞI, Şehime GÜLSÜN TEMEL Click here for Oral Presentation Sessions
	Showcase of local and international research projects, with a focus on regional initiatives.

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16 November 2025	
Day 2: Translational Research and Global Collaboration	
09:00 - 10:30	Session 5: Economic and Public Health Perspectives Chair: Rumen STEFANOV, Hakkı Muammer KARAKAŞ
09:00 - 09:30	Cost-Effectiveness of Rare Disease Therapies: Balancing innovation and affordability. <i>Georgi ISKROV</i>
09:30 - 10:00	Regional Initiatives: Examples from Turkey, the Balkans, and the Middle East. <i>Rumen STEFANOV</i>
10:00 - 10:30	WHO Resolution “Rare Diseases: a Global Health Priority for Equity and Inclusion” <i>Domenica TARUSCIO</i>
10:30 - 11:00	Coffee Break
11:00 - 12:30	Session 6: Scientific Breakthroughs and Emerging Therapies Chair: Hamdi AKAN, Mehmet Birhan YILMAZ
11:00 - 11:30	Updates on Clinical Trials: Progress in gene therapy and other innovative treatments <i>Heather GRAY-EDWARDS</i>
11:30 - 12:00	CNS Disorders: Advances in therapies for rare neurological conditions. <i>V. Göknur HALILOĞLU</i> - Hacettepe Univ, Türkiye
12:00 - 12:30	Evolving landscape of the treatment for Duchenne muscular dystrophy. Bulgarian experience. <i>Teodora CHAMOVA</i> - Sofia Medical University (<i>ONLINE</i>)
12:30 - 13:30	Lunch Break
13:30 - 15:00	Session 7: Education and Capacity Building Chair: Domenica TARUSCIO, Levent ALTINTAŞ
13:30 - 14:00	Training Healthcare Professionals: Enhancing skills for rare disease diagnosis and management. <i>Manuel POSADA</i>
14:00 - 14:30	Patient and Family Education: Empowering patients through knowledge and resources. <i>Stephen C. GROFT</i> (<i>ONLINE</i>)
14:30 - 15:00	Regional Programs: Transferring expertise to Latin America, South Asia, and other regions. <i>Emilio ROLDAN</i>
15:00 - 16:00	Closing Ceremony and Future Directions
	Summary of key takeaways and actionable recommendations.
	Announcement of ICORD 2026 location and themes.
	Networking reception.

ORAL PRESENTATIONS

O-01 WHO Resolution “Rare Diseases: A Global Health Priority for Equity and Inclusion”: From Principles to Actions

Domenica Taruscio, Former Director of the National Centre Rare Diseases, Istituto Superiore di Sanità (Italy), Permanent UDNI Board Member; ICORD Past-President. President Study Centre KOS-Science, Art, Society. domenica.taruscio@gmail.com

The Resolution “Rare Diseases: a Global Health Priority for Equity and Inclusion” has been officially adopted at the 78th World Health Assembly (WHA78) on 24 May, 2025.

This first-ever WHO Resolution declares rare diseases a global health priority, underscores equity and inclusion, emphasizing the need to ensure that no patient is left behind and the importance of adopting an integrated, person-centered approach.

The landmark decision recognizes that over 300 million people globally live with one of more than 7000 rare diseases, most of which begin in childhood and can lead to significant physical, emotional, and financial hardship.

The document represents a milestone in global healthcare, it commits countries to integrate rare diseases into national health planning, improve diagnosis and care through universal health coverage, promote inclusive policies, and accelerate innovation, research, and access to affordable treatment. In particular, the Resolution highlights the need for inclusive and sustainable policies that ensure access to adequate care and support for patients and families: it urges Countries implementing comprehensive action plans that integrate increased scientific knowledge, healthcare and social care organization, taking into account people's quality of life.

Importantly, the document commits WHO to stimulating and monitoring Member States' actions and developing a 10-year global action plan with measurable indicators to guide progress towards equity, accessibility, inclusion, and universality of healthcare and social care services.

The Resolution represents a unique opportunity to revitalize country's national plans or strategies for rare diseases, as well as to initiate action in the many Countries that are still lagging behind; meanwhile, it contributes to raise awareness toward rare diseases as a global health issue. Therefore this important WHO initiative can foster international scientific co-operation, sharing expertise, data and good practices as well promote reducing healthcare inequalities among rare disease patients in different Countries or world's areas.

O-02 Role of Serological Methods in Infantile Myasthenia Gravis Masked by Central Nervous System Findings

Merkezi Sinir Sistemi Bulgularıyla Maskelenen İnfantil Miyastenia Graviste Serolojik Yöntemlerin Rolü

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Introduction: Myasthenia gravis (MG) is a rare autoimmune neuromuscular disorder in infancy, characterized by fluctuating muscle weakness due to impaired neuromuscular transmission. Diagnosing MG in early childhood is particularly challenging because of its nonspecific symptoms. In preterm infants with neuroimaging abnormalities such as periventricular leukomalacia (PVL), central nervous system (CNS) etiologies are often prioritized, potentially delaying the correct diagnosis.

Case: We present a 19-month-old girl, born at 31 weeks of gestation weighing 900 grams as a small-for-gestational-age preterm dizygotic twin, with a two-month neonatal intensive care unit stay. She presented with eyelid drooping, first noticed on the left side at 16 months, initially thought to be post-traumatic. Over time, bilateral ptosis became evident, fluctuating throughout the day and improving after rest. Mild limitation of left eye adduction was also observed. Other neurological examinations were unremarkable.

Cranial magnetic resonance imaging (MRI) showed periventricular FLAIR hyperintensities compatible with periventricular leukomalacia (PVL), initially leading to the suspicion of central causes. The acetylcholine receptor (AChR) antibody test was initially performed using the RIA (radioimmunoassay) method and found to be negative. However, due to persistent clinical suspicion, the test was repeated using the IRMA (immunoradiometric assay) method, which yielded a positive result (0.84; reference>0.40).

Repetitive nerve stimulation was within normal limits. However, single-fiber electromyography (SFEMG) of the facial muscles revealed increased jitter in 7 out of 8 fiber pairs, consistent with a neuromuscular transmission defect. Orbital MRI and thoracic computerized tomography were normal.

Pyridostigmine treatment (0.5 mg/kg/dose, 4 times/daily) led to a marked improvement in ptosis, and the dose was adjusted to 1.5 mg/kg/day with continued benefit.

Discussion: This case highlights the need to consider infantile MG in the differential diagnosis of fluctuating ptosis, even in preterm infants with CNS findings such as PVL. Initial AChR antibody testing by RIA was negative, but retesting with the more sensitive IRMA method confirmed the diagnosis. The rapid response to pyridostigmine emphasizes the importance of clinical suspicion and appropriate serological testing. This case illustrates how CNS findings due to prematurity can obscure the diagnosis and how the choice of serological method plays a critical role in accurate identification.

O-03 Impact of the R67 Genetic Panel on Hearing Loss Diagnostics in a UK Tertiary Centre

Authors: **Irmak Sakin**¹, Harriet Cuncliffe¹, Jessica Ball¹, Jessica Bewick¹

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The National Health Service (NHS) R67 genetic hearing loss panel was introduced in England in 2021, expanding access to comprehensive molecular diagnostics for patients with hearing impairment. This study evaluates the diagnostic yield and clinical impact of the R67 panel at a designated regional referral centre.

A retrospective review was undertaken of all patients who underwent R67 testing between January 2021 and April 2023 at a large tertiary hospital. Data collected included demographics, referral source, family history, degree of hearing loss, R67 results, and chosen habilitation strategy. Outcomes were analysed descriptively.

Eighty-four patients with mild-to-profound hearing loss were included, comprising 46 paediatric and 38 adult cases. A monogenic cause was identified in 54.8% (n = 46), while 8.3% (n = 7) harboured at least one variant of uncertain significance. No genetic diagnosis was established in 36.9% (n = 31). Although patients with severe hearing loss were referred more frequently, patients with mild hearing loss had a higher rate of positive genetic outcome, suggesting patients with mild hearing loss might have been overlooked when considering referral to genetic testing.

Implementation of the NHS R67 hearing loss panel and establishing a multidisciplinary clinic involving clinical genetics, ENT, paediatrics and audiology have substantially improved diagnostic yield for genetic causes of hearing impairment. Earlier and more accurate diagnosis has enhanced counselling and prognostic information for families, with potential to guide habilitation choices. Aggregated data across centres will be critical in determining priority genes for emerging gene-targeted therapies.

O-04 Cc2D1A Causes Ciliopathy

Irmak Sakin¹, Angelo Haesoo Kim², Sehime G Temel³, Engin Deniz², Stephen Viviano, Gulden Tuncel, Stephanie Marie Aguilera, Gizem Goles, Lauren Jeffries, Weizhen Ji, Saquib Lakhani, Canan Ceylan Kose, Fatma Silan, Sukru Sadik Oner, Oktay I. Kaplan, MarmaRare Group, Mahmut Cerkez Ergoren, Ketu Mishra-Gorur, Murat Gunel, Sebnem Ozemri Sag,

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CC2D1A causes ciliopathy Intellectual and developmental disabilities result from abnormal nervous system development. Over a 1,000 genes have been associated with intellectual and developmental disabilities, driving continued efforts toward dissecting variant functionality to enhance our understanding of the disease mechanism. This report identified two novel variants in CC2D1A in a cohort of four patients from two unrelated families. We used multiple model systems for functional analysis, including *Xenopus*, *Drosophila*, and patient-derived fibroblasts. Our experiments revealed that *cc2d1a* is expressed explicitly in a spectrum of ciliated tissues, including the left–right organizer, epidermis, pronephric duct, nephrostomes, and ventricular zone of the brain. In line with this expression pattern, loss of *cc2d1a* led to cardiac heterotaxy, cystic kidneys, and abnormal CSF circulation via defective ciliogenesis. Interestingly, when we analyzed brain development, mutant tadpoles showed abnormal CSF circulation only in the midbrain region, suggesting abnormal local CSF flow. Furthermore, our analysis of the patient-derived fibroblasts confirmed defective ciliogenesis, further supporting our observations. In summary, we revealed novel insight into the role of CC2D1A by establishing its new critical role in ciliogenesis and CSF circulation.

Keywords: Ciliopathy, novel gene, *xenopus*

O-05 Management of Movement Disorders in Patients with PKAN: A Single-Center Experience

PKAN Hastalarında Hareket Bozukluklarının Yönetimi: Tek Merkez Deneyimi

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Introduction: Pantothenate kinase-associated neurodegeneration (PKAN) is a rare and progressive neurodegenerative disorder caused by mutations in the *PANK2* gene, with an estimated prevalence of approximately 1–2 per 1,000,000 individuals.

This disorder primarily arises due to dysfunction of the **PANK2 enzyme**, which plays a critical role in the biosynthesis of **coenzyme A** from **vitamin B5 (pantothenic acid)**. Mutations in the *PANK2* gene result in impaired coenzyme A, iron, and dopamine metabolism, leading to the pathological accumulation of iron, **lipofuscin**, and **neuromelanin** within the **substantia nigra** and **globus pallidus**.

PKAN typically presents before the age of six and follows a progressive course. Clinical features include motor, cognitive, and language impairment, spasticity, extrapyramidal signs, and visual disturbances. Dystonia is the most common manifestation. The most common ocular manifestation in PKAN is retinitis pigmentosa. Ocular involvement arises as a consequence of retinal degeneration, which is attributed to iron accumulation, mitochondrial energy dysfunction associated with coenzyme A deficiency, and the subsequent oxidative stress. Homozygous mutations usually result in the classic form (75%), whereas compound heterozygous mutations are associated with the atypical form. The classic phenotype typically manifests before age six, progresses rapidly, and may lead to death within 1–2 years.

Diagnosis of PKAN is primarily based on **clinical suspicion**, the characteristic “**eye-of-the-tiger**” sign visible on **magnetic resonance imaging (MRI)**, and subsequent **genetic confirmation**. As of now, no disease-modifying therapies are available for PKAN. Treatment of the movement disorders associated with PKAN typically involves symptomatic management, including **oral medications**, **botulinum toxin injections**, **physiotherapy**, occasionally, **surgical interventions**.

Objective: PKAN is a progressive neurodegenerative disease in which the most severe complication is status dystonicus, a potentially fatal condition. In this study, we aimed to present our clinical experience with PKAN patients, focusing on the course of their movement disorders, therapeutic strategies for uncontrolled dystonia, and our management approach to status dystonicus.

Methods: We analyzed the medical records of four genetically confirmed PKAN patients followed at the Department of Pediatric Neurology, Gazi University Faculty of Medicine. Clinical data, including medical history, physical examination findings, neuroimaging results, genetic analyses, longitudinal clinical course, and treatment modalities, were reviewed.

Results: The four PKAN patients, currently aged between 16 and 20 years, initially presented with frequent falls and visual disturbances. Diagnosis was established based on characteristic MRI findings and was subsequently confirmed by genetic testing.

All patients received a combination of **lifestyle modifications**, oral pharmacological therapy, and physiotherapy to control movement disorders and prevent the development of status dystonicus. Despite these interventions, the patient developed status dystonicus subsequent to a humeral fracture secondary to dystonia, and the condition was managed through surgical intervention.

Conclusion: PKAN is a rare and progressive neurodegenerative disorder. Due to the potentially severe complications associated with movement disorders, particularly **status dystonicus**, therapeutic strategies should prioritize effective symptom management and prevention of this life-threatening condition.

O-06 Long-read whole genome sequencing identifies pathogenic variants missed by standard approaches: A case series with Oxford Nanopore Technology

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Background: Although clinical exome sequencing (CES), whole-exome sequencing (WES), Sanger sequencing, and short-read whole-genome sequencing (srWGS) are widely implemented, many individuals with suspected monogenic diseases remain without a molecular diagnosis. These conventional methods are often limited in detecting complex genomic alterations and variants in non-coding regions. Oxford Nanopore Technologies (ONT)–based long-read whole genome sequencing (lrWGS) provides improved resolution for identifying such variants, including structural abnormalities and deep intronic mutations.

Methods: ONT-lrWGS was applied to six patients who exhibited unresolved diagnostic outcomes despite prior CES, WES, and srWGS testing. The cohort presented with neurodevelopmental features such as global developmental delay, autism spectrum disorder, speech apraxia, language impairment, and epilepsy. High-quality genomic DNA was sequenced using the PromethION Solo 2 platform, and long-read–specific analytic pipelines were utilized for variant detection and clinical interpretation.

Results: Causative or likely causative variants were identified in all six patients. These included splice-altering intronic variants, structural rearrangements, and insertions not detectable with short-read sequencing. Each case resulted in a definitive molecular diagnosis, directly informing clinical management and genetic counseling.

Conclusion: ONT-lrWGS demonstrates significant diagnostic utility in patients with unresolved neurodevelopmental disorders, particularly when short-read sequencing is inconclusive. Its application should be considered in scenarios with strong clinical suspicion but negative conventional testing outcomes.

Keywords: Neurodevelopmental disorders; Long-read whole genome sequencing; Oxford Nanopore Technology (ONT); Undiagnosed monogenic disorders

O-07 Expanding The Clinical And Molecular Spectrum Of Dtymk-Related Neurodegenerative Disorder

Durdugul Ayyıldız Emecen¹, Ceren Yılmaz Uzman¹, Ünsal Yılmaz¹, Ayşen Gök¹, Esra Er¹, Filiz Hazan¹

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Expanding the Clinical and Molecular Spectrum of DTYMK-Related Neurodegenerative Disorder Durdugül AYYILDIZ EMECEN¹, Ceren YILMAZ UZMAN¹, Ünsal YILMAZ², Ayşen GÖK², Esra ER³, Filiz HAZAN¹ 1 Dr. Behcet Uz Pediatric Diseases And Surgery Training And Research Hospital, Genetic Diseases Diagnosis Center 2 Dr. Behcet Uz Pediatric Diseases And Surgery Training And Research Hospital, Department of Pediatric Neurology 3Dr. Behcet Uz Pediatric Diseases And Surgery Training And Research Hospital, Department of Pediatric Metabolic Disorders Background: DTYMK encodes thymidylate kinase (TMPK), a key enzyme in deoxythymidine triphosphate (dTTP) biosynthesis. Loss-of-function variants in DTYMK have recently been reported in two families with severe neurodevelopmental phenotypes, including microcephaly, global developmental delay, seizures, and progressive cerebral atrophy. Functional studies in patient fibroblasts and zebrafish models demonstrated impaired dTTP synthesis, genomic instability, and neuronal loss, establishing DTYMK deficiency as a novel cause of childhood-onset neurodegeneration. We describe the third family reported worldwide with DTYMK-related disease. Case presentation: Two siblings, aged 10 and 4 years, from a consanguineous family presented with hypotonia, microcephaly and progressive loss of acquired motor and cognitive skills. The clinical course was similar in both children, with gradual regression of previously acquired abilities. The older sibling showed developmental regression after the age of two, while the younger sibling developed gait regression at 3.5 years. Neuroimaging revealed cerebral atrophy. Genetic testing in the 10-year-old patient, including MECP2 sequencing and chromosomal microarray analysis, yielded normal results. Whole-exome sequencing subsequently identified a novel homozygous frameshift variant, DTYMK c.265_270del, which was confirmed by Sanger sequencing. Both parents were heterozygous carriers. Conclusion: This report represents the third family with DTYMK-related neurodevelopmental disorder and broadens the clinical and molecular spectrum of the disease. Our findings contribute to the delineation of the natural history, highlight the progressive nature of neurological decline, and provide further evidence supporting the essential role of TMPK in genome integrity and neuronal survival.

Keywords: DTYMK, neurodegenerative disease, molecular genetic

O-08 Association Between Dystrophin Gene Mutation Sites And Neuropsychiatric Features In A Cohort Of Dystrophinopathy Cases

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Neuropsychiatric involvement in dystrophinopathies has been associated with defective synthesis of dystrophin isoforms in the central nervous system (CNS). It has been reported that distally located mutations in the dystrophin gene affect CNS-selective dystrophin isoforms to a greater extent. The localization of the genetic mutation may therefore be associated with the presence of psychopathology. A total of 243 patients aged between 1 and 18 years with dystrophinopathy were included in this study. The patients were divided into three groups based on the dystrophin isoforms expected to be affected by their mutations. Psychiatric assessments were conducted using neurodevelopmental scales. Patients identified with psychopathology were compared according to their mutation localization. Among the 243 patients (median age: 9 years, IQR: 7), 193 (79.4%) had a DMD genotype and 50 (20.5%) had a BMD genotype. Mutations were located between exons 1–44 (affecting Dp427 expression) in 76 patients (31.2%), between exons 45–62 (affecting expressions of Dp427, Dp140) in 153 patients (62.9%), and between exons 63–79 (affecting expressions of Dp427, Dp140, Dp71) in 14 patients (5.7%). Psychiatric evaluation revealed psychopathology in 138 patients (56.7%). Fifty-eight patients (23.8%) were assessed using WISC-IV and 32 (13.1%) using WISC-R. Intellectual disability was found in 28 patients (11.5%), attention deficit hyperactivity disorder (ADHD) in 24 (9.8%), speech disorder in 21 (8.6%), anxiety disorder in 16 (6.5%), depressive disorder in 9 (3.7%), autism spectrum disorder (ASD) in 8 (3.4%), specific learning disability in 8 (3.4%), and other psychiatric disorders in 24 (9.8%). No statistically significant differences were found between the presence of psychopathology and the DMD/BMD phenotype or corticosteroid use ($p=0.17$, $p=0.26$). However, psychopathology was observed in 43.4% of patients with mutations between exons 1–44, 60.1% between exons 45–62, and 92.9% between exons 63–79, and this difference was statistically significant ($p<0.001$). Among the 58 patients assessed with WISC-IV, those with distally located mutations had significantly lower performance scores ($p=0.002$). Psychopathology presence and WISC-IV scores differed significantly by mutation localization. These findings support previous reports linking distal mutations to more pronounced neuropsychiatric involvement and suggest that genetic localization may help predict cognitive outcomes and guide early interventions.

Keywords: DMD, Dystrophinopathy, Dystrophin, Dystrophin isoform Dp427, Dystrophin isoform Dp140, Dystrophin isoform Dp71, Neuropsychiatric findings

O-09 Symptomatic Improvement in Ataxia with N-Acetyl-L-Leucine in a Boy with GM1 Gangliosidosis

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Background: GM1 gangliosidosis is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in the *GLB1* gene, leading to β -galactosidase deficiency, accumulation of GM1 ganglioside, and progressive neurodegeneration. The clinical spectrum includes developmental delay, cognitive decline, movement disorders, and cerebellar ataxia. Currently, no approved disease-modifying therapy exists, and treatment is mainly supportive. N-acetyl-L-leucine (NALL), a modified amino acid, has recently emerged as a potential symptomatic therapy, showing encouraging results in patients with inherited ataxias and lysosomal storage disorders, including Niemann-Pick disease type C and GM2 gangliosidosis (1,2).

Case Presentation: We present the case of a 10-year-old boy, born to consanguineous parents, who exhibited global developmental delay, non-intelligible speech, strabismus, and progressive gait disturbance characterized by truncal ataxia and wide-based walking. Neurological examination confirmed cerebellar signs, and genetic testing identified homozygosity for a pathogenic *GLB1* variant (c.1769G>A, p.Arg590His), establishing the diagnosis of GM1 gangliosidosis. His baseline SARA (Scale for the Assessment and Rating of Ataxia) score was 19, reflecting moderate to severe ataxia.

In October 2023, off-label treatment with N-acetyl-L-leucine was initiated, titrated to 2.5 g/day. After six weeks, notable clinical improvement was observed: the patient gained the ability to independently ascend and descend stairs with support from handrails—a previously unattainable skill. Parents reported clearer speech articulation, enhanced fine motor performance, and increased confidence in ambulation. His fear of falling diminished significantly, and no adverse effects were reported during treatment.

Conclusion: This report represents, to our knowledge, the **first case in the literature** describing symptomatic improvement with N-acetyl-L-leucine in GM1 gangliosidosis. The observed benefits, particularly in cerebellar ataxia and functional independence, are consistent with prior findings in related lysosomal storage disorders. These results highlight the potential role of NALL as a symptomatic therapy in GM1 gangliosidosis, while emphasizing the urgent need for prospective controlled trials to confirm long-term efficacy and safety.

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O-10 Investigating The Capability Of Large Language Models To Diagnose Cystic Fibrosis Patients

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Our research project investigates the performance of Large Language Models (LLMs) in the diagnosis of cystic fibrosis cases through analyzing anonymized textual health records. We limited our scope to nine open-source LLMs and tested eight different prompting strategies on 18 records from the MIMIC IV dataset made of cystic fibrosis cases and matched controls. We found that Falcon3-3B achieved the highest average performance across prompting strategies (0.72 accuracy, 0.62 F1-score), but the top performances were achieved when combining “few-shot” prompting with Qwen2.5-1B or Llama3.1-8B (0.83 accuracy, 0.86 F1-score and 0.83 accuracy, 0.80 F1-score, respectively). Our results showed that, in the right context, LLMs hold potential as rare disease diagnosis assistants, as evidenced here on cystic fibrosis, and that further research is warranted into their optimization and capabilities with other rare diseases.

Keywords: Large Language Models (LLMs), Rare Diseases, Cystic Fibrosis, Disease Diagnosis, MIMIC IV, Prompt Engineering

O-11 Protein Truncating Mutation Occurring In C-Terminus Of Fyr Domain Of Kabuki Syndrome-Associated Kmt2D Gene Causes Major Changes In Chromatin Organization

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Kabuki Syndrome, a rare disease affecting roughly 1 in 32,000-86,000 individuals is mainly caused by mutations in chromatin modifier gene, KMT2D. KMT2D functions in MLL4 complex, mediating active chromatin organization. KMT2D is a large protein consisting over 5000 amino acids, which includes several domains including the phenylalanine/tyrosine-rich (FYR) domain. Although the exact function of FYR domain is not entirely clear, it is thought to be involved in protein-protein interactions. Examinations of the mutations occurring in FYR domain of KMT2D gene reveals that the majority of the mutations at N-terminal part of FYR domain (FYRN) are in missense character, while truncating mutations are seen more frequently at the C-terminal part of FYR domain (FYRC). Here, we studied one Kabuki Syndrome patient with the truncating mutation R5282* at FYRC. Similar to the patients having R5282* mutations in literature, the patient had the major characteristics of Kabuki Syndrome on a mild basis. We characterized the impact of this truncating mutation on chromatin organization via performing ATAC-seq on patient blood material and cell line models. Our analysis revealed differential chromatin accessibility at genomic regions linked with genes involved in neurogenesis and chromatin regulation. Further, our results showed distinct chromatin organization in cell line models overexpressing KMT2D FYRN mutant (R5179C) vs KMT2D FYRC mutant (R5282*) constructs, arguing for the differential effect of mutations on KMT2D function. Next, transcription factor motif analysis at genomic regions with reduced chromatin accessibility in R5282* mutant Kabuki patient and cell line model disclosed the enrichment of RBBP5, WDR5, and ASH2L, which are WRAD core components of MLL4 complex. Change in KMT2D and WRAD-core component interactions in connection to the R5282* mutation were also substantiated by AlphaFold modeling. This study is ultimately believed to contribute to a better understanding of domain-specific functions of KMT2D and associated pathogenesis of Kabuki Syndrome.

Keywords: Kabuki Syndrome, KMT2D, chromatin organization, FYR domain

O-12 In silico Characterization of a Rare Chromatin Disease

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Rahman Syndrome (RS) is a rare and severe genetic disease linked to frameshift mutations in the gene coding **linker histone H1.4**, a critical constituent of chromatin architecture. Pathogenic mutations are located in **the carboxy-terminal domain (CTD) of H1.4**, a domain that is responsible for the compaction of linker DNA and therefore the regulation of DNA-templated processes such as transcription and repair. Using tools of molecular modeling and high performance computing, we characterized the dynamics of different frameshift RS H1.4 CTD mutations in the nucleosome, and we calculated the affinity of histone H1.4 proteins to the DNA in the healthy and diseased cases. We find that the DNA affinity of the pathogenic H1.4 may be up 2-3 kcal/mol lower in comparison to the healthy individuals' protein. Furthermore, we correlated these findings with clinical-phenotypic characterizations by defining a disease severity index. Our results suggested that electrostatically altered structure of RS H1.4 CTD reduces **the affinity of histone H1.4 protein to the genomic DNA**. Mutations more upstream in sequence display reduced affinities compared to mutations more downstream. Additionally, the protein affinity-clinical phenotype correlation revealed that **earlier mutations with less affinity are associated with more severe clinical symptoms** in RS patients. This molecular etiology of the disease suggests that thermodynamic characterization of a pathological protein can be accurately linked to clinical outcomes in the context of a rare chromatin disease.

Keywords: Rahman Syndrome, overgrowth syndrome, linker histone H1.4, chromatin, molecular Dynamics

O-13 Time is Brain: Case Series From Two Family With Creatine Deficiency Syndrome

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Introduction:

Creatine deficiency syndromes (CDS) are rare inborn errors of metabolism that affect creatine biosynthesis or transport. Based on the disrupted step in the synthesis pathway, CDS are classified into three types: guanidinoacetate methyltransferase (GAMT) deficiency, arginine:glycine amidinotransferase (AGAT) deficiency, and creatine transporter (CRTR) defect. Among these, GAMT and AGAT deficiencies are autosomal recessive and are potentially treatable if diagnosed early. Supplementation with creatine monohydrate, and in some cases ornithine and sodium benzoate, can significantly improve clinical outcomes.

Case: We present a case series involving two families with confirmed GAMT deficiency. In the first case, the index case was a 7-years-old girl diagnosed after presenting with neurodevelopmental delay. Following her diagnosis, her two younger siblings were tested shortly after birth and diagnosed in the neonatal period. Both received early treatment with creatine monohydrate, and their neurodevelopmental outcomes have been significantly better compared to their older sister.

In the second case, a 2-years-old girl was diagnosed with GAMT deficiency after similar neurodevelopmental symptoms were observed. Her younger sibling was diagnosed antenatally due to known familial mutation and was started on treatment shortly after birth. Early intervention resulted in preserved developmental milestones and absence of seizures during follow-up.

Conclusion: This case series highlights the profound impact of early diagnosis and treatment in creatine biosynthesis disorders. Delayed diagnosis is associated with irreversible neurological damage, whereas early treatment can prevent or greatly reduce the severity of symptoms.

O-14 Transcriptomic Analyses As A Critical Complement To Genomic Sequencing In Rare Disease Diagnostics

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Despite the progress from next-generation sequencing (NGS), many rare disease cases remain unsolved after whole exome (WES) or whole genome sequencing (WGS). A major limitation of these genome-based methods is that they cannot directly show the functional effects of genetic variants. Transcriptome profiling with RNA-Seq provides a crucial second layer of evidence by revealing abnormal splicing, aberrant gene expression levels, and allele-specific transcription. This study demonstrates the value of transcriptomic methods for finding the molecular cause in unsolved cases from the RareBoost cohort. We included a total of 127 unresolved or undiagnosed cases from 117 families in our study group. In cases that remained unsolved after WES reanalysis and WGS, we performed RNA-Seq for 12 patients where we suspected a splicing or regulatory variant. The transcriptomic data were analyzed to find abnormal splicing patterns, gene expression outliers, and allele-specific expression. These findings were then combined with genomic data and patient clinical information in multidisciplinary discussions. Our transcriptomic analyses provided clear answers in several cases. For two patients, RNA-Seq confirmed that a synonymous variant caused exon skipping and subsequently decreased expression, and for one patient, a splice site region variant identified by WGS was shown to cause loss of splice donor sequence and subsequently usage of an alternative donor, which validated its role in the disease through a partial exon loss. Lastly, transcriptome analysis revealed an enrichment of minor intron splicing anomalies in a patient with biallelic pathogenic variants in RNU4ATAC gene, which functions in minor intron splicing complex. In short, adding transcriptomic data helped us both achieve definitive diagnoses and reclassify previously uncertain variants. This study confirms that transcriptomic data is a vital complement to genome sequencing for diagnosing rare diseases. RNA-Seq not only solves cases that WES/WGS misses but also gives us deeper insights into gene regulation and expression related to disease mechanisms. Routinely using transcriptomic analysis in diagnostic workflows has the potential to significantly increase the rate of diagnosis and advance precision medicine for rare diseases. Grant: This project is funded by the European Union’s Horizon 2020 Research and Innovation-supported ERA Chair project “RareBoost.” (Grant number: 952346).

Keywords: RNAseq, transcriptomics, rare diseases

O-15 Assessment Of Quality Of Life And Caregiver Burden Among Parents Of Children With Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is known to significantly affect the lives of both patients and their caregiving parents. This study aimed to evaluate the quality of life and caregiving burden among parents of children with SMA and to compare the findings according to parental gender, educational status, SMA type, treatment duration, and diagnostic approach. Parents of 32 children diagnosed with SMA (age range: 4–300 months; median: 36 months, IQR: 54.5 months) were included in the study. The diagnosis of SMA was established through the newborn screening program in 15 cases (46.9%) and based on clinical findings in 17 cases (53.1%). Parents were administered the WHOQOL-TR, Zarit Caregiver Burden Scale (ZCBS), and PedsQL Family Impact Module. Among the 32 parents, 17 (53.1%) were female and 15 (46.9%) were male. Twelve parents (37.5%) had primary or secondary school education, 11 (34.4%) were high school graduates, and 9 (28.1%) had a university degree. According to the ZCBS, 4 parents (12.5%) had a mild burden, 20 (62.5%) had a moderate burden, and 8 (25%) had a severe burden. WHOQOL-TR domain scores were 78.6 (± 17.1 SD) in the physical domain, 65.6 (± 18.4 SD) in the psychological domain, 70 (± 23.8 SD) in the social relationships domain, and 62.6 (± 21 SD) in the environmental domain. The internal consistency of the domain scores was very good (Cronbach's Alpha: 0.82). When compared with the national reference data obtained via the WHOQOL Turkish Communication Center, the psychological domain scores of the parents were lower than the Turkish average. The mean total score of the PedsQL Family Impact Module was 59.1 (± 17.5 SD). A positive correlation was found between WHOQOL-TR and PedsQL Family Impact Module scores (Spearman's rho $p < 0.05$). No statistically significant differences were observed in ZCBS, WHOQOL-TR or PedsQL Family Impact Module scores with respect to parental gender, educational status, SMA type or treatment duration ($p > 0.05$). Screening-based diagnosis was associated with higher ZCBS scores. Moreover, as caregiver burden increased, WHOQOL-TR physical and psychological scores and PedsQL Family Impact Module total, physical, social, and daily activity scores significantly decreased ($p < 0.05$). Therefore, higher caregiving burden correlated with poorer parental quality of life and functioning.

Keywords: SMA, WHOQOL, PedQL Family Impact Module, Zarit Caregiver Burden Scale

O-16 “Development and Validation of a Novel Antibody for Detection of Mutant Histone H1E in Rahman Syndrome”

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Abstract

Rahman syndrome is a rare neurodevelopmental disorder caused by pathogenic variants in the histone H1E gene; however, research into its molecular mechanisms has been limited by the lack of specific analytic tools. Here, we report the generation and characterization of a polyclonal antibody directed against the C-terminal domain of the mutant H1E protein. A recombinant protein was used as an antigen for immunization of rabbits, and antibody specificity was assessed by Western blotting and immunofluorescence. For validation, we employed embryonic stem cell (ESC) lines engineered to express the Rahman-associated H1E variant. The antibody detected a protein of the expected molecular weight in mutant H1E-expressing ESC lysates but not in wild-type controls, and it exhibited robust nuclear staining in immunofluorescence assays. These findings establish the novel antibody as a specific and reliable reagent for detection of mutant H1E, providing a critical resource for studies of chromatin biology and Rahman syndrome pathogenesis. To our knowledge, this is the first antibody validated against the Rahman H1E mutant protein expressed at physiological levels, with potential applications in both basic and translational research.

Keywords: Rahman syndrome, HISTH1E, antibody development, embryonic stem cells, antibody validation

O-17 Beyond Single Diagnoses: High Diagnostic Yield And Dual Findings In Consanguineous Pediatric Neurodevelopmental Disorders

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Background Rare and ultra-rare neurodevelopmental disorders often remain undiagnosed despite extensive laboratory, imaging, and biopsy-based investigations. Approximately 80% of rare diseases are of genetic origin, and next-generation sequencing (NGS), particularly whole-exome sequencing (WES), has emerged as a powerful diagnostic tool. Establishing a molecular diagnosis provides prognostic insights, facilitates genetic counseling, and may enable targeted therapies. **Methods** Between 2022 and 2025, we evaluated 101 pediatric patients with unexplained neurodevelopmental delay after exclusion of exogenous causes and completion of conventional laboratory and imaging studies. Eligible patients were further enriched by at least one additional risk factor, including positive family history (e.g., consanguinity, affected siblings) or multisystem involvement. WES was performed on all cases, and variants were classified according to ACMG criteria, with genotype–phenotype correlation assessed using clinical and bioinformatic data. **Results** Of the 101 pediatric patients evaluated, a molecular diagnosis was established in 63, corresponding to a diagnostic yield of 62.3%. 37 were male (58.7%) and 26 were female (41.3%). The ages ranged from 2 days to 30 years, with a mean age of 10.6 years and a median age of 11 years. Consanguinity was present in 23 cases (36.5%). The most frequent clinical features, apart from global developmental delay, included epilepsy in 25 patients (39.7%), hypotonia in 10 (15.9%), speech delay in 7 (11.1%), and skeletal/dysmorphic findings in 7 (11.1%). Pathogenic variants spanning a broad spectrum of inheritance patterns—including autosomal dominant, autosomal recessive, and X-linked—enabled the establishment of definitive molecular diagnoses. In addition, dual diagnoses were identified in seven patients (6.9%), further highlighting the complexity of genetic etiologies within the cohort. **Conclusion** This study demonstrates that WES provides a significantly higher diagnostic yield than previously reported in neurodevelopmental disorders, particularly in high rate of consanguineous populations. Dual diagnoses were more common than anticipated, reflecting the importance of broad genomic testing. While WES remains limited in detecting structural or noncoding variants, complementary approaches such as whole-genome sequencing (WGS) and RNA sequencing may further enhance diagnostic success. Our findings highlight the indispensable role of genetic testing in ending the diagnostic odyssey for children with rare neurodevelopmental disorders.

Keywords: Whole-exome sequencing; neurodevelopmental delay; consanguinity; dual diagnosis; rare disease.

O-18 Whole-Genome Sequencing Strategies for Diagnosing Rare and Undiagnosed Diseases: Insights from the RareBoost Project

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Introduction: Rare diseases (RDs) pose a significant global health challenge, leaving millions of patients in uncertainty due to delayed or missed diagnoses and limited treatment options. For many, the diagnostic journey can take years, and some individuals may never receive a genetic diagnosis. The RareBoost Project aims to overcome these obstacles by focusing on patients with unresolved rare genetic diseases, using translational genomics to improve diagnostic accuracy and clinical outcomes.

Materials and Methods: The study cohort comprised 130 undiagnosed patients from 116 families referred to the Rare and Undiagnosed Disease Advisory Board at IBG. Genomic data were systematically re-evaluated using next-generation sequencing (NGS) approaches, including exome sequencing (ES) and whole-genome sequencing (WGS). Selected unresolved cases also underwent RNA sequencing and epigenome profiling for additional diagnostic insight

Results: NGS analyses identified pathogenic or likely pathogenic (P/LP) variants in **25 families (21.36%)**, establishing the overall diagnostic yield. Clinically relevant variants of uncertain significance (VUSs) were detected in **28 families (23.9%)**, for which functional and transcriptomic validation is ongoing. Among these, **WGS** was performed in **58 patients from 51 families**, yielding **14 P/LP** and **10 VUS** variants. Of these, **7 (29.2%) represented genome-required diagnoses**, including deep intronic or structural variants, while **17 (70.8%)** could have been detected by ES upon reanalysis. Missed variants were primarily due to low coverage or capture bias in prior ES data.

Conclusion: This study highlights the value of comprehensive genomic evaluation in unresolved rare diseases. **Genomic reanalysis and high-throughput sequencing significantly improved diagnostic yield**, while **whole-genome sequencing complemented exome analyses by detecting variants otherwise missed**, including structural and noncoding changes. **Periodic re-evaluation of data and incorporation of transcriptomic, epigenomic, and functional analyses** further enhanced variant interpretation, facilitating the resolution of

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challenging cases. Together, these strategies underscore the critical role of integrative genomics in advancing diagnosis and patient care in rare disease research.

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O-19 Strengthening Rare Disease Research Capacity Through Multidisciplinary Education And Training

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Rare diseases (RDs) are defined based on their low incidence rate of ≤ 1 in 2000 people in Europe. Collectively, RDs affect an estimated 350-400 million people worldwide. In Turkey alone, around 5-6 million people are believed to be living with rare diseases, a figure influenced by high consanguinity rates. Although RD awareness has increased in recent years, it remains insufficient worldwide. In most medicine and life sciences programs, only limited RD education and training are provided. Moreover, current healthcare curricula usually lack sufficient information required for RD patient care and management. Training programs should cover the economic, ethical, social, and medical aspects of RDs⁹ and further raise RD awareness by providing teaching, training, and mentoring on RD research. To address this, the RareBoost, a Horizon 2020 ERA Chair project at the Izmir Biomedicine and Genome Center (IBG, Izmir, Türkiye), works actively to strengthen rare disease research, education, and training. Rare and Undiagnosed Disease workshops, organized by RareBoost brings together RD experts and stakeholders in Türkiye, leading to several actionable recommendations to support RD capacity building that align closely with recommendations of other studies. RareBoost has implemented a comprehensive and multidisciplinary education and training initiative, including formal and non-formal learning activities, like seminars, webinars, symposiums, workshops, and hackathons. The effectiveness of these activities has been evaluated through online questionnaires and face-to-face interactions which indicated that the activities were highly helpful and valuable for the attendees, enhancing their RD awareness and understanding. In particular, hackathon event carried out by RareBoost to raise awareness and knowledge of the students indicated that students' RD knowledge has increased significantly. These initiatives demonstrate that structured and multidisciplinary education and training models can effectively bridge RD knowledge gaps and strengthen research capacity. RareBoost's experience provides a practical framework for integrating rare disease education and training strategies for improving RD diagnosis, research, and patient care worldwide.

Keywords: Education and Training, Research Capacity Building, Rare Diseases, Capacity Building

O-20 Carbohydrate sulfotransferase 6 (*chst6*) gene and keratan sulfate proteoglycans are involved in the fine-tuning of central nervous system development and function in zebrafish

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The *carbohydrate sulfotransferase 6 (chst6)* gene encodes GlcNAc-6-ST, which sulfates keratan sulfate proteoglycans (KSPGs) in both humans and zebrafish. Loss of *chst6* function causes macular corneal dystrophy (MCD) due to the accumulation of unsulfated KSPGs. Previously, we generated *chst6* mutant fish, which develop MCD-related blindness because of the loss of KSPG sulfation. In these fish, low-penetrance defects were detected in the jaw and bones, a symptom rarely documented in MCD patients. Although some KSPGs have been suggested to play roles in neurodegenerative diseases such as ALS, their functions in the brain remain poorly understood. The mechanisms by which KSPGs act in brain cells and the extracellular matrix to regulate brain development and function remain to be investigated. The *chst6* mutant zebrafish provides a unique opportunity to inactivate all KSPGs with different core proteins by inhibiting sulfation, essential post-translational modification of KSPGs.

Here, we aimed to understand the roles of *chst6* and KSPG sulfation in the central nervous system using behavioural assays, histopathology, transcriptomic, and proteomic approaches. *chst6* is strongly expressed in the larval brain, and a decrease in cKS sulfation in the brains of mutants was demonstrated by immunofluorescence staining. *chst6* mutants displayed low-penetrance morphological defects that were compensated in inbred fish, indicating a complex regulatory network. Touch-response experiments demonstrated decreased sensitivity to touch in the trunk. Histopathological analysis of mutant larval brain tissue revealed a fragmented structure, while an expansion of the hindbrain at the expense of the forebrain was observed in mutant embryos. Transcriptomic analyses revealed that the most affected processes include regulation of development, neuronal projection, and neurogenesis. The affected genes were further validated via RT-qPCR. Finally, expression patterns of glial and myelin genes were analysed in wild-type and mutant larvae. A change in the expression pattern of the *glial fibrillary acidic protein (gfap)* gene was detected in the trunks of mutant larvae.

Future studies involving proteomic analyses, Ca²⁺ imaging, and advanced behavioural testing will be conducted to further elucidate the molecular mechanisms. The findings presented here suggest a KSPG-linked regulatory network fine-tuning CNS patterning and function.

Keywords: Macular corneal dystrophy, neurogenesis, neurodegeneration, central nervous system, keratan sulfate proteoglycan, zebrafish, disease modelling

O-21 Maternal Mosaicism in the *SMS* Gene: Expanding the Genetic Spectrum of Snyder–Robinson Syndrome

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Abstract

Background: Snyder–Robinson syndrome (SRS) is a rare X-linked intellectual disability disorder caused by pathogenic variants in the *SMS* gene, which encodes spermine synthase.

Case presentation: We report a 7.5-month-old male with dysmorphic features, camptodactyly, and severe bilateral myopia, found to have a hemizygous missense variant in *SMS* (c.166G>A; p.Gly56Ser), classified as pathogenic according to ACMG guidelines. The mother was identified as a mosaic carrier with 9–10% variant allele frequency (VAF) in blood and buccal mucosa, respectively.

Conclusion: This represents the **second documented case of maternal mosaicism** associated with SRS, underscoring the need for deep sequencing when low-level mosaicism is suspected. Maternal mosaicism has significant implications for recurrence risk and genetic counseling.

Introduction: Snyder-Robinson syndrome (SRS) is an X-linked intellectual disability syndrome characterized by asthenic build, facial dysmorphism with a prominent lower lip, kyphoscoliosis, osteoporosis, speech abnormalities, and seizures. Developmental delay usually presents as failure to meet early developmental milestones and then evolves to moderate to profound intellectual disability (which appears to remain stable over time) and variable motor disability. Asthenic habitus and low muscle mass usually develop during the first year, even in males who are ambulatory. During the first decade, males with SRS develop osteoporosis, resulting in fractures in the absence of trauma (1). The spermine synthase (*SMS*) gene, located on chromosome Xp22, encodes a ubiquitously expressed enzyme responsible for catalyzing the conversion of spermidine to spermine—a polycationic polyamine essential for normal mammalian cell growth and differentiation. Spermine plays critical roles in cellular proliferation, nucleic acid and protein synthesis, cell adhesion, intracellular signaling, and the regulation of ion channels. Within the central nervous system, it is further implicated in neuronal growth and repair, responses to neuronal stress or injury, ionic homeostasis, and modulation of the excitatory N-methyl-D-aspartate (NMDA) glutamate receptor (2). Pathogenic missense and splicing variants in the *SMS* gene impair the structural integrity of the spermine synthase protein, leading to misfolding, degradation, or defective dimerization (3). These alterations reduce enzymatic activity, resulting in low intracellular spermine levels and an imbalanced spermine/spermidine ratio, which underlies the pathogenesis of *SMS*-related disorders (4).

Case Presentation: A 7.5-month-old male infant had presented with dysmorphic features, camptodactyly, and severe high myopia (−8.5 D). He had been born at 36+6 weeks of gestation via cesarean section, with a birth weight of 3140 grams. Prenatal screening tests had been reported as normal. In the postnatal period, he had required hospitalization for a total of 6 days due to elevated bilirubin levels secondary to neonatal jaundice. He had been referred for genetic evaluation because of dysmorphic facial features and camptodactyly. On physical examination, tall stature, broad forehead, hypertrichosis, synophrys, thin eyebrows, hypotelorism, strabismus, short palpebral fissures, large ears, broad nasal tip, retrognathia with micrognathia, high-arched palate, camptodactyly of the fingers, long fingers, widely spaced nipples, and overriding of the toes on both feet had been noted. All growth parameters were in the normal range. Neurologically, head control had been achieved by 6 months of age, but supported sitting remained weak, indicating a delay in gross motor milestones. Echocardiography had revealed a 5 mm secundum-type atrial septal defect (ASD). Audiological screening had been normal,

while ophthalmological examination had shown severe bilateral myopia (−8.5 diopters). A brain MRI performed at 4 months of age had shown a thin corpus callosum. Karyotyping had revealed a normal male chromosomal constitution (46,XY). Exome sequencing revealed a hemizygous mutation in the X-linked *SMS* gene. The c.166G>A variant identified in our patient is absent from large population cohorts such as gnomAD and ExAC and results in a missense change (p.Gly56Ser). According to the guidelines established by the American College of Medical Genetics and Genomics (ACMG), this variant has been classified as pathogenic. In our study, targeted next-generation sequencing revealed a variant allele frequency (VAF) of 9% in the mother, raising suspicion of mosaicism. To further investigate this, DNA was isolated from a second tissue (buccal mucosa), and both targeted next-generation sequencing and Sanger sequencing were performed. The analysis identified a VAF of 10% in the buccal sample, thereby confirming the mosaic status of the mother (Figure 1).

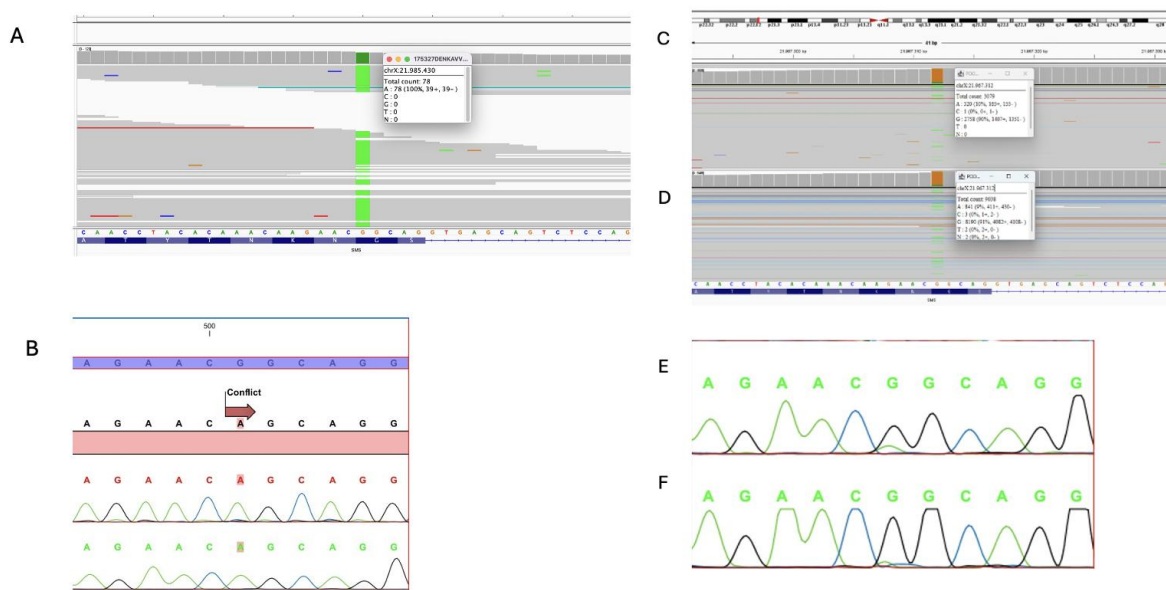


Figure 1.

A) IGV image of the hemizygous c.166G>A variant identified in the proband. **B)** Sanger sequencing image of the hemizygous c.166G>A variant in the proband. **C–D)** IGV images of the c.166G>A variant (VAF 9% and 10%) detected in the buccal mucosa and peripheral blood of the mother. **E–F)** Sanger sequencing images of the mosaic c.166G>A variant detected in the maternal buccal mucosa and peripheral blood, showing a residual signal consistent with low-level mosaicism

Discussion: Snyder-Robinson syndrome (SRS) is a rare genetic disorder characterized by intellectual disability and delayed development beginning early in childhood. It was first described in a single family in 1969 as a sex-linked disorder (Snyder & Robinson, 1969) and has since been only identified in less than 100 individuals worldwide. Inherited in an X-linked recessive pattern, SRS has only been identified in males thus far. Affected males display a collection of clinical features including intellectual disability ranging from mild to profound, speech and vision impairment, osteoporosis, hypotonia, and increasing loss of muscle tissue with age, kyphoscoliosis, seizures, and distinctive facial features including a prominent lower

lip and facial asymmetry (5). Core features of the Snyder–Robinson syndrome (SRS) phenotype—such as intellectual disability, hypotonia, osteoporosis, muscle atrophy, and facial dysmorphism—are consistent with the cellular effects of reduced spermine levels and the accumulation of spermidine (6-7). In particular, neurodevelopmental manifestations are associated with dysfunction caused by decreased polyamine levels in processes such as synaptic plasticity, ion channel regulation, and neurotransmission. Disruption of polyamine homeostasis may adversely affect not only the central nervous system but also biological processes such as bone mineralization and muscle cell growth (5). The broad clinical spectrum of the syndrome can be explained by the diversity of *SMS* gene variants identified in individuals of different ethnic backgrounds. Some of these variants directly affect the enzymatic active site, while others impair *SMS* dimerization, indirectly reducing the enzyme’s stability and function. Consequently, each mutation leads to a different degree of reduction in spermine biosynthesis, which may explain the variable severity of the phenotype observed among individuals (8). In most reported cases, pathogenic variants in the *SMS* gene have either been inherited from heterozygous carrier mothers or have arisen de novo. However, the study by Marhabaie et al. is notable as it describes the first documented case of maternal mosaicism associated with Snyder–Robinson syndrome (SRS). Initially, the c.388C>T (p.Arg130Cys) variant was interpreted as de novo based on Sanger sequencing. However, the detection of a low-level variant signal in the maternal sample prompted deep targeted resequencing, which revealed that the mother was mosaic for the variant at approximately 3% allele frequency in blood (9). The case presented here represents the second reported instance of maternal mosaicism associated with Snyder–Robinson syndrome (SRS) in the literature. The c.166G>A (p.Gly56Ser) variant in the *SMS* gene was identified as hemizygous in the proband, and targeted next-generation sequencing revealed variant allele frequencies of 9% and 10% in the mother’s blood and buccal mucosa, respectively, confirming mosaic carrier status. Maternal mosaicism has important implications for recurrence risk and genetic counseling, particularly in families with a history of affected male offspring. Since low-level mosaicism may be missed by conventional sequencing methods, deep targeted sequencing proves to be a valuable tool in detecting such cases. Therefore, in families undergoing risk assessment, investigating potential maternal mosaicism is critically important for preventing recurrence of affected cases.

Conclusion: In conclusion, this study presents the second reported case of maternal mosaicism for a pathogenic *SMS* variant associated with Snyder–Robinson syndrome (SRS). Our findings highlight the importance of high-depth sequencing technologies in detecting low-level mosaicism that may be missed by conventional methods. Recognition of maternal mosaicism is essential for recurrence risk assessment and genetic counseling, and should be carefully considered in families with a history of affected male offspring.

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O-22 Coexisting Genetic Disorders in Phenylketonuria: Clinical and Molecular Insights

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Introduction: Phenylketonuria (PKU) is an autosomal recessive inherited metabolic disorder caused by pathogenic variants in the PAH gene, which encodes the phenylalanine hydroxylase (PAH) enzyme. In some cases, the clinical presentation cannot be fully explained by a single diagnosis. This study aimed to present the clinical and genetic characteristics of patients with phenylketonuria who were followed up in the metabolic outpatient clinic who were also diagnosed with an additional concomitant disease.

Methods: The medical records of all patients diagnosed with phenylketonuria and followed up by the pediatric metabolic disorder department were retrospectively reviewed. Age, clinical history, findings, and genetic analysis results of patients with phenylketonuria with a coexisting diagnosis were recorded.

Results: Among 473 patients diagnosed with phenylketonuria (PKU) and followed in our clinic, five were found to have an additional disease. All patients were referred to the metabolic outpatient clinic due to elevated phenylalanine levels detected in the national newborn screening program. In four of these patients, further biochemical and molecular genetic investigations were performed during follow-up because of the clinical and biochemical findings that could not be explained by PKU alone, leading to the diagnosis of a second disorder. One patient was diagnosed with Duchenne muscular dystrophy due to persistent elevations of creatine kinase levels; another with congenital hemolytic anemia based on anemia and reticulocytosis; one with dihydropteridine reductase deficiency due to early-onset seizures and ataxia; and another with glucose-6-phosphate dehydrogenase deficiency identified through whole-exome sequencing performed for developmental delay.

Conclusion: Although coexisting diagnoses are rare among metabolic and genetic disorders, they substantially complicate the clinical course and patient management. The possibility of a second genetic disorder should be considered in patients presenting with atypical features or a clinical course that deviates from expectations. In the follow-up of individuals with phenylketonuria, it is essential not to rely solely on phenylalanine levels but to evaluate advanced biochemical and genetic analyses according to the evolution of clinical findings. Therefore, recognizing the possibility of dual diagnoses in patients with phenylketonuria with atypical clinical manifestations is crucial for accurate diagnosis and effective management.

O-23 In Silico Analysis Of A Novel Variant In The β 3 Propeller Domain Of Lrp4 And Its Potential Association With Congenital Myasthenic Syndrome Type 17

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Congenital myasthenic syndrome (CMS) is a genotypically heterogeneous group of rare diseases characterized by defects in the organization and function neuromuscular junction (NMJ). Acetylcholine is the neurotransmitter released from the nerve cell and recognized by the acetylcholine receptors (AChRs) in the muscle terminal of the NMJ. Agrin/LRP4/MuSK signalling regulates the clustering of AChRs, an essential step for efficient induction of muscle contraction. The binding of Agrin to LRP4, followed by LRP4 binding to MuSK, is needed to form an active Agrin-LRP4-MuSK complex. To date, only three pathogenic variants (E113A, E1233K, and R1277H) in the β 3 propeller domain of LRP4 have been reported to be associated with CMS type 17 (CMS17). Herein, we report a novel homozygous missense variant in the β 3 propeller domain of LRP4 (c.3388G>A, p.A1130T). The variant was determined by whole-exome sequencing in a one-year-old patient with CMS symptoms, including hypotonia, muscle weakness, and respiratory distress. In silico analyses were performed to predict the structural and functional effects of the identified A1130T by comparing it with pathogenic E1233K and R1277H. A1130 was found to be highly conserved in vertebrates, using the Consurf tool. A1130T was predicted to be deleterious and pathogenic using Mutation Tester, MutPred-2, and CADD tools. DynaMut predicted that the A1130T variant destabilizes the LRP4 structure. Moreover, the A1130T causes a decrease in the flexibility of LRP4 with a Δ vibrational entropy energy change value of 0.240. The 3D model of the variant was created with I-TASSER-MTD. A1130T change leads to the formation of two additional H bonds (I1172 and L1129) and two hydrophobic bonds (W1140 and V1173), presumably increasing the rigidity of the β 3 propeller domain. These findings suggest that the A1130T mutation would change the affinity via locally interfering with the interaction of the β 3 propeller domain with MuSK, without engaging directly with MuSK. Further experimental studies are needed to validate these results and clarify the underlying mechanisms, which may aid in creating novel therapeutic strategies for CMS17 treatment. This project is funded by the European Union's Horizon 2020 Research and Innovation-supported ERA Chair project “RareBoost” (Grant number: 952346)

Keywords: Congenital Myasthenic Syndrome; LRP4; β 3 Propeller Domain; Neuromuscular Transmission; In Silico Analysis

O-24 A Catastrophic Finding In 15 Years Old Male Presenting With Short Stature

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1. Introduction Alexander disease is a progressive neurodegenerative leukodystrophy of the cerebral white matter caused by heterozygous pathogenic variants in the gene encoding glial fibrillary acidic protein (GFAP). The clinical spectrum is heterogeneous, often presenting with nonspecific neurological manifestations that may delay or obscure diagnosis. Based on the age at onset and presenting features, four clinical subtypes have been described: neonatal, infantile, juvenile, and adult. The juvenile form typically presents with milder and variable symptoms, which may overlap with other syndromic or skeletal disorders, making diagnosis challenging.

2. Materials and Methods We report a case of a 15-year-old male who initially presented with short stature and skeletal abnormalities and was eventually diagnosed with Alexander disease.

3. Results The patient was born to non-consanguineous parents and had normal neurodevelopment. He had consistently been shorter than average, and following a trauma, he was incidentally found to have scoliosis. At the age of 15, on physical examination, his weight, height, and head circumference were found to be -5.2, -3.9, and -3.38 SD, respectively. Dysmorphic features included a triangular face, prominent nasal bridge, septal deviation, short and prominent philtrum, prognathism, high-arched palate, downturned corners of the mouth, anteverted and low-set ears, pectus carinatum, square shoulders, cachectic and asthenic appearance, and clinodactyly of the second finger of the right hand. Significant scoliosis was also observed. A clinical exome panel revealed a pathogenic missense variant, c.1246C>T (p.Arg416Trp), in the GFAP gene, which is characteristically associated with the juvenile form of Alexander disease. Subsequent brain MRI demonstrated findings consistent with Alexander disease, confirming the diagnosis.

3. Conclusion The clinical features of the juvenile form of Alexander disease may mimic those of skeletal dysplasias, leading to potential diagnostic confusion. In this case, despite normal neurodevelopment and absence of neurological symptoms, the patient's failure to thrive and progressive scoliosis prompted further investigation, ultimately resulting in the diagnosis of Alexander disease. This case highlights the importance of considering Alexander disease in the differential diagnosis of short stature and skeletal abnormalities, as well as the need to inform families about incidental yet significant genetic findings.

Keywords: GFAP, Alexander Disease, failure to thrive

O-25 Spinocerebellar Ataxia Type 17: A Rare Case with Borderline TBP Repeat Expansion

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Introduction:

Spinocerebellar ataxia type 17 (SCA17) is a rare autosomal dominant neurodegenerative disorder characterized by ataxia, dementia, chorea, dystonia, and other involuntary movements. Psychiatric symptoms, pyramidal signs, and rigidity are also common. The age of onset varies widely, between 3 and 55 years. Diagnosis is based on detecting an expansion of ≥ 41 CAG/CAA trinucleotide repeats in the *TBP* gene.

Case Presentation: A 62-year-old woman presented with a two-year history of progressive dizziness and memory loss, followed by gait disturbance and incontinence. Her medical history included thyroid carcinoma and Crohn's disease. Family history revealed an undiagnosed tremor in her father starting at age 40 and Parkinson's disease in her uncle. There was no parental consanguinity. Brain imaging showed cerebellar atrophy and hypometabolism in the cerebellum and bilateral upper temporal cortices. With a preliminary diagnosis of spinocerebellar ataxia, fragment analysis targeting *SCA* types 1, 2, 3, 6, 7, 12, 17, and *DRPLA* genes was performed. The *TBP* gene showed 40/40 CAG/CAA repeats. Due to the borderline result and possible methodological differences, Sanger sequencing with specific primers for the *TBP* region was conducted, revealing 42/43 repeats.

Discussion: The clinical findings were consistent with SCA17, and the patient carried a compound heterozygous genotype. Reports vary on the repeat size required for full penetrance. Expansions of 41–45 repeats are associated with reduced penetrance, but moderate expansion in both alleles likely contributed to symptom onset in this case. Previous homozygous or compound heterozygous cases showed cerebellar ataxia with dementia, psychiatric manifestations, pyramidal signs, involuntary movements, parkinsonism, myoclonus, or epilepsy. Our patient exhibited dementia, dizziness, gait disturbance, and incontinence without thalamic or basal ganglia involvement.

Conclusion: This report describes the first known SCA17 case diagnosed with 42 and 43 CAG/CAA repeats. SCA17 should be considered in patients with Huntington-like symptoms, and borderline repeat results should be confirmed by secondary methods for accurate diagnosis.

O-26 Clinical And Genetic Insights Into Mitochondrial Dna Depletion Syndromes

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Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are a heterogeneous group of rare autosomal recessive genetic disorders characterised by a decrease in the number of mtDNA copies inside the organ involved. As posited by various scholars, there are three distinct forms of MDS, including the hepatocerebral, the myopathic and the encephalomyopathic forms. The broad clinical and genetic heterogeneity of these conditions poses significant challenges in terms of diagnosis. In this study, we delineate the clinical manifestations and the genetic profile of three patients diagnosed with myelodysplastic syndrome (MDS). The subject and methods: The present study comprised three patients from three unrelated families. A comprehensive history was obtained from all patients, and they underwent a meticulous general and neurological examination. Basic laboratory investigations were conducted, encompassing lactic acid and ammonia, amino acids, acylcarnitine profiles, and brain MRI. Whole-exome sequencing was performed on all subjects to confirm suspicions of mitochondrial disorder. Results: In the present series, three patients presented with the hepatocerebral form of MDS, with the major presenting manifestation of progressive liver cell failure, severe hypotonia and global developmental delay. The MPV17 has been identified in two variants. One patient was diagnosed with an encephalomyopathic form, presenting with persistent lactic acidosis and global delay due to a homozygous variant in the POLG gene. Conclusion: MDS is characterised by a wide spectrum of heterogeneous clinical presentations and approximately nine different genes are involved. Whole exome sequencing (WES) has been shown to facilitate a more expeditious diagnosis of these challenging cases, given the overlap in phenotype with numerous other disorders. This should be regarded as the primary diagnostic evaluation, thus obviating the necessity for more invasive procedures such as muscle biopsies.

Keywords: MPV17, POLG, Mitochondrial DNA Depletion Syndromes

O-27 Rare Genetic Epilepsies Onset in Neonatal Period

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Introduction: Neonatal seizures frequently represent the earliest clinical manifestation of an underlying genetic disorder. Advances in next-generation sequencing (NGS) have identified pathogenic or likely pathogenic variants in a considerable proportion of infants with early-onset epilepsy (1). Early molecular diagnosis enables genotype-directed management, rational antiepileptic selection, and precise genetic counseling.

Objective: To characterize the clinical, electrophysiological, neuroimaging, and molecular findings of patients presenting with neonatal-onset seizures confirmed to carry pathogenic or likely pathogenic variants by clinical exome sequencing (CES).

Methods: Six patients were evaluated across a secondary and a tertiary referral center. Inclusion criteria were seizure onset within the neonatal period and availability of CES data. Demographic information, seizure semiology, EEG and MRI findings, and treatment responses were reviewed. Variant pathogenicity was interpreted in accordance with the ACMG/AMP (2015) and Sherloc (2017) guidelines (1,2).

Results: Four disease-associated variants were detected: *CDKL5*, *RNASEH2B*, *DIAPH1*, and *KCNQ2*. All cases presented with seizures during the neonatal period. Clinical features, neuroimaging, and EEG findings are summarized in **Table 1**, highlighting the genotype–phenotype relationship and pathogenic classification.

Table 1. Genetic and Clinical Findings with Genotype–Phenotype Correlation and Pathogenicity

Gene / Variant	Sex	Seizure Onset & Type	EEG Findings	MRI Findings	Phenotype	Pathogenicity (ACMG)
CDKL5 (p.Ala177Thr) Het.	M	Neonatal myoclonic & spasms	Hypsarrhythmia	Normal	Developmental delay	Pathogenic (PM1 + PP3)
RNASEH2B (p.Glu22Valfs*7) Hom.	F	Neonatal focal–generalized	Multifocal	Calcification, WM hyperintensity	Microcephaly, psychomotor delay	Pathogenic (PVS1 + PM2 + PP4)
DIAPH1 (p.Ser558Asn) Het.	M	Neonatal focal seizures	Multifocal	Corpus callosum thinness	Mild delay	Likely pathogenic (PM1 + PP2 + PP3)
KCNQ2 (p.Ser530Asn) Het.	M	Neonatal multifocal	Multifocal	Normal	Mild delay	Pathogenic (PM1 + PP3 + PP4)

Variants were classified according to ACMG/AMP (2015) and Sherloc (2017) guidelines., WM: White matter

In the *KCNQ2*-related family (X family), four siblings and their parents were analyzed. The index case and two sisters carried the heterozygous *KCNQ2* c.1589G>A (p.Ser530Asn) variant, each exhibiting neonatal seizure onset with varying clinical severity. One sister was unaffected and untested. The mother, who had a history of childhood seizures, also carried the same variant, whereas the father was wild-type. This pattern supports an autosomal dominant inheritance with incomplete penetrance and variable expressivity (**Table 2**).

Table 2. KCNQ2 (X Family): Genotype–Phenotypic Outcome

Individual	Sex	Seizure Onset & Type	EEG / MRI	Treatment	Genotype	Phenotypic Outcome
Index case (Proband)	M	Neonatal multifocal seizures	Multifocal / normal MRI	LEV + PB	KCNQ2 c.1589G>A Het.	Mild developmental delay
Sibling 1	F	Neonatal seizures (resolved 3 mo)	Multifocal	LEV + PB	KCNQ2 c.1589G>A Het.	Seizure-free
Sibling 2	F	Neonatal focal–generalized (resolved 7 mo)	Multifocal	LEV + PB + PHT	KCNQ2 c.1589G>A Het.	Seizure-free
Sibling 3	F	No seizures	Not tested	—	Unknown	Normal
Mother	F	Childhood seizure history	—	—	KCNQ2 c.1589G>A Het.	Normal
Father	M	Asymptomatic	—	—	Wild-type	Normal

Het.: Heterozygous; LEV: Levetiracetam; PB: Phenobarbital; PHT: Phenytoin; WM: White matter.

Discussion: Neonatal-onset epilepsies exhibit marked heterogeneity, both clinically and genetically. In our series, *CDKL5* and *DIAPH1* variants were associated with developmental and epileptic encephalopathy, while *RNASEH2B* mutation produced an Aicardi–Goutières–like phenotype characterized by microcephaly and basal ganglia calcifications (3,4). The *KCNQ2* variant demonstrated phenotypic variability among carriers, consistent with previous reports of heterozygous missense mutations leading to a wide clinical spectrum from benign familial neonatal epilepsy to severe epileptic encephalopathy (5,6).

Conclusion: Seizure onset in the neonatal period should prompt evaluation for underlying genetic etiologies. Integrating clinical, neurophysiological, and genetic data enhances diagnostic accuracy, facilitates targeted treatment, and improves prognostic precision. Expanding variant classification frameworks through detailed genotype–phenotype analyses remains crucial for advancing individualized care in neonatal epilepsies.

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O-28 Polr1c-Related Leukodystrophy in Two Turkish Siblings: A Genetically Confirmed Case Series and Literature-Based Insight

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Abstract

Objective: To report two genetically confirmed Turkish siblings with POLR1C-related hypomyelinating leukodystrophy (POLR3-HLD), initially misdiagnosed with neuronal ceroid lipofuscinosis (NCL), and to contextualize their phenotype within the spectrum described in international literature.

Methods: We conducted clinical, radiological, and molecular assessments of two siblings born to consanguineous parents, presenting with early-onset ataxia, motor regression, and developmental delay. Whole-exome sequencing (WES) was used for molecular diagnosis. A structured literature review was performed in October 2025.

Results: Both patients exhibited delayed developmental milestones and progressive speech regression. MRI revealed diffuse hypomyelination, subcortical U-fiber involvement, and bilateral T2 hypointensity of the globus pallidus and ventrolateral thalami. These radiologic patterns strongly mimicked NCL. Genetic testing identified a homozygous c.326G>A (p.Arg109His) variant in POLR1C in both siblings, with heterozygous parental carriage.

Compared to published cases from Tunisia (Kraoua et al.), China (Liu et al.), India (Meena et al.), and Saudi Arabia (Naseer et al.), our patients showed overlapping MRI features but lacked craniofacial dysmorphism, dental anomalies, hearing loss, or endocrine dysfunction—traits variably reported in the POLR1C spectrum. Despite the identical mutation, their phenotype was consistent but not identical, supporting previously described variability and incomplete penetrance.

Interpretation: These are, to our knowledge, the first genetically confirmed sibling cases of POLR1C-related leukodystrophy reported from Turkey. The marked radiological overlap with NCL underscores the need for genetic analysis in leukodystrophy cases with atypical presentations. Our findings expand the known genotypic and phenotypic spectrum of POLR1C-related disorders and highlight the diagnostic utility of early exome sequencing in consanguineous populations. (Based on literature search updated as of October 2025.)

Keywords: POLR1C gene; leukodystrophy; neurodevelopmental regression; next-generation sequencing; consanguinity; genotype–phenotype correlation.

O-29 Rare Genetic Etiologies of Intellectual Disability in Childhood

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Background: Both monogenic variants and copy number variations (CNVs) contribute significantly to intellectual disability (ID) in childhood. This study aims to provide a greater understanding of the phenotypic features and phenotype-genotype relations of children with ID.

Methods: Twenty-six patients with genetically confirmed ID were retrospectively analysed. Demographic, genetic and phenotypic characteristics of the patients, were evaluated. All genetic results were verified and re-evaluated using international genetic databases (ClinVar, OMIM, Varsome, DGV, DECIPHER).

Results: The mean age was 8.6 ± 4.7 years with a Female/Male ratio of 14/12. Eleven patients (42.3%) had monogenic variants in several genes including *MCM3AP*, *DDX3X*, *IQSEC2*, *MED12*, *OPHN1*, *PPP2R5D*, *RORA*, *USP9X*, and *NBEA*, while fifteen patients (57.7%) had copy number variants (CNVs) detected by array-CGH. Among the monogenic group, autosomal recessive inheritance predominated (42%), and parental consanguinity was present in 54%. The most frequent diagnostic method in this group was next-generation sequencing (45.5%, n = 5). The most frequently accompanying phenotypic features were motor delay/disability (65%) and epilepsy (61%).

Conclusion: This case series demonstrates that both monogenic variants and CNVs are rare but important contributors to ID in the pediatric population. The findings of this study highlight the necessity for in-depth genetic and neurological counselling in order to optimise the management of ID and the associated phenotypes.

Keywords: Copy number variation; genetic; intellectual disability; monogenic.

O-30 Clinical Features and Immunotherapy Response in Patients with PANDAS Syndrome: A Retrospective Evaluation of Nine Cases

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Introduction: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) is a rare autoimmune neuropsychiatric syndrome characterized by the sudden onset of obsessive-compulsive symptoms or tics following a group A beta-hemolytic streptococcal infection. This study aimed to retrospectively evaluate the clinical characteristics and response to intravenous immunoglobulin (IVIG) therapy in pediatric patients diagnosed with PANDAS.

Methods: Nine patients diagnosed with PANDAS between 2020 and 2024 were included in the study. Demographic characteristics, clinical findings, laboratory results, neuroimaging and EEG data, as well as treatments administered, were reviewed.

Results: Of the nine patients, four were female and five were male, with a mean age of 11.3 years (range: 6–17). All patients presented with abrupt onset of tics or obsessive-compulsive symptoms. Elevated antistreptolysin-O (ASO) titers were detected in all cases. Patients received IVIG therapy at a dose of 2 g/kg for 2–6 courses. Clinical improvement exceeding 50% was observed in six patients, while two showed limited response. No specific abnormalities were identified on neuroimaging or EEG studies.

Conclusion: PANDAS should be considered in pediatric patients presenting with acute-onset neuropsychiatric symptoms. Early diagnosis and appropriate immunotherapy may lead to significant clinical improvement. In our study, a high rate of favorable response to IVIG treatment was observed (66.6%). Larger case series are needed to better define the long-term outcomes of immunotherapy in PANDAS syndrome.

Keywords: PANDAS syndrome; intravenous immunoglobulin(IVIG); Tics

O-31 A Pathway to Train Future Rare-Disease Researchers - ERDERA Work Package 20 Task 4 Experience

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Abstract

Background: Rare-disease (RD) research in Europe is hampered by fragmented training pathways, small and heterogeneous patient populations, complex cross-border regulation, and dispersed data assets. These conditions demand researchers with competencies that extend beyond standard biomedical training. ERDERA Work Package 20 Task 4 (WP20.4) addresses this capacity gap with a pragmatic, scalable model that preserves institutional autonomy while ensuring RD-specific competence across borders.

Method: We first conducted structured meetings, partner consultations, and a multi-country needs analysis to understand national and institutional contexts and to identify common ground. This analysis showed that a single pan-EU “RD degree” would be impractical; the most suitable approach is a **labelling-and-modules** pathway. In this model, an **ERDERA Labelling System** will recognise MSc/PhD programmes that deliver agreed **generic biomedical and research competencies**, while centrally delivered **online modules** will teach **specific RD competencies**. Students in labelled programmes who complete both their program and the ERDERA training modules will receive the **ERDERA Rare Disease Researcher Certificate**.

To develop the labelling system and its underpinning competency model, we are using a **modified Delphi** with partner institutions to gather input and build consensus on (i) the RD researcher competency framework and (ii) how labelling should work in practice. We are currently conducting the **third Delphi round**, which we expect to be the final consensus step.

What is next: Following Delphi completion, we will (1) constitute a **Labelling Committee** and a **Curriculum/Modules Committee**; (2) finalise criteria, self-evaluation templates, evidence checklists, and reviewer guidance for labelling; (3) complete the blueprint and assessments for priority training modules and run pilot deliveries; (4) launch the certificate pathway; and (5) implement evaluation, quality assurance, and sustainability plans.

WP20.4 provides a feasible route to expand Europe’s RD research workforce by recognising local strengths while guaranteeing RD-specific competencies at scale—supporting faster study start-up, better data use, and stronger patient-centred, multinational RD research.

O-32 Two Sisters With Angelman Syndrome Caused By A Rare Maternal Ube3A Missense Variant

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We report two sisters with a prolonged diagnostic odyssey before molecular confirmation of Angelman syndrome (AS). The proband, a 10-year-old girl, was referred for seizures and developmental delay. She was born at term after an uneventful pregnancy to non-consanguineous parents. Growth parameters were normal except for obesity. Dysmorphic features included a broad forehead and a thick everted lower lip. Her 7-year-old sister showed a similar phenotype without seizures. Both had delayed milestones, absent speech, and characteristic behavioral features such as frequent laughter, fascination with water, sleep disturbance, and stereotypic hand movements. Karyotype and chromosomal microarray were normal. AS was clinically suspected, but methylation–deletion analysis by MLPA also yielded normal results, delaying diagnosis. Clinical exome sequencing subsequently revealed a heterozygous missense variant in UBE3A, NM_130839.5:c.1576C>T (p.Arg526Cys), present in both sisters and maternally inherited. This case illustrates a rare mechanism of AS due to UBE3A missense mutations. Approximately 90% of AS cases result from 15q11–q13 deletions, paternal uniparental disomy, or imprinting defects. For missense variants, pathogenicity occurs only when the maternal allele is affected. Mothers may therefore remain asymptomatic carriers if the same variant is located on their paternal allele. Our report underscores the importance of UBE3A sequencing in suspected AS with normal methylation testing.

Keywords: Rare diseases; Angelman syndrome; Missense mutation; Genomic imprinting

POSTER PRESENTATIONS

P-01 Novel HCK Gene Mutation Associated with a Rare Autoinflammatory Disease with Pulmonary Involvement .

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Abstract

Background: Autoinflammatory diseases (AIDs) are characterized by dysregulation of the innate immune system, leading to recurrent systemic inflammation. Recently, mutations in the hematopoietic cell kinase (HCK) gene have been implicated in autoinflammatory syndromes, but their clinical spectrum remains largely undefined.

Case Presentation: We report a 6-year-old female presenting with recurrent febrile episodes, petechial rashes, chronic cough, exertional dyspnea, and recurrent lower respiratory tract infections starting from 1.5 years of age. Imaging revealed atelectasis and bronchial wall thickening consistent with small airway disease. Molecular genetic testing for common autoinflammatory disease was negative. Whole exome sequencing identified a novel heterozygous splice site mutation (c.1016-5T>C) in the HCK gene, not previously reported in genomic databases. The patient showed clinical improvement with IL-1 β antagonist monoclonal antibody therapy.

Discussion: This case expands the mutational spectrum of HCK-associated autoinflammatory disease, emphasizing the gene's role in myeloid cell activation and pulmonary inflammation. Our findings correlate with prior reports linking HCK mutations to early-onset pulmonary and cutaneous vasculitis. **To date, only a single patient with an HCK-related autoinflammatory syndrome (caused by p.Tyr515X truncating mutation) has been reported in the literature. Our patient represents an additional, independently observed pediatric case with pulmonary and cutaneous involvement, bringing the total number of published patients with an HCK driven autoinflammatory phenotype to two.** The clinical response to IL-1 blockade supports the pathogenic role of HCK hyperactivation in driving systemic inflammation.

Conclusion: A novel HCK mutation causes an early-onset autoinflammatory disease with pulmonary and cutaneous manifestations, with a robust response to anti-IL1 β therapy suggesting a promising treatment approach.

P-02 Whole-Exome Sequencing Identified a Novel Mutation of the Nr2F1 Gene Causing Bosch-Boonstra-Schaaf Optic Atrophy Syndrome

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Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS) is an autosomal dominant disorder characterized by mainly visual impairment due to optic nerve abnormalities and/or cortical visual impairment (CVI), intellectual disability (ID) and developmental delay (DD). BBSOAS results from mutations in NR2F1, which encodes for a highly conserved orphan nuclear receptor and transcriptional regulator that involved in neurogenesis, cortical patterning and visual processing. Here, we report a novel mutation of NR2F1 gene in a 16 months male patient with global developmental delay, mild hypotonia, unilateral strabismus and delayed myelination in brain MRI. Whole-exome sequencing revealed a heterozygous missense mutation in NR2F1 gene (NM_005654.6: exon3: c.1196T>A, p.Ile399Asn) in the patient and then using NGS sequencing it was absent in his parents. To our knowledge, this is one of the few reported case presented with BBSOAS, caused by mutation in the NR2F1 gene from Turkey.

Keywords: Bosch-Boonstra-Schaaf optic atrophy syndrome, NR2F1, WES, de novo mutation

**P-03 Phenotypic Overlap of Neuropathy-Like Appearance and Limb Malformation
Genes: A Case with Gli3 And Hoxd13 Mutations**

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Thenar and hypothenar muscle atrophy with distal contractures usually suggests neuromuscular disorders such as peripheral nerve lesions or motor neuron disease, but certain genetic syndromes affecting skeletal morphogenesis may also cause similar hand muscle wasting and contractures. We report a 17-year-old male who presented with bilateral thenar and hypothenar atrophy, finger contractures and weakness, initially suggesting a neurogenic cause. He had polydactyly in all four extremities and underwent surgery at 3 months for extra digits. His mother and maternal grandmother also had polydactyly and webbed toes. Physical examination revealed an asthenic body habitus (BMI 17.3 kg/m², <3rd percentile) subtle dysmorphic features including a short/webbed neck. The hands showed multiple anomalies such as rudimentary thumbs, bilateral camptoclinodactyly, and prominent atrophy of the thenar and hypothenar eminences. In the right hand, the index finger showed an extension deficit, with MCP limited to ~45° and PIP to ~30°, preventing full straightening. The left hand had muscle atrophy as well. The feet showed anomalies with broadened great toes, second-toe clinodactyly, and X-rays demonstrating bifurcated “Y-shaped” second metatarsals, a feature of synpolydactyly. Despite the striking hand muscle atrophy, there were no upper motor neuron signs or sensory deficits. Given the constellation of limb malformations and a family history of polydactyly, a genetic workup was performed. Whole exome sequencing identified two significant variants: (1) a heterozygous GLI3 gene mutation, NM_000168.8: c.1622C>T, which is a known likely pathogenic variant predicted to result in a p.Thr541Met amino acid change in the GLI3 protein. (2) A 27-bp deletion was identified in the first exon of the HOXD13 gene, encompassing the polyalanine tract and predicted to result in the loss of nine alanine residues. Hand surgeon performed a tendon transfer procedure: the extensor indicis proprius was surgically connected side-to-side to the extensor digitorum communis tendon of the index finger. The coexistence of two genetic mutations affecting limb development is exceptionally rare; each of these alone could explain polydactyly and syndactyly but their combination likely accounts for the complex phenotype seen in our patient. This case underscores the need for a multidisciplinary approach in managing morphogenetic diseases.

Keywords: Thenar atrophy, hypothenar atrophy, GLI3, HOXD13, skeletal morphogenesis

P-04 Horizontal Gaze Palsy Caused by a Novel Biallelic Robo3 Variant: A Case Report

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The ROBO3 gene, located on chromosome 11q24.2, encodes the ROBO3 protein, which plays a critical role in neuronal migration and axonal growth. We present a case diagnosed with nystagmus and bilateral horizontal gaze palsy at 9 months of age due to a homozygous mutation in this gene. Our case was born by cesarean section at 41 weeks' gestation, weighing 3550 g, to a 19-year-old G1P0 mother. The upward gaze and convulsive jerks in the right arm, which began in the neonatal period, were interpreted as seizures. Complete blood count, blood glucose, liver and kidney function tests, electrolytes, vitamin B12, thyroid function tests, and creatine kinase were within normal limits. Primary metabolic screening was unremarkable. Electroencephalography (EEG) was normal. Brain MRI revealed age-appropriate diffuse hypomyelination in the parieto-occipital white matter of both cerebral hemispheres and a diffusely thinned corpus callosum. Seizures did not recur after antiepileptic treatment was initiated. At 5 months of age, during follow-up in the pediatric neurology clinic, the patient experienced spontaneous nystagmus with bilateral horizontal eye movement limitations and a lack of visual pursuit. Given the developmental delay, history of seizures and nystagmus, and first-degree parental consanguinity, whole-exome sequencing was performed, and the homozygous c.775_784dupTCATTCCTGC/p.ARD262fs class 2 variant in the ROBO3 gene was identified. Although this variant has not been previously reported in the literature, ACMG guidelines indicate that it may have a damaging effect because it causes frame shift. Thus, our patient was diagnosed with familial horizontal gaze palsy (HGPPS1) with progressive scoliosis-1 at 9 months of age. On follow-up, in line with the mutation, he developed bilateral restriction of horizontal gaze, scoliosis, and sensorineural hearing loss, while nystagmus persisted. We highlight this mutation to emphasize that, in patients presenting with ophthalmoplegia, early genetic testing should be considered, as it may facilitate timely diagnosis. Our case expands the genotypic spectrum of the ROBO3 gene and supports the genotype-phenotype relationship. Early diagnosis in our patient enabled rapid recognition and management of scoliosis and hearing loss. Multidisciplinary follow-up of such cases can improve overall quality of life.

Keywords: Gaze palsy, ROBO3 gene

P-05 Candidate Gene Variants in a Patient with Cleft Lip and Palate, Microcephaly, and Radial Ray Defects Identified by Whole-Exome Sequencing

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Craniofacial malformations and limb anomalies frequently arise from disruption of early embryonic patterning, yet the underlying molecular determinants often remain unresolved. We describe a patient with syndromic manifestations including cleft lip and palate, microcephaly, and radial ray defects characterized by thumb hypoplasia. Whole-exome sequencing was undertaken to elucidate the genetic basis, yielding rare variants in several candidate genes: *ACSS2*, *NRG1*, *MCTP2*, and *ATXN3*. These genes participate in critical developmental and cellular pathways, acetyl-CoA metabolism (*ACSS2*), neuronal signaling (*NRG1*), calcium-regulated membrane trafficking (*MCTP2*), and ubiquitin–proteasome regulation (*ATXN3*). The pleiotropic functions of these genes suggest potential combinatorial effects on craniofacial morphogenesis, brain growth, and limb patterning. While the precise contribution of each variant to the observed phenotype remains to be established, this case underscores the complexity of interpreting multilocus variation in rare congenital disorders. Future studies integrating functional assays, model systems, and expanded cohort analyses will be essential to clarify the pathogenic relevance of these findings and to advance understanding of the genetic architecture underlying syndromic clefting and radial ray anomalies.

P-06 Expanding The Phenotypic Spectrum of Ayme-Gripp Syndrome: Report of Two Unrelated Patients with Pathogenic Maf Variants

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Background: Ayme-Gripp syndrome is a rare autosomal dominant multisystem disorder caused by MAF variants. It is characterized by distinctive facial features, sensorineural hearing loss, congenital cataracts, developmental delay, and variable neurological and skeletal anomalies. Since its first description, only a limited number of cases have been reported, and the phenotypic spectrum continues to expand. We present two unrelated patients with Ayme-Gripp syndrome, both carrying pathogenic MAF variants but with some atypical features. Case Presentation: Case 1: A 1-year-old boy presented with developmental delay, hydrocephalus, and facial dysmorphism including a flat face, prominent frontal bone, short nose, depressed nasal root, and midfacial hypoplasia. He was born small for gestational age and showed growth retardation during follow-up. Brain MRI revealed benign external hydrocephalus and cavum septum pellucidum et vergae. Electroencephalography demonstrated paroxysmal abnormalities without seizures. Auditory and visual functions were preserved. Targeted next generation sequencing panel testing identified a heterozygous MAF (NM_005360.5) variant (c.188C>G; p.Pro63Arg). Case 2: A 12-year-old girl exhibited global developmental delay, intellectual disability, speech delay, microcephaly, short stature, and seizures. Bilateral optic disc pallor was noted in infancy, followed by severe sensorineural hearing loss. Dysmorphic features included brachycephaly, flat face, prominent forehead, downslanting palpebral fissures, depressed nasal root, long philtrum, cleft palate, lobulated tongue, low-set ears, clinodactyly, and camptodactyly. Neurological evaluation revealed coordination difficulties, and skeletal survey demonstrated scoliosis. Genetic testing confirmed a heterozygous MAF variant (c.185C>G; p.Thr62Arg). Discussion: These cases emphasize the variable spectrum of Ayme-Gripp syndrome. While congenital cataracts and hearing loss are recognized cardinal features, Case 1 lacked both, illustrating that absence of these signs does not exclude the diagnosis. Growth impairment, neurological involvement, and skeletal anomalies showed marked variability between cases. Pathogenic MAF variants reported to date, including those in our patients, cluster within the GSK3 recognition motifs of the N-terminal transactivation domain. Early recognition and systematic follow-up for vision, hearing, and neurological issues remain essential. Conclusion: Ayme-Gripp syndrome should be suspected in patients with characteristic craniofacial features and developmental delay, even without cataract or hearing loss. Detailed phenotyping combined with molecular confirmation enables timely diagnosis, genetic counseling, and multidisciplinary care.

Keywords: Ayme-Gripp syndrome, congenital cataracts, hearing loss, hydrocephalus, seizures

P-07 Integrative Transcriptomic Insights Into Mirna–Gene Interactions in Alzheimer’S Disease

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Objective: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. Growing evidence suggests that microRNAs (miRNAs) are involved in the pathogenesis of AD. The purpose of this study was to identify differentially expressed genes (DEGs) and their regulatory miRNAs using bioinformatic analyses, which may serve as potential biomarkers for diagnosis/follow-up, and could also provide novel targets for future therapeutic applications. **Materials and Methods:** The GSE5281 gene expression dataset, which includes samples from Alzheimer's disease and normal aged brains, was retrieved from the Gene Expression Omnibus (GEO) database. DEGs between AD and control samples were determined using GEO2R with a significance threshold of $p < 0.05$ and $|\log FC| > 2$ to ensure both statistical and biological significance. Metascape was used for functional enrichment and gene ontology (GO) analyses. Protein-protein interaction (PPI) networks were constructed via the STRING database and visualized in Cytoscape. The top 10 genes with the highest connectivity were selected as hub genes. Potential miRNAs regulating these hub genes were predicted using the appropriate databases. **Results:** A total of 94 DEGs were identified, comprising 41 upregulated and 53 downregulated genes. PPI analysis revealed 10 hub genes: SNAP25, CALM1, SNCA, PSMD8, SST, UCHL1, YWHAZ, UBE3A, CCT5, and TUBB3. miR-15a-5p, miR-124-3p, and hsa-let-7 family of miRNAs were predicted as potential regulators. **Conclusion:** Central hub genes and their regulatory miRNAs associated with AD were identified. Functional enrichment analysis was performed for both upregulated and downregulated genes, indicated that these genes are associated with neuronal processes, affecting pathways such as chemical synaptic transmission and axon guidance. The identified miRNAs may significantly regulate these pathways. These findings may aid in the development of novel diagnostic biomarkers and therapeutic approaches once experimentally validated. Moreover, integrating transcriptomic data with regulatory miRNA networks provides deeper insight into the molecular mechanisms underlying AD progression. Such integrative approaches not only highlight potential targets for early diagnosis and therapeutic intervention but also open new avenues for precision medicine strategies tailored to neurodegenerative diseases.

Keywords: Alzheimer’s disease, miRNAs, DEGs, biomarker

P-08 Synonymous Yet Pathogenic: PEX16 c.111A>G Alters Splicing Pattern Causing Zellweger Spectrum Disorder

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Zellweger spectrum disorders (ZSD) are rare, severe genetic disorders resulting from defects in peroxisome biogenesis, leading to metabolic accumulation and multi-organ dysfunction. We report a male infant homozygous for a synonymous PEX16 variant (c.111A>G;p.Ala37=) presenting with clinically confirmed peroxisomal dysfunction. Although synonymous variants are often considered “silent,” they can disrupt RNA splicing or processing, producing pathogenic effects. Using molecular, in silico, and functional analyses, we demonstrate how this seemingly silent change can drive disease and highlight the clinical significance of synonymous variants in rare genetic disorders. The patient exhibited early-onset global developmental delay, severe hypotonia, recurrent seizures, characteristic facial dysmorphism, and Dandy–Walker malformation. Biochemical profiling revealed elevated very-long-chain fatty acid ratios (C26/C22, C24/C22), increased alanine, threonine, serine, glutamate, lysine, and dicarboxylic acids, and reduced tryptophan and phenylalanine, consistent with biallelic pathogenic PEX16 variants and confirming the diagnosis of ZSD (OMIM #614877).

Whole-exome sequencing (WES), initially performed in 2017 using the GENNEXT platform (GRCh38), was reanalyzed in 2024. Variants were systematically evaluated for population frequency (gnomAD), clinical significance (ClinVar), and literature evidence (HGMD) and classified according to ACMG/AMP guidelines. Potential splicing effects were assessed using Human Splice Finder, MaxEntScan, and RBP motif analyses, and validated experimentally by PCR and Sanger sequencing. Protein topology and secondary structure alterations were predicted through a consensus approach combining Phobius, TOPCONS, SCAMPI, PolyPhobius, and PSIPRED.

The c.111A>G variant, located one nucleotide upstream of the canonical donor site, was absent from population databases (PM2) and predicted to impair splicing (PP3) with a splicing loss score of 0.91. RBP motif analyses suggested that novel binding sites for EIF4G2, TAF15, HNRNPA2B1, RBM4, and RBM4B could form potentially modulating exon dynamics and contributing to the observed splicing changes. Structural modeling indicated that the altered transcript may modify membrane organization and introduce an additional N-terminal transmembrane segment. Biochemical confirmation of peroxisomal dysfunction supports the functional relevance of these findings.

In conclusion, the homozygous c.111A>G variant impairs splicing, alters RBP binding and PEX16 topology, highlighting the need for integrative analyses of rare variant interpretation. This work was supported by the RareBoost Project, funded by the European Union’s Horizon 2020 (Grant No: 952346).

P-09 Familial Photodermatosis Cases Presenting with Cutaneous, Ocular and Neurological Findings

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Introduction: Photodermatoses represent a heterogeneous group of disorders characterized by abnormal cutaneous responses to ultraviolet radiation. While common forms such as polymorphic light eruption or chronic actinic dermatitis typically involve only the skin, syndromic variants may present with accompanying ocular and neurodevelopmental manifestations. Despite substantial advances in genomic testing, the underlying etiology remains undefined in some patients, highlighting the complexity of genotype–phenotype correlations. This report presents cases from the same family exhibiting multisystem involvement in whom a definitive diagnosis could not be established despite comprehensive genetic and clinical investigations.

Case Presentation: A 26-year-old male patient was evaluated for recurrent skin lesions triggered by sun exposure since the age of two. The lesions were confined to sun-exposed areas and characterized by erythematous, burn-like patches with crusting and healing phases at different stages. Ophthalmologic examination revealed ectropion and pronounced nystagmus, while neurodevelopmental delay was also noted. The family history included two siblings with similar photosensitive lesions and nystagmus, as well as one completely healthy sister; both parents were unaffected. Whole-exome sequencing identified no pathogenic variants, revealing only a heterozygous **AHR c.544C>T** variant classified as a *variant of uncertain clinical significance (VUS)*. Although the AHR gene has been associated with retinitis pigmentosa, this variant does not account for the present phenotype. Chromosomal microarray analysis and conventional karyotyping yielded normal results. Brain magnetic resonance imaging demonstrated subcortical T2 hyperintense lesions consistent with a metabolic disorder. A biopsy taken from the preauricular region, initially suspected to be squamous cell carcinoma, was found to be compatible with atypical fibroxanthoma. Skin biopsies obtained from photosensitive areas showed hyperkeratosis and acanthosis.

Discussion: The coexistence of photosensitivity, ocular anomalies, neurodevelopmental delay, and atypical fibroxanthoma suggests the possibility of a syndromic form of photodermatosis. Disorders associated with DNA repair defects, particularly xeroderma pigmentosum, were primarily considered; however, no molecular confirmation could be established. The concurrent presence of brain MRI abnormalities and neoplastic findings further complicates the clinical phenotype.

Current diagnostic approaches remain limited in detecting intronic variants, structural rearrangements such as translocations and inversions, low-level mosaicism, and repeat expansion regions. These technical limitations may account for the potentially negative molecular results observed in this case.

Conclusion: This report describes a case of photodermatosis with multisystem involvement in which a definitive diagnosis could not be established despite comprehensive genetic investigations. The coexistence of cutaneous, ocular, and neurological manifestations suggests either an as-yet-unidentified DNA repair defect or a complex phenotype with multifactorial etiology. Elucidation of the underlying cause is likely to be achievable through advanced approaches such as whole-genome sequencing, long-read sequencing technologies, and transcriptomic analyses.

**P-10 The Role of Chromosomal Microarray Analysis in the Diagnosis of Rare Diseases:
A Single-Center Experience**

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Introduction

The prevalence of rare diseases worldwide is estimated to be between 3.5% and 6%, with over 8,000 identified conditions. In rare diseases, difficulties in diagnosis can arise due to the inability to identify the responsible gene or chromosomal region or other genetic etiology. Chromosomal microarray analysis(CMA) is an important tool in the diagnosis of rare diseases due to its ability to identify defined microdeletion-duplication syndromes, unique copy number variations in individuals, major chromosomal abnormalities, chromosomal numerical anomalies, single gene disorders, imprinting disorders; providing insight into mosaicism, and detecting loss of heterozygosity. We aim to present our center's experience with CMA in rare diseases.

Methods And Material: Molecular karyotyping was conducted on the Illumina iScan System 300K (in 72 patients) and Illumina iScan System 700K (in 623 patients) microarray platforms for 695 patients who presented with various indications at the Çanakkale Onsekiz Mart University Genetic Diagnosis and Treatment Center between 2020 and 2025.

Results: Rare diseases were diagnosed in 47 out of the 695 patients we analyzed (%6.7). Copy number variations were detected in 10 patients, with a single gene (SHANK3, CHRNA7, GLI3, HNF1B, NRXN1, ABCG2, NF1, HBA1, BHLHA9) responsible for the clinical manifestations. Copy number variations were detected in rare regions among 14 patients, with sizes ranging from 145 KB to 7.7 MB, along with identified variations in microdeletion/duplication syndrome regions including 22q11.2 microdeletion syndrome in 4 patients, Prader-Willi/Angelman syndrome in 3 patients, 3q29 microduplication syndrome in 4 patients, and other syndromes found in 1 patient each such as Phelan McDermid syndrome, 1q21.1 duplication syndrome, 9q31.1q31.3 microdeletion syndrome, cat eye syndrome, 6q25 microdeletion syndrome, and 8q21.11 microdeletion syndrome. . Additionally major numerical and structural chromosomal anomalies, such as trisomy 9 p, partial monosomy 11q, 6q25 microdeletion syndrome, Turner syndrome, and derivative Y chromosome, were detected in 7 of these patients, which can also be identified through chromosome analysis.

Conclusion: In today's context where sequencing technologies have emerged as prominent tools for diagnosing rare diseases, the significance of CMA technology remains crucial in the diagnosis of rare diseases due to its ability to diagnose genetic disorders arising from various mechanisms.

P-11 Integrating Deep Phenotyping and Exome Sequencing for Rare Genetic Epilepsies: The South Kazakhstan Experience

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Keywords – rare genetic epilepsies, deep phenotyping, exome sequencing, pathogenic variants, likely pathogenic variants, variants of uncertain significance

Abstract

Introduction: Rare genetic epilepsies represent a highly heterogeneous group of disorders frequently presenting with pharmacoresistant seizures and neurodevelopmental impairment. Accurate diagnosis is often delayed due to overlapping phenotypes and limited access to genomic testing in developing regions. Integrating deep phenotyping with exome sequencing may substantially improve diagnostic yield. This study aimed to evaluate the clinical and molecular spectrum of pharmacoresistant epilepsies within a regional cohort from South Kazakhstan.

Methods: A total of 78 patients with pharmacoresistant epilepsy were recruited in 2025. Deep phenotyping was performed using Human Phenotype Ontology terms, including seizure types, age at onset, cognitive and motor status, and comorbidities. Exome sequencing was conducted in collaboration with 3billion Inc. (Seoul, Republic of Korea). Genetic variants were classified according to ACMG guidelines as pathogenic, likely pathogenic, or variants of uncertain significance (VUS).

Results: The study included 78 individuals aged 18 to 65 years (mean age $\pm$ SD: 34.6 ± 11.8 years), comprising 40 males (51%) and 38 females (49%). All participants had pharmacoresistant epilepsy with disease duration ranging from 3 to 28 years.

Deep phenotyping revealed a wide clinical spectrum. The predominant seizure types were generalized tonic-clonic (62.8%), focal impaired-awareness (47.4%), and myoclonic seizures (19.2%), often in mixed combinations. Cognitive impairment was identified in 80.8% of the cohort. Additional findings included motor deficits, coordination disturbances, and in some cases, facial dysmorphism.

Following exome sequencing, clinically relevant variants were identified in 29 out of 78 patients (37.2%). Most of these variants were associated with genes implicated in developmental and epileptic encephalopathies. The detected genes included LAMC3, PCDH19, GABRG2, GRIA2, SIK1, and PHACTR1.

Discussion and Conclusions: The integration of exome sequencing and systematic deep phenotyping substantially improved diagnostic yield and clarified the phenotypic spectrum of rare genetic epilepsies in South Kazakhstan. This regional experience highlights that phenotype-guided genomic diagnostics are feasible and effective even in resource-limited healthcare systems, paving the way toward sustainable precision neurology in Central Asia.

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P-12 Cognitive Spectrum of Rare Genetic Epilepsies: Findings from a South Kazakhstan Cohort

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Keywords – rare genetic epilepsies; orphan neurological diseases; MoCA; Raven’s Progressive Methods; IQ; cognitive impairment

Abstract

Introduction: Rare genetic epilepsies represent a heterogeneous group of orphan neurological diseases often characterized by pharmacoresistant seizures and developmental impairment. Cognitive dysfunction constitutes a major determinant of long-term outcome and quality of life in these patients. This study aimed to assess cognitive function in adults with genetically confirmed rare (orphan) epilepsies from South Kazakhstan and to characterize domain-specific cognitive profiles.

Methods: From a cohort of 78 individuals with pharmacoresistant epilepsy, 29 patients (37.2%) carrying pathogenic, likely pathogenic, or uncertain variants associated with rare neurogenetic disorders were included. Cognitive performance was evaluated using standardized tools — the Montreal Cognitive Assessment (MoCA), Raven’s Progressive Methods (RPM), and age-adjusted IQ testing. Domains of executive function, attention, visuospatial ability, memory, and language were analyzed. Descriptive and correlational statistics were applied using SPSS 26.0.

Results. The study group comprised 16 males (55%) and 13 females (45%), aged 19–61 years (mean 32.8 ± 10.4). The mean MoCA score was 19.4 ± 4.6 , mean RPM percentile was 37 ± 9 , and mean IQ was 71 ± 11 , indicating mild-to-moderate cognitive impairment. Cognitive deficits were present in all patients but varied in intensity and structure. The most affected domains were executive and visuospatial, while language and memory were relatively preserved.

A significant correlation between earlier seizure onset and lower MoCA scores ($r = -0.63$, $p < 0.01$) indicated that early disease manifestation contributes to greater cognitive decline. No gender differences were observed.

Discussion and Conclusions: This study provides one of the first quantitative evaluations of cognitive functioning in adults with genetically confirmed orphan epilepsies in Central Asia. Cognitive impairment was universal among affected individuals, underscoring the need for systematic neuropsychological monitoring. Applying standardized cognitive scales such as MoCA, Raven’s Progressive Methods, and IQ testing may facilitate early recognition of cognitive decline and support individualized rehabilitation within the framework of rare neurological disease management.

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P-13 A Rare Genetic Disease Presenting with Toe Walking: MYOT Associated Myofibrillar Myopathy

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Introduction: *MYOT* gene encodes the cytoskeletal protein myotilin, which is essential for Z-disc organization and sarcomere integrity. Mutations in *MYOT* are associated with myofibrillar myopathies (MFMs), a group of slowly progressive muscle disorders. In our case, we present a patient who was diagnosed with myofibrillar myopathy after presenting with tiptoe walking, highlighting an unusual early-onset presentation.

Case Presentation: A 10-year-old male patient, born at term, presented to our department due to tiptoe walking. Neuromotor milestones were reported as normal, with tiptoe walking first noticed around six to seven years. Cognitive function was within normal limits, and the patient reported no history of muscle weakness, exercise intolerance, or undue fatigability. On physical examination, muscle strength was 5/5 in upper extremities and 4/5 in distal lower extremity muscles, with normal muscle tone. No muscle atrophy was observed. Deep tendon reflexes were absent in the lower extremities; the Babinski sign was normal. Achilles reflexes were absent. He was unable to walk on heels, but tiptoe walking was preserved. Serum creatine kinase (CK) level was 118 U/L. Craniospinal MRI revealed a 13-mm retrocerebellar arachnoid cyst, with no other pathological findings. Cardiac evaluation, including echocardiography, was normal. Electroneuromyography (ENMG) revealed findings consistent with sensory axonal neuropathy in the lower extremities. On the neuromuscular disorders panel, a heterozygous pathogenic de novo variant in the **MYOT** gene (c.163T>C, p.S55P) was detected.

The patient was diagnosed with myofibrillar myopathy due to a heterozygous pathogenic de novo variant in the **MYOT** gene and continues regular follow-up with physical therapy and orthopedic management.

Conclusion: Myofibrillar myopathy is a slowly progressive disorder, typically characterized by distal and sometimes proximal muscle weakness, muscle atrophy, tendon contractures, lower extremity hyporeflexia, muscle stiffness or aching, tiptoe walking, peripheral neuropathy, EMG abnormalities, mild CK elevation, and possible cardiac involvement. Other genes associated with this condition include **DES**, **CRYAB**, **BAG3**, **FLNC**, **LDB3**, **TTN**, **FHL1**, and **DNAJB6**, highlighting its genetic heterogeneity. The clinical features observed in our patient — including distal muscle weakness, Achilles tendon contractures, lower extremity hyporeflexia, tiptoe walking, and EMG evidence of mixed myopathic and neurogenic changes — are consistent with the known phenotype of myofibrillar myopathy. Although MFM most often manifests in adulthood, this case demonstrates that characteristic features may also present in childhood.