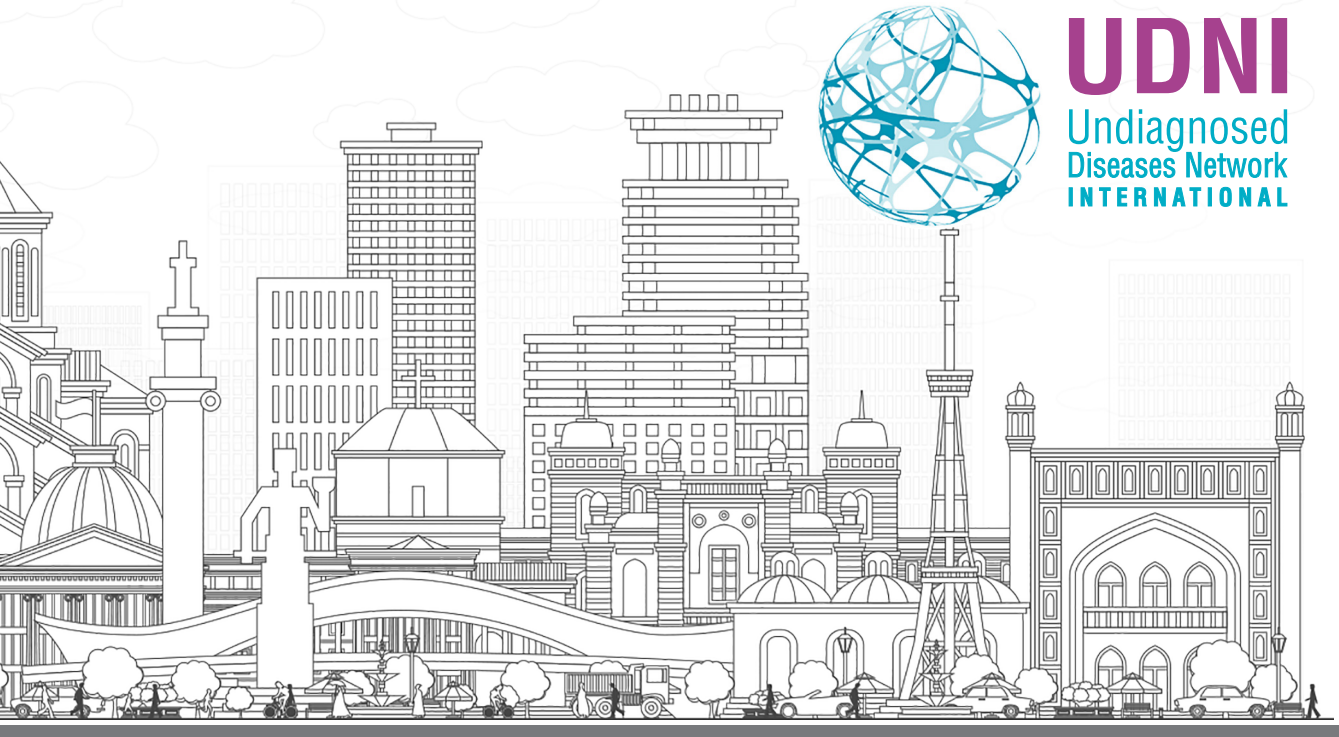

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THE ABSTRACT BOOK

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IGHMBP2-related disease: expanding the mutational spectrum and genotype-phenotype correlation

The IGHMBP2 gene encodes a well-established protein with ATPase/helicase activity. Mutations in the IGHMBP2 gene are associated with two distinct phenotypes: Charcot-Marie-Tooth disease type 2S (CMT2S) and distal spinal muscular atrophy 1 (DSMA1).

We report four patients with IGHMBP2 gene mutations. Patient 1 is a 7-month-old female who presented with stridor, weak cry, and proximal muscle weakness from one month of age. The symptoms progressed into diaphragmatic paralysis requiring intubation. Patients 2 and 3 are 12 and 7-year-old brothers with congenital bilateral foot drop, walking difficulty, slowly progressive distal limb muscle wasting, and weakness with progressive sensory loss. EMG showed slow nerve conductance. Patient 4 is a 28-year-old female, who presented initially with weak hand grip starting within the first decade of life, that later progressed to muscle weakness in all four limbs. EMG showed diffuse chronic motor axon loss changes in cervical and lumbosacral segments, with rare active denervation. Patient 5 is a 4-year-old male with intrauterine growth restriction, severe generalized hypotonia, hyporeflexia, delayed speech and language development, talipes equinovarus, with height, and weight below 3rd percentile.

Whole exome sequencing (WES) was performed in all patients. Patient 1 was revealed to have two heterozygous nonsense variants: c.127C>T, (p.Arg43*) and c.958C>T, (p.Arg320*), creating premature translational stop signals in the IGHMBP2 gene. For patients 2 and 3, genetic testing showed two novel heterozygous missense variants c.181G>C, (p.Gly61Arg) and c.613T>C, (p.Ser205Pro) in the IGHMBP2 gene. Patient 4 was diagnosed with homozygous missense variant c.1591C>A, (p. Pro531Thr) variant in IGHMBP2 gene. Interestingly, WES was negative in patient 5; however, reanalysis of WES data (during UDNI Hackathon) revealed a homozugous missense variant c.1328G>A, (p.Arg443His) in the IGHMBP2 gene. The variant is loctaed in highly conserved region and is predicted to disrupt the protein's function.

The current cases illustrate several major points: 1) confirm the existence of genotype-phenotype correlation in IGHMBP2-related disease: missense variants with residual function producing milder phenotype consistent with CMT2S and nonsense variants with null mutations presenting with a severe form of DSMA1; 2) detected c.181G>C (p.Gly61Arg), c.613T>C (p.Ser205Pro) and c.1328G>A, (p.Arg443His) variants represent novel variants and expand the mutation spectrum of the IGHMBP2-related disease; 3) reanalysis of WES data in test-negative patients is a useful and cost-effective tool to diagnose the undiagnosed patients; 4) IGHMBP2 should be considered in any infant presenting with symptoms consistent with spinal muscular atrophy with diaphragmatic insufficiency.

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DIAGNOSTIC IMPLICATIONS OF PITFALLS IN CAUSAL VARIANT IDENTIFICATION BASED ON 4577 MOLECULARLY CHARACTERIZED FAMILIES

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Despite large sequencing and data sharing efforts, previously characterized pathogenic variants only account for a fraction of Mendelian disease patients, which highlights the need for accurate identification and interpretation of novel variants. In a large Mendelian cohort of 4577 molecularly characterized families, numerous scenarios in which variant identification and interpretation can be challenging are encountered. We describe categories of challenges that cover the phenotype (e.g. novel allelic disorders), pedigree structure (e.g. imprinting disorders masquerading as autosomal recessive phenotypes), positional mapping (e.g. double recombination events abrogating candidate autozygous intervals), gene (e.g. novel gene-disease assertion) and variant (e.g. complex compound inheritance). Overall, we estimate a probability of 34.3% for encountering at least one of these challenges. Importantly, our data show that by only addressing non-sequencing-based challenges, around 71% increase in the diagnostic yield can be expected. Indeed, by applying these lessons to a cohort of 314 cases with negative clinical exome or genome reports, we could identify the likely causal variant in 54.5%. Our work highlights the need to have a thorough approach to undiagnosed diseases by considering a wide range of challenges rather than a narrow focus on sequencing technologies. It is hoped that by sharing this experience, the yield of undiagnosed disease programs globally can be improved.

Aung Min Saw[1]

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CHALLENGES UNMASKED: NAVIGATING THE COMPLEXITIES OF ADULT RARE AND UNDIAGNOSED DISEASE CARE

In the landscape of medicine, undiagnosed and rare diseases have long been a challenge that defies conventional approaches. In early 2022, Syndrome Without a Name (SWAN) clinic was set up in Cardiff, capital of Wales, the UK by Welsh Health Specialist Services Committee (WHSSC) as a pilot project to shorten the diagnostic odyssey for patients with rare and undiagnosed conditions. It comprises of adult and pediatric services overviewed by one clinical lead and one genetic lead each and runs as an outpatient service empowered by multi-disciplinary meetings.

Traditionally, undiagnosed and rare disease services focus heavily on pediatric population, which reflects significant unmet needs in adult patients with such conditions. Much was learnt during our two-year journey, and we discovered that there are challenges specific to or disproportionately affecting the adult population. This abstract explores those unique challenges with real world examples of cases we encountered and shares our successful strategies in dealing with them, including our ongoing struggles.

We learn that clinical presentations of adult patients are relatively more complex due to cumulative comorbidities, aging and environmental factors, leading to larger pool of differential diagnosis. Their diagnostic odyssey is also more soul consuming owing to significant lack of holistic care and limited access to resources in the current world of pediatric priority undiagnosed and rare disease services. One important lesson learn is that the clinic's positive impact is directly related to the engagement and investment of various other specialties (immunology, metabolic medicine and neurology in particular) and growing network nationally and internationally. Despite many success stories, our ongoing challenges include difficult patient selection due to significant functional overlap in adult patients, need for easier access to novel diagnostic and therapeutic resources and threat to sustainability of the clinic.

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CHANGING LIVES, ONE DIAGNOSIS AT A TIME: AN IMMUNOLOGY CASE REPORT FROM SWAN CLINIC, THE UK

Individuals affected by rare diseases often face a journey spanning years from development of first symptoms to achieving a definitive diagnosis. Here we describe the experience of a gentleman with a diagnostic odyssey 27 years long, culminating in a molecular diagnosis made by the UK adult SWAN clinic.

At age of 14, the disease first manifested as inflammatory ulceration in legs requiring 14 days of intravenous antibiotics. Over the next 27 years, he required a further 46 inpatient or day care admissions, 132 days of hospital stay and 279 outpatient appointments across 3 Welsh Health Boards. Despite those, he tragically lost vision in one eye.

To uncover the molecular origin of his multi-system inflammatory disease, we performed whole exome sequencing which revealed a variant of unknown significance, predicted to trigger nonsense-mediated decay of the cytoskeletal protein "moesin." Flow-cytometric analysis of peripheral blood cells from the individual confirmed absent protein. A pivotal turning point in his healthcare journey was the initiation of anti-cytokine therapy with IL-1 receptor antagonist, Anakinra, which has remarkably stopped period of unprovoked inflammation.

This case demonstrates how achieving a molecular diagnosis can have substantial benefits in rare disease, including access to molecularly targeted therapy, unlocking the potential for genetic counselling in the wider family, and reducing health care utilization. Moreover, this extends the phenotype of moesin-deficiency.

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SOLVING UNDIAGNOSED DISEASE BEYOND THE EXOME: FUNCTIONAL ENHANCERS WITH MEDICAL RELEVANCE IDENTIFIED BY COMPUTATIONAL ANALYSIS AND CHIP-STARR-SEQ IN NEURAL CELL MODELS ENABLE PRIORITIZING NON-CODING VARIANTS FROM PATIENT WHOLE GENOME SEQUENCING STUDIES

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One of the biggest puzzles in genetics is how to interpret functional relevance of variation in the non-coding genome in the context of Mendelian disease. Transcriptional enhancers are distal non-coding regulatory elements that play crucial roles in the regulation of cell-type specific gene expression, particularly during development and cell differentiation. The massively parallel reporter assay ChIP-STARR-seq enables high-throughput functional annotation of enhancers and quantification of their activity (Cell Stem Cell 2018, PMID: 30033119). Tissue-specific screens for enhancer function have the potential to greatly expand our understanding of the role of non-coding sequences in development and disease. To identify enhancers that are likely active during early stages of neural development we here generated ChIP-STARR-seq plasmid libraries for various neural cell types using ChIP for H3K27ac, H3K4me1, and selected transcription factors and identified ~15 thousand enhancers showing high activity. These enhancers are linked to genes that are highly expressed during neural development and are susceptible to loss-of-function intolerance. When testing the same neural stem cell (NSC)-derived plasmid libraries in embryonic stem cells (ESCs), we find that enhancers exhibit differential activity in NSCs compared to ESCs. Highly active enhancers specifically in NSCs are linked to genes involved in transcriptional regulation, while ESC-specific highly active enhancers are still linked to genes involved in nervous system development. These enhancers are likely inactive at the endogenous chromatin context as they are not marked by H3K27ac and H3K4me1 in ESCs, but are primed for activity later on during neural development. A convolutional neural network trained on these functional genomics data furthermore allows to identify crucial DNA sequence motifs relevant for enhancer activity. Together with our previous large scale integrative computational analysis of virtually all available human fetal brain epigenome data (Genomics in Medicine 2021, PMID: 34663447) and ongoing high-throughput functional validation in zebrafish models, our work expands knowledge on gene regulation during brain development, and identifies non-coding regulatory elements linked to human disease genes, which are primed targets to investigate variants identified by whole genome sequencing to help address missing heritability in neurodevelopmental disorders. We are currently implementing our atlas of regulatory elements for brain development into routine WGS analysis at our center, and would like to discuss possibilities for collaborative efforts within the Undiagnosed Disease Network to further advance diagnostics for neurodevelopmental disorders beyond the exome.

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A FOUNDER COL4A3 PATHOGENIC VARIANT RESULTING IN ALPORT SYNDROME AND THIN BASEMENT MEMBRANE DISEASE: A CASE REPORT SERIES

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Alport syndrome is a rare genetic condition characterized by renal disease, hearing impairment, and ocular abnormalities. It exhibits various inheritance patterns involving pathogenic variants in COL4A3, COL4A4, and COL4A5 genes. The phenotypes can range from isolated hematuria with a non-progressive or very slowly progressive course to progressive renal disease with extrarenal abnormalities. Timely diagnosis of Alport syndrome facilitates the early and effective implementation of treatment, as well as genetic counseling. Here, we report the COL4A3 c.765G>A, p.((=)) mutation in three ethnically Azerbaijani, apparently unrelated, consanguineous families from the village of Algeti in the Marneuli region of Georgia. We speculate that this variant could represent a founder mutation within this population and recommend offering genetic testing to Algeti village residents with persistent hematuria.

Michael Brudno[1]

CAPTURING AND SHARING DATA ON RARE DISEASE PATIENTS IN THE CANADIAN CARE4RARE PROJECT

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Despite recent progress in the understanding of the genetic etiologies of rare diseases (RDs), a significant number remain intractable to diagnostic and discovery efforts. Broad data collection and sharing of information among RD researchers is therefore critical. Care4Rare is a pan-Canadian effort to provide a genetic diagnosis to patients with RDs through the application of new genetic technologies. To help Care4Rare manage patient and genomic data, we have developed Genomics4RD, an integrated web-accessible platform to share Canadian phenotypic and multiomic data between researchers, both within Canada and internationally, for the purpose of discovering the mechanisms that cause RDs. Genomics4RD has been designed to standardize data collection and processing, and to help users systematically collect, prioritize, and visualize participant information. Data storage, authorization, and access procedures have been developed in collaboration with policy experts and stakeholders to ensure the trusted and secure access of data by external researchers.

One innovation recently implemented in Genomics4RD is the One-Sided Matching Portal (OSMP), a platform capable of performing one-sided matchmaking queries across thousands of participants stored in genomic databases. The OSMP returns variant-level and participant-level information on each variant occurrence (VO) identified in a queried gene and displays this information through a customizable data table. A workflow for one-sided matchmaking was developed so that researchers could effectively prioritize the many VOs returned from a given query. This workflow was then tested through pilot studies where we queried data from >5,000 individuals. Two sets of genes were queried: 130 genes that were newly associated with disease in OMIM, and 178 candidate genes that were not yet associated with a described disease-gene association in OMIM. The OSMP workflow successfully filtered out over 99.8% of the VOs in these genes before they were sent for review by a patient's clinician. Filters on participant-level information, such as variant zygosity, participant phenotype, and whether a variant was also present in unaffected participants were especially effective in this workflow at reducing the number of false positive matches. This pilot has already resulted in two diagnoses and over a dozen other strong candidate genes.

Jaeso Cho[1], Myungae Jung[1], Soo Yeon Kim[1], Jong Hee Chae[1], Yong Jin Kwon[1]

QUALITATIVE ANALYSIS ON THE DIAGNOSTIC ODYSSEYS OF PEDIATRIC UNDIAGNOSED DISEASE PATIENTS: FOCUSED ON MEDICAL UTILIZATION, PERCEPTIONS ON INFORMATION SHARING AND QUALITY OF LIFE IN PATIENT'S GUARDIANS

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Background: While numerous approaches are being pursued to shorten the diagnosticodyssey for pediatric undiagnosed disease patients, there remains a lack of knowledgeconcerning the qualitative aspects of their journey. This study aims to analyze the medical utilization patterns of pediatric undiagnosed disease patients and the quality of life of their guardians

Method: We conducted a qualitative survey that centered on the medical utilization ofpatients and the quality of life of their guardians. This survey was conducted among patients and families who had received a 'undiagnosed' status following exhaustive molecular diagnostic efforts, including whole exome/genome sequencing, conducted at Seoul National University Hospital (SNUH). The assessment of the quality of life was performed using the Korean-translated version of the WHOQOL-BREF survey. All patients were recruited during the Positive Exposure Photo Project held in Korea.

Results: A total of 20 patients were recruited for the survey. The mean age at the time of the survey was 10.1 years, with a range of 3 to 25 years, while the mean age of symptom onset was 3.7 months, ranging from birth to 36 months. The most common presenting symptoms were seizures (6, 30.0%), followed by apnea at birth (4, 20.0%), and hypotonia (4, 20.0%). Initially, the majority of patients sought care at tertiary hospitals (15, 75.0%), followed by emergency rooms (4, 20.0%), and local primary clinics (1, 5.0%). On average, genetic tests were performed 3.2 times within this patient group (ranging from 0 to 10). Across all domains of the WHOQOL-BREF results, the quality of life in guardians of rare disease patients was significantly lower compared to their age-matched counterparts in the normal population group. However, clinical factors and characteristics of medical utilization did not have a significant impact onthe quality of life of the guardians. On an open-ended question asking "What are your feelings about sharing your children's information to the public through Positive Exposure and Undiagnosed Disease Network International (UDNI)", 18 patients (90.0%) responded that "they are concerned but willing to share medical information to hopefully find a correct diagnosis for their child".

Conclusion: Diagnostic odyssey of pediatric undiagnosed disease patients significantly impacts the quality of life in their families. Further considerations should be made within the undiagnosed disease patient clinic to support their families. Efforts in increasing awareness of medical information sharing in the undiagnosed disease patient community could be beneficial in the undiagnosed disease patient community.

Jaeso Cho[1], Jong Hyeon Ahn[2], Jihoon G Yoon[1], Seongbok Lee[1], Man Jin Kim1, Yong Jin Kwon[3], Jong Hee Chae[1], Jangsup Moon[1]

CLINICAL UTILITY OF GENETIC DIAGNOSIS IN ADULTS WITH UNDIAGNOSED DISEASE: AN EXPERIENCE FROM KOREAN ADULT UNDIAGNOSED DISEASE PROGRAM

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Background and Objectives: A limited number of studies have concentrated on genetic diagnosis in adults with undiagnosed diseases, with the majority of diagnostic efforts primarily directed toward pediatric patients. In this study, we conducted an Adult Undiagnosed Disease Program with the objectives of demonstrating the clinical utility of the genetic diagnosis in adults with undiagnosed disease.

Methods: The Adult Undiagnosed Program commenced patient recruitment from August 2020 and continued through August 2023 at both Seoul National University Hospital and Samsung Medical Center. This program enrolled individuals exhibiting a range of phenotypic manifestations suspected to be of genetic origin. Diagnostic investigations were tailored to each patient's specific clinical presentation and included the utilization of gene panels, chromosomal arrays followed by tandem repeat analysis, as well as whole exome and genome sequencing when deemed necessary. Subgroup analysis on patients who visited Seoul National University Hospital (166 patients) were performed by obtaining clinical information including age of onset, primary phenotype based on Human Phenotype Ontology and previous genetic tests.

Results: A total of 237 patients were enrolled in the program, with molecular diagnoses successfully established in 31.2% (74 patients) of the cases. In our subgroup analysis, the mean age of onset was 29.7 years, and the mean duration between symptom onset and molecular diagnosis was 13.1 years. The most prevalent primary phenotype observed was abnormalities in the nervous system (62.7%), followed by musculoskeletal system (10.8%) and hematologic system (3.6%), with diagnostic rates of 27.8%, 22.2%, and 22.5%, respectively. Patients with a family history demonstrated a significantly higher diagnostic rate (40.5%) compared to patients without a family history (24.2%). Among the 47 diagnosed cases, 21 patients benefited from the cessation of further molecular investigations (44.6%), 16 patients necessitated additional investigations within their families (34.0%), 7 patients had their drug repositioned based on their molecular diagnoses (14.9%), and 3 patients required regular screening visits (6.4%). Among genetically diagnosed patients, 3 patients with variants in DDR2, RIT1 and EPHB4 experienced significant improvement of the symptoms after drug repositioning.

Conclusion: The adult undiagnosed program yielded a molecular diagnostic rate of 31.2%, which was lower than the diagnostic rate observed among undiagnosed pediatric patients but comparable to or relatively higher than the diagnostic rates reported for previously studied adult undiagnosed disease patients. Diagnostic rate was significantly higher in patients with family history. Diagnosed patients benefited by cessation of further investigations, investigations to families, screening visits and drug repositions.

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STRUCTURAL VARIANT CALLING IN THE SOLVERD WHOLE EXOME SEQUENCING COHORT, DATA FREEZES ONE TO THREE: ADDED VALUE TO CNV ANALYSIS

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Here we present the results of structural variant analysis on SolveRD whole exome sequencing data. Structural variants (SVs) consist of boths simple deletions and duplications and more complex variants such as inversions and translocations. Many simple deletions and duplications, if they are large enough, can be discovered using standard read-depth based copy-number variant (CNV) calling. However, the analysis of short CNVs,(i.e. affecting a single exon or even a part thereof) as well as copy-number balanced events (inversions and translocations) are usually omitted in exome sequencing analysis since the probability of breakpoints being covered by sequencing reads is low due to the targeted nature of data. Here we evaluate how large scale reanalysis of exome sequencing data from unsolved patients may benefit from dedicated SV analysis using the standard SV caller Manta, in comparison with conventional read depth CNV calling. We present the final results from the analysis of ES data from the first two freezes and work in progress on data from the third freeze, using an updated filtering and prioritization procedure.

Sofia Douzgou Houge[1] and Gunnar Douzgos Houge[1] on behalf of the Norwegian ERN-ITHACA network.

THE POST-EXOME CLINIC: IMPROVING THE IMPACT OF EXOME SEQUENCING FOR DEVELOPMENTAL DISORDERS IN NORWAY

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The Norwegian ERN-ITHACA network is a panel of medical geneticists from all major medical genetic centres across the country who meet regularly using Norsk Helsenett, a secure digital arena for operators in the healthcare sector, in which it is possible to communicate and exchange insights and patient information securely, to address the needs of undiagnosed individuals following clinical exome sequencing (CES). We investigate the added value of expert clinical evaluation and expert-guided, post-exome, additional molecular investigations of individuals with NeuroDevelopmental Disorders (NDD) and syndromes after normal CES, in the Norwegian healthcare system. Over a period of 8 months, 27 individuals with a genetic syndrome/NDD were identified as eligible for a post-exome intervention: 15/26 (30%) had clinical re-phenotyping/reverse phenotyping; in 2/26 (7%) consideration of a new or extended phenotype in the case of a known genetic diagnosis; 3/26 (11%) had functional tests, 2 locally and 1 abroad, as part of an international collaboration and 16/26 (60%) had DNA methylation profiling. In 2/16 (12%) DNA methylation profiling was diagnostic and in 1 case a novel episignature was delineated as part of an international collaboration. In 7/26 (30%) this led to a novel or confirmation of a genetic diagnosis, all from very to extremely rare; in 15/26 (58%), the delineation of the recurrence risk of the family; in 19/26 (73%), allowed ad hoc clinical follow-up; in 3/26 (11%) this led to treatment possibilities: in 2 cases to local, off-label use of an available drug following ethics approval and in 1 occasion to eligibility for inclusion in an EU-based clinical trial (ethics decision awaited). Two of these conditions are known to affect only approximately 10 individuals around the world. Finally, in 4/26 (15%) a candidate novel gene as a possible cause of a novel genetic condition was identified. We discuss current and future plans of our collaborative effort.

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OROMANDIBULAR-LIMB HYPOGENESIS SYNDROME WITH ASSOCIATED MOEBIUS SYNDROME: A CASE REPORT

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In this case report, we present the clinical assessment of a 2-year-old male who was referred to genetic appointment at Casa Dos Raros due to developmental delay, congenital limb and facial abnormalities. The patient displayed limb reduction defects, facial paralysis, stiff elbow, micrognathia, and facial palsy. A diagnosis of Pierre Robin Sequence was established, and mandibular distraction surgery was performed at 4 months of age. Throughout the distraction period, the patient remained immobilized, and upon removal of the distractors, a delay in neurodevelopment was observed. Additionally, the patient exhibited strabismus, leading to the diagnostic hypothesis of Moebius Syndrome. Past medical history revealed recurrent ear infections necessitating bilateral ventilation tube placement, and the patient had previously undergone mandibular distraction. He is the first child of non-consanguineous young parents and no reported familial malformations. Gestational history was uneventful, without any identified fetal malformations, and no known environmental exposures during pregnancy. Developmental milestones included achieving neck support at 7 months after mandibular distraction, independent sitting at 10 months, delayed crawling, first words at 18 months, and independent walking at 2 years and 3 months. The physical examination revealed facial paralysis, convergent strabismus, horizontal extraocular muscle paresis, bilateral adactyly in the lower limbs, partial absence of hand phalanges, left shoulder hypoplasia, sustained left elbow extension, and upper limb shortening, without glossopalatine ankylosis. While the patient experienced speech delay, he comprehended commands and interacted with the examiner. Therapeutic interventions were initiated, and genetic assessments, including Microarray and Exome sequencing, yielded normal results. After extensive negative genetic etiological investigation, the clinical diagnosis of this case was consistent with Oromandibular-Limb Hypogenesis Syndrome (OLHS), with Moebius Syndrome as a recognized associated feature. OLHS encompasses a group of rare and complex conditions characterized by congenital malformations involving the tongue, jaw, maxilla, and limbs. The connection between facial and limb anomalies may result from simultaneous development during 4th-8th embryonic weeks. Both genetic and environmental factors have been proposed to be responsible for the occurrence, and most cases occur sporadically.

Bibiana Mello de Oliveira[1], Bruna Baierle Guaraná[1], Franciele Trapp[1], Alessandra Pereira[1], João Krause[1], Mariluce Riegel-Giugliani[1], Carolina Fischinger Moura de Souza[1], Roberto Giugliani[1]

A COMPLEX PEDIATRIC CASE: UNRAVELING NEUROLOGICAL REGRESSION AND GASTROINTESTINAL SYMPTOMS

[1]Casa dos Raros, Porto Alegre, RS, Brazil

A 3-year and 10-month-old male patient was evaluated at Casa Dos Raros due to neurodevelopmental regression and movement disorder. Medical history includes an uneventful perinatal period with planned gestation and no complications at birth. Family history reveals non-consanguineous, healthy young parents with no known diseases. Initial breastfeeding had some difficulties but progressed up to the sixth month. However, at 7 months, the patient showed gastrointestinal symptoms, constipation, severe colic, and milk refusal, in addition to sleep pattern abnormalities. Tremors in the legs and hands, muscle weakness, body stiffness, and a marked regression in motor development occurred subacutely over a week, with loss of previously acquired motor milestones. Post-symptom onset, the patient exhibited poor weight gain, with limited oral intake, and needed gastrostomy. Additional identified symptoms included stagnation in cognitive development, irritability, self-mutilation behavior and astigmatism. At physical exam, the patient presented a dystonic, spastic syndrome with pyramidal involvement. Two consecutive hospitalizations for investigation were conducted, RMI was normal and CT scans showed basal ganglia calcifications. EEG pattern was disorganized, but seizures have never been observed. He received immunoglobulin therapy with some transitory improvement in sleep and stiffness. Rehabilitation therapies were initiated at nine months, including sensory integration occupational therapy, physiotherapy, speech therapy for both speech and swallowing, equine therapy, and osteopathy. Despite exhaustive genetic and metabolic assessments, encompassing Microarray and Whole Exome Sequencing - with normal reanalysis, the origin of the patient's condition remains undiagnosed, hinting at the possibility of an undiagnosed genetic or rare disorder.

Rodrigo Rosa de Stefani[1], Carolina Fischinger Moura de Souza[1], Fabiano Poswar[1], Roberto Giugliani[1] and Ida Vanessa Doederlein Schwartz[1]

UNDIAGNOSED SYNDROMIC HYPERINSULINEMIC HYPOGLYCEMIA IN AN INFANT

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A female patient, three months old, born at term by cesarean section with normal weight, no intercurrences during labor or need for resuscitation maneuvers. Adequate prenatal care, without exposure to teratogens. There is no family history of consanguinity or genetic disorder, except for a healthy 11-year-old maternal half-brother and a paternal half-sister who died at age 14 from complications of Immune Thrombocytopenic Purpura. In the first days of life, she had an episode of urinary tract infection (UTI), progressing to neonatal sepsis. Urinary tract study was performed showing severe vesicoureteral reflux. She was transferred to our hospital due to episodes of hyporesponsiveness, associated with dysphagia and laryngomalacia. Significant axial hypotonia, facial dysmorphisms and dorsal hirsutism were noted. Karyotype and Prader-Willi methylation analysis showed normal results. Chronic hyponatremia with no defined etiology was diagnosed and sodium replacement was initiated. Focal seizures were also observed, with a diagnosis of epilepsy after two altered electroencephalogram results. Phenobarbital was started and the patient remained clinically stable, being discharged from the hospital at 6 months of age. After three days, she returned to emergency due to persistent fever and a new UTI was confirmed. New episodes of hyporesponsiveness were observed, with normal serum sodium levels. Episodes of hypoglycemia were accessed by glycemic control, due to hyperinsulinism. Diazoxide was started, with good glycemic control. Screening tests for inborn errors of metabolism have been performed, showing abnormal type I profile on transferrin isoform analysis. A multigene panel showed a pathogenic variant c.652A>T(p.Lys218*) in heterozygosity in MPI, which is associated with autosomal recessive congenital disorder of glycosylation (MPI-CDG). After 9 episodes of UTI and several cycles of antibiotic therapy, the patient persisted with daily episodes of fever and growth of resistant bacteria in urine analyses. She had a severe acute episode of hyporesponsiveness in the presence of sustained fever, presumed to be sepsis, being transferred to the pediatric intensive care unit. After five days of antibiotic therapy, the fever ceased, but the patient remained in a comatose state. Magnetic resonance imaging of the brain showed T2/FLAIR hypersignal in the globus pallidus, cerebral peduncles and substantia nigra. Whole genome analysis was performed not presenting additional results. In the following two weeks, the patient remained in a comatose state and began to present episodes of dysautonomia and hydroelectrolytic disturbances. Unfortunately, the patient died at 11 months of age, with no definite diagnosis.

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CARDIOFACIOCUTANEOUS SYNDROME AND NON-SYNDROMIC DEAFNESS: A CASE REPORT

This case report is about a 12-years-old female who was referred to Casa Dos Raros medical team due to neurodevelopmental delay, seizures, bilateral deafness, short stature and skeletal abnormalities. At the time of our evaluation, the patient had already been investigated with karyotype, FISH to Williams syndrome (7q11.23), both normal, and array-CGH. The array analysis showed a 47 kb homozygous interstitial deletion at chromosome 15 (15q15.3), arr[GRCh37]: 15q15.3 (43,892,893-43,940,205)x0. This chromosomal region has STRC and CATSPER2 genes and is associated with recessively inherited non-syndromic sensorineural deafness (DFNB16). This girl was born at term, with 3500g, 49 cm of stature, 36 cm of cephalic perimeter and 9/10 Apgar scale. In the neonatal and post neonatal period, she evolved with gastroesophageal reflux disease, short stature and important neurodevelopmental delay. The patient walked alone for the first time with 4 years and 9 months old. At the age of 8 years, she presented motor restriction due to a progressive genus valgus. Also, she showed her first seizure and then evolved with absence seizures, when medication treatment was started. At our evaluation, the patient showed speech delay – she doesn't speak sentences, only a few words – and the clinical findings were: short stature, reduced global trophism, hyperkeratosis pilaris, nevi, sparse eyebrows, ulerythema ophryogenes, left palpebral ptosis, wiped nasolabial philtrum, thick lips, high palate, transverse palmar crease in the right hand, deep palmar crease, bilateral clinodactyly of fifth finger, thoracic kyphosis, genus valgus, bilateral proximal syndactyly of second and third toes, hallux valgus and flat feet. There were no similar cases in the family history and the family was non-consanguineous. Exome sequencing was performed and found the heterozygous missense pathogenic variant p.Tyr130Cys in MAP2K1 gene (NM_002755.4). Thus, clinical and molecular evaluation allowed establishing cardiofaciocutaneous syndrome 3 (CFC3) diagnosis, which is a rasopathy and has an autosomal dominant inheritance. Despite the syndrome usually presents heart disease in 75% of cases, in MAP2K1 gene the frequency is 25% of cases and our patient did not present this feature. This report shows a patient with two genetic variants, found in different cytomolecular analysis, one associated with DFNB16-related deafness and the other with CFC syndrome. Therefore, further evaluation is always recommended when one single variant does not explain all the patient phenotype.

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BOSCH-BOONSTRA-SCHAAF OPTIC ATROPHY SYNDROME (BBSOAS) - CASE REPORT

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Background and aims: NR2F1-related BBSOAS is a rare autosomal dominant disorder (<1/1,000,000) caused by heterozygous mutations in the NR2F1 gene located on chromosome 5 (5q15) and characterized by intellectual disability, hypotonia, visual impairment, epileptic seizures, behavioral and autistic spectrum disorders, and abnormalities of the corpus callosum on MRI. However, The clinical signs of the disease are variable, and the treatment strategies are symptomatic. The aim of our case report was to share our experience on clinical symptoms and effectiveness of Antiseizure medications (ASDs) for seizure control in patient with NR2F1-related neurodevelopmental disorder and epilepsy.

Case report: In a clinical case of a 12-year-old girl with neurodevelopmental disorder and visual impairment (partial optic atrophy) associated with NR2F1 gene mutation, hypotonia, behavioral dysfunctions and epileptic seizures were also detected. From early anamnesis was revealed that she started walking at 22 months and uttered the first words at 3 years of age. From the age of 3 started the episodes with a sharp change in consciousness, tension and clonic movements of the right half of the face, accompanied by a grimace of a smile, and sometimes urination, 1-2 times a week. These episodes were classified as epileptic seizures and treatment was started with Valproic acid (VPA). As the frequency of attacks decreased but did not revealed effective outcome, levetiracetam (LEV) was added to VPA. A few months later were revealed another type of seizure, when patient was conscious, her facial expression was changing, movement of the tongue to the right side, presses the tongue against the teeth, as a result of which cyanosis appears on the tongue, the face becomes hot and red. Such episodes were often followed by sleep.

Results: MRI of the brain (3T) showed partial agenesia of the corpus callosum: the posterior part was missing. On long-term video-EEG: Interictal slow-wave activity and sharp-slow-wave complexes in the left temporal, left parieto-occipital and right temporal regions with predominance in the left temporal area was revealed; Ictal focal seizure originating from the left temporal area with loss of consciousness was detected. In the ASDs treatment LEV was gradually replaced by lamotrigine (LTG) and added to VPA. After changing the ASDs treatment, the seizures completely stopped within seven weeks and behavioral changes were significantly reduced (follow-up 8 months). Whole exome sequencing (WES) was performed, which revealed NR2F1 heterozygous novel variant c.313G>C, p.(Gly105Arg). Parental analysis confirmed de novo status.

Conclusions: Our case demonstrated that in people with NR2F1-related developmental disorders and epilepsy a combination of LTG and VPA could be effective treatment for seizures and for behavioral improving. WES represents the first-line diagnostic test in individuals with neurodevelopmental delay and epilepsy.

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THE IMPORTANCE OF GENETIC TESTING IN THE DIAGNOSIS AND TREATMENT OF MODY DIABETES (MODY 3)

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Introduction: Maturity-onset diabetes of the young (MODY), is a monogenic form of diabetes. Whereas type 1 and type 2 diabetes are polygenic, MODY is caused by a single gene mutation that leads to a defect in beta cell insulin secretion in response to glucose stimulation. Most genetic versions of MODY have autosomal dominant transmission. MODY gets commonly misdiagnosed as type 1 or type 2 diabetes mellitus. It is a genetically heterogeneous form of monogenic diabetes that is caused by mutations occurring in different genes thus tends to cause a slightly different variant of diabetes and treatment options. There are now at least 14 different known MODY mutations. They include GCK, HNF1A, HNF4A, HNF1B, INS, NEURO1, PDX1, PAX4, ABCC8, KCNJ11, KLF11, CEL, BLK, and APPL1. The different genes vary with respect to the age of onset, response to treatment, and the presence of extra-pancreatic manifestations. The gene mutation in hepatocyte nuclear factor 1-alpha-HNF1A (MODY 3) acts by inhibiting the key steps of glucose transport and metabolism as well as mitochondrial metabolism in pancreatic beta cells. HNF1A is very responsive to sulfonylureas and meglitinides. The mechanism of action involves the binding of the medication to sulfonylurea receptors on beta-cell membranes. This triggers the influx of calcium, which leads to the fusion of vesicles containing stored insulin. the use of sulfonylureas can frequently delay the need for insulin replacement for many years

Case report: 10 years old girl, Height 144.8 cm; weight 38 kg; BMI-18.1 kg/m2. Fasting glycemia - 150 mg/dl was observed with patient by self-monitoring. 2 hours after meal- 250 mg/dl. Symptoms: polyuria, polydipsia, no weight loss was observed. Family history: mother – diabetes was diagnosed at the age of 21, till today treated with oral antidiabetic medications. Grandmother from mother side- type 2 diabetes. uncle from mother side- type 2 diabetes. The test results showed: Fasting Glucose 138.6 mg/dl; Glucose 2h after meal 203.4 mg/dl; HbA1c-9%; Insulin and C-peptide was normal; GAD, IA2, ICA, ZnT8 antibodies were negative. An opinion was expressed about the existence of MODY diabetes and geneticist consultation was recommended. Genetic testing was performed and HNF1A mutation was detected (MODY 3).

Treatment option: Persons with HNF1A diabetes can initially be treated with diet. Most will need pharmacological treatment as they show progressive deterioration in glycemic management. They are extremely sensitive to sulphonylureas. The initial dose of SUs should be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. As long as there no problems with hypoglycemia, they can be maintained on low-dose SUs (e.g., 20–40 mg gliclazide daily) for decades.

Conclusion: Advances in molecular genetics have led to the identification of genes associated with many clinically identified subgroups of diabetes. Molecular genetic testing should now be considered an essential clinical diagnostic tool that can help define the diagnosis and determine the appropriate treatment of children with diabetes.

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ISTISNA- ISTANBUL UNDIAGNOSED AND RARE DISEASES SOLUTION PLATFORM SURVEY RESULTS

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Rare diseases are important health problems, affecting approximately 6-10 million people across Türkiye. Here we present a national rare disease project, İSTisNA- Istanbul Undiagnosed and Rare Diseases Solution Platform, which is designed to serve Türkiye rare disease community by incorporating activities such as Biobank, translational research and national undiagnosed disease program that can shed light on diagnosis and treatment, it aims to establish a platform that can also provide social support through intensive training activities, awareness and dissemination activities. Within the scope of the disadvantaged groups theme, which is among the priority areas in the 2019 Feasibility Support Program of the Istanbul Development Agency, ISTisNA has been prepared for the development of sustainable, original and a model project for facilitating the accessibility of disadvantaged groups to social, cultural and physical services. One of the subprojects of ISTisNA is a comprehensive survey analysis conducted among the rare and undiagnosed patients and their families. A total of 498 individuals responded to the survey. The majority of the patients were in the age range of 1–10 years (44.7%), and 91% of all the patients had a precise diagnosis. The diagnosis rate in the first 6 months was 69%, and almost 10% of the patients remained undiagnosed. The mothers were the primary caregivers (72%). Nearly 30% of the caregivers had to quit their jobs and 25% of the patients (0–18 years) had to leave school. Accessing physicians with relevant specialization and reaching treatments/medications/supplements were the two main obstacles the participants mentioned, with a frequency of 81% and 73%, respectively. Around 50% of participants noted that they commonly faced difficulties at work/school and in their social lives. The highest expectation or priority was the establishment of rare disease-specific diagnosis and treatment centers, accurate and detailed information on diseases in the Turkish language, and easy access to physicians, treatments, and supportive therapies. To the best of our knowledge, this is the most comprehensive survey conducted on the rare disease community in Türkiye. These results show that regardless of the country, the individuals affected by rare diseases and their families have similar problems and expectations. On the other hand, regional and country-specific issues are still in the line to be solved. These studies can provide a deeper insight into rare diseases and guide the activities of Türkiye's national rare disease action plan.

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THREE NEW CASES OF OLIGOGENIC HYPERCHOLESTEROLEMIA

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Background. Oligogenic familial hypercholesterolemia (FH) is the simultaneous presence of pathogenic heterozygous variants in two different genes, causing hypercholesterolemia and/or another type of rare dyslipidemia. Cases of oligogenic FH have been described - LDLR\LDLRAP1, LDLR\CYP27A1, PCSK9\ABCG5. Second pathogenic variants contribute to the worsening of the FH phenotype. We present three new cases of oligogenic hypercholesterolemia identified through routine genetic diagnostics of hypercholesterolemia by NGS.

Methods. All probands have total cholesterol significantly higher than normal and have no secondary cause of dyslipidemia. The proband's DNA was analyzed using a custom AmpliSeq™ panel on an Ion Torrent S5 next generation sequencer. The panel consist of coding gene sequences for rare dyslipidemias includes ABCA1, ABCG1, ABCG5, ABCG8, ANGPTL3, APOA5, APOB, APOC2, APOE, CREB3L3, GPD1, GPIHBP1, LCAT, LDLR, LDLRAP1, LIPA, LIPC, LIPG, LMF1, LPL, MTTP, PCSK9, SAR1B, SCARB1 genes. Sequencing results were analyzed using a standard automated algorithm for data analysis. The detected variants were called according to the nomenclature presented on the http://varnomen.hgvs.org/recommendations/DNA. The identified variants in the proband and its relatives were verified by Sanger sequencing.

Results. Patient 1 (2011 year of birth) have pathogenic variants in the heterozygous state in the LDLR and APOB (NM_000527.5: c.862G>A p.Glu288Lys and NM_000384.3:c.10580G>A p.Arg3527Gln). LDLR is the key membrane receptor of LDL, APOB plays a leading role in the formation of lipid-containing particles and their interaction with cellular receptors. Patient 2 (1978 year of birth) have pathogenic variants in the LDLR and ABCG8 (c.1997G>A p.(Trp666*) and NM_022437.3_two variants in trans_ c.1715T>C p.(Leu572Pro) and c.1705T>C p.(Ser569Pro). This patient has elevated sitosterol and campresterol. The ABCG8 transporter limits the absorption of sterols in the intestine and promotes their excretion in bile. Patient 3 (2012 year of birth) have pathogenic variants LDLR and SCARB1 (c.986G>A p.Cys329Tyr and NM_005505.5:c.727-2A>C). SCARB1 is a key membrane receptor of HDL. Segregation of genetic variants correlates with the lipid profile of probands and relatives (if material was available).

Conclusion. Clinical and genetic matches allowed dual diagnoses to be established: Hypercholesterolemia familial, 1 OMIM#143890 and Hypercholesterolemia familial, 2 OMIM#14410; Hypercholesterolemia familial, 1 OMIM#143890 and Sitosterolemia 1 OMIM#210250; Hypercholesterolemia familial, 1 OMIM#143890 and Hyperalphalipoproteinaemia OMIM#610762. Genetic testing for FH by NGS is useful not only for making a diagnosis but also for risk stratification and prediction of prognosis in each patient.

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ANALYSIS OF C9ORF72 REPEAT EXPANSIONS IN GEORGIAN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Background: Amyotrophic lateral sclerosis (ALS) is a fatal progressive neurodegenerative disorder that affects the upper and lower motor neurons. Several genetic risk factors have been identified in the past decade with a hexanucleotide repeat expansion in the C9orf72 gene being the most significant. However, the presence of C9orf72 repeat expansion has not been examined in the Transcaucasian region, therefore we aimed to analyze its frequency in Georgian patients with ALS.

Methods: We included 64 self-reported Georgian patients with ALS from different parts of the country, fulfilling the Gold Coast criteria. To investigate the presence of an expanded GGGGCC hexanucleotide repeat in the non-coding region of the C9orf72 gene, we performed Repeat-Primed PCR (RP-PCR).

Results: In total, 64 sporadic and two familial ALS cases were identified. Patients were aged 26 to 84 years with a mean age of 58.3 years at disease onset. Bulbar onset was observed in 21.88%, upper limb onset in 34.38%, and lower limb onset in 43.75% of the patients. Frontotemporal dementia (FTD) fulfilling the Strong criteria was diagnosed in seven patients (10.94%). C9orf72 repeat expansion was detected in only one case using RP-PCR; the patient had a family history of dementia.

Conclusions: Our results indicate that C9orf72 hexanucleotide expansion does not belong to the major genetic risk factor of ALS in Georgian patients. Further genetic studies in a bigger study population are needed to reveal the genetic causes of ALS in the Transcaucasian population.

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AWARENESS OF RARE DISEASES AMONG MEDICAL STUDENTS

Rare diseases (RD) are acknowledged as a medical, legal, economic, social, and public health hazard because they affect about 8% of the world's population. According to studies, medical professionals' lack of familiarity with rare diseases results in the detection and diagnosis of RD being frequently delayed and their management being inadequate. Our study aims assessment medical students' understanding of rare diseases. Utilizing specially created questionnaires, the cross-sectional study was carried out. 380 questionnaires were distributed and 88.9% (n=338) fully completed were returned. Study shows that 96,7 % (n=327) respodents had heard the term „rare disease“ (RD), 89,3 % (n=302) knew the main cause, only 33,2% (n=111) know that RD is more common in infants and children. The majority of students 75,7% (n=256), believe that only geneticists should manage and diagnose RD diseases, so they must be educated and trained on RD issues. The majority of students 92,3% (n=312) believe that they lack sufficient information and they require additional specialized expertise in order to recognize and treat patients with RD. 71,1% (n=242) believe that brief courses for RD early identification should be included in medical curriculum. Our study's conclusions emphasize the need to raise awareness of RDs among students in order to better understand and manage these conditions.

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UNCOVERING INFANTILE TREMOR SYNDROME: A CASE REPORT OF DELAYED DIAGNOSIS IN AN EXCLUSIVELY BREASTFED INFANT

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Infantile Tremor Syndrome (ITS) is a rare disorder predominantly affecting exclusively breastfed infants aged 6 to 24 months, often from low socioeconomic backgrounds. ITS is characterized by a clinical triad of pallor, pigmentary changes, developmental delay and hypotonia, frequently accompanied by tremors. Despite its clinical significance, ITS remains poorly understood and often underdiagnosed.

We present a case of a 7-month-old exclusively breastfed boy who experienced a delayed diagnosis of ITS. The child exhibited increased skin hyperpigmentation, thinning scalp hair, brittle nails and anemia for 3 months and, notably, right hand tremor that progressed from intermittent to strong and continuous over a span of five days. Importantly, these tremors were observed even during sleep, though with reduced intensity.

The clinical presentation raised suspicion of ITS, prompting the initiation of treatment with vitamin B12, zinc, and folate supplementation. Remarkably, the patient responded positively to the intervention, with the tremors subsiding within just five days. ITS is often challenging to diagnose due to its subtle clinical presentation and many cases go undiagnosed. In this instance, it took three months for the condition to be recognized.

This case highlights the importance of early recognition and intervention of ITS, particularly in infants exclusively breastfed from low socioeconomic backgrounds. Early diagnosis and nutritional intervention are crucial to prevent long-term developmental consequences associated with ITS and in reducing the burden of underdiagnosed cases.

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UNRAVELING NEONATAL SEVERE HYPERBILIRUBINEMIA: POSSIBLE HEREDITARY SPHEROCYTOSIS

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This case report presents a 24-day-old neonate admitted to our clinic with severe hyperbilirubinemia, which developed two days after birth. The infant was born full-term, and both maternal and neonatal blood groups were A positive, eliminating ABO incompatibility. Laboratory findings revealed low hemoglobin, elevated MCHC, and a total serum bilirubin level of 494 mmol/L, with a direct bilirubin level of 26.4 mg/dL. Complete blood count indicated a low hemoglobin and low RBC count high. The hemolytic index (HS ratio) was 0.39, and reticulocyte count was 75%. Thyroid function tests and liver enzymes were within normal limits, and immune-mediated hemolysis was excluded. Screening for TORCH infection yielded negative results. Given these findings, a diagnosis of neonatal non-immune hemolytic jaundice was considered, with the primary differentials being G-6 PD deficiency and hereditary spherocytosis. Treatment involved intensive phototherapy and a blood transfusion, resulting in a significant reduction in total serum bilirubin levels to 112.3 mg/dL. The infant remained clinically stable and continued breastfeeding. Despite normal G-6 PD quantitative test results, an absence of spherocytes on peripheral blood smear, and parental normal blood smears, the clinical presentation and laboratory findings prompted consideration of hereditary spherocytosis as the likely diagnosis. Hereditary spherocytosis, characterized by genetic defects leading to alterations in red cell membrane structure and reduced deformability, affects approximately 1 in 2000 individuals in Europe and North America. Most cases are autosomal dominant and exhibit mild to moderate severity, but our case presented with severe clinical symptoms, suggesting an autosomal recessive form. Genomic DNA sequencing studies were initiated to confirm the diagnosis. This case underscores the importance of genetic analysis in diagnosing hereditary spherocytosis in neonates with severe hyperbilirubinemia, particularly when clinical symptoms are severe and atypical.

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GENETIC PROFILING AND DIAGNOSTIC STRATEGIES FOR PATIENTS WITH ECTODERMAL DYSPLASIAS IN KOREA

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Background: Ectodermal dysplasia (ED) is a rare genetic disorder that affects structures derived from the ectodermal germ layer.

Results: In this study, we analyzed the genetic profiles of 27 Korean patients with ED. Whole exome sequencing (WES) was performed on 23 patients, and targeted panel sequencing was conducted on the remaining 4 patients. Among the patients in the cohort, 74.1% (20/27) tested positive for ED. Of these positive cases, EDA and EDAR mutations were found in 80% (16/20). Notably, 23.1% (3/13) of EDA-positive cases exhibited copy number variations. Among the 23 patients who underwent WES, we conducted a virtual panel analysis of eight well-known genes, resulting in diagnoses for 56.5% (13/23) of the cases. Additionally, further analysis of approximately 5,000 OMIM genes identified four more cases, increasing the overall positivity rate by approximately 17%. These findings underscore the potential of WES for improving the diagnostic yield of ED. Remarkably, 94.1% of the patients manifesting the complete triad of ED symptoms (hair/skin/dental) displayed detectable EDA/EDAR mutations. In contrast, none of the 7 patients without these three symptoms exhibited EDA/EDAR mutations.

Conclusions: When conducting molecular diagnostics for ED, opting for targeted sequencing of EDA/EDAR mutations is advisable for cases with classical symptoms, while WES is deemed an effective strategy for cases in which these symptoms are absent.

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UNSOLVED CASES AMONG PATIENTS WITH DIFFERENCES OF SEX DEVELOPMENT IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Introduction: Differences of Sex Development (DSDs) are a group of rare congenital conditions with atypical sex chromosomes, anatomical or gonadal development.

Individuals with DSDs, even in developed countries, experience long diagnostic odysseys, often without final etiological diagnosis. In low-resourced settings the situation is much more dire, with limited access to basic genetic testing and to specialized care. Individuals with DSDs suffer stigma and poorer outcomes and quality of life. A causative diagnosis is a first step to better understanding and care. Here we show the diagnosis outcome of our cases with long and complex diagnostic trajectories from our clinical network in the Democratic Republic of the Congo.

Methods: Patients identified at health facilities throughout the DRC with atypical genitalia and biological parents were consented and asked to donate saliva samples, alongside phenotypic and sociodemographic data. Saliva samples were then sent to Children's National Hospital (USA) for Whole Exome or Whole Genome Sequencing.

Results: 39 participants (age 2 months to 26 years) were recruited from December 2020 to August 2023. Among 28 patients with available genetic results so far, some pathogenic or likely pathogenic variants were identified, however, the majority of cases remain unsolved. An intronic variant in AR established a diagnosis of partial androgen insensitivity in a 22 year-old XY male, raised as a female until age 5. A recurrent homozygous SRD5A2 variant described in the historical cases of 5 α-reductase deficiency in the Dominican Republic was found in a family with two XY females, but a single SRD5A2 variant in an unrelated XY male with perineal hypospadias. Others were a stop gain in NR5A1 and NR5A1 and AR missense variants. No definitive diagnosis could be made in the 8 individuals where short-read sequencing suggested XX sex complement. A single CYP21A2 Gln319* variant was found in an XX male, but a diagnosis of Congenital Adrenal Hyperplasia could not be established as short-read sequencing is inadequate to identify the gene conversions responsible for most pathogenic alleles in this gene. We also detected SRY reads at low level in XX patients with masculinization, suggesting a possible mosaicism. Many cases of atypical genitalia remain without a final etiology identified.

Conclusion: We shared for discussions the large number of unsolved cases encountered in our DSD care network. International collaboration is likely to help solve more rare DSDs, possibly reduce the long and frustrating diagnostic odyssey, and extend the precision medicine approach to underserved settings.

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RARE FORMS OF CONGENITAL SEX DEVELOPMENT DISORDERS (DSD)

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Background: Disorders of congenital sex development (DSD) belong to uncommon pathologies. In addition, there are especially rare forms, which is related to problems in diagnostics and management.

Aim: To determine diagnostic and management criteria for rare forms of DSD.

Material and Methods: 326 patients with DSD were studied. All patients underwent clinical, genealogical, hormonal, ultrasonographic and cytogenetic examinations (karyotyping). In 32 cases, gonadectomy was performed. Histomorphological study of excised gonads was carried out.

Results: In 57 out of 326 cases of DSD, rare forms were identified: 1 patient - with Tetrasomy X, 1 patient - with Turner syndrome with spontaneous menarche – karyotype 45, X / 47, XXX, 3 patients - with Turner syndrome and female phenotype – karyotype 45, X /46, XY, 1 patient - with male phenotype and karyotype 45,X/46,XY, 1 patient – with 46,X, dic (X) (p11.3). ish idic(X) (DXZ1++, XIST++, DXYS154++), 3 patients - with Swyer syndrome, 33 patients - with complete androgen insensitivity syndrome, 9 patients - with partial androgen insensitivity syndrome and 1 patient - with mild androgen insensitivity syndrome and female psychosexual orientation, 1 patient - with 46, XX testicular DSD, 3 patients with ovotesticular DSD (2 patients with karyotype 46, XY, 1 patient – 46, XX). Before the correct diagnosis of these rare forms were clarified, preliminary diagnosis were often inaccurate.

Conclusions: Determining the prognosis and management should be based on an accurate diagnosis, for which in rare atypical cases of DSD is necessary to use molecular diagnostic research methods in addition to karyotyping. Histomorphological study of gonads is especially important. Regarding to the risk of gonadal malignancy timely gonadectomy or monitoring of intra-abdominally located gonads from puberty is recommended.

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UNRAVELING THE GENETIC BASIS OF RARE HEREDITARY NEUROLOGICAL DISEASES IN MALI

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Introduction: Hereditary neurological diseases are genetically heterogeneous disorders caused by hundreds of genes. However, the genetic basis of several clinically characterized cases is not established yet.

Methods: Patients were carefully examined, and brain and spinal imaging, EEG, blood chemistries and HIV and HTLV-1 serology were performed to refine the diagnosis. DNA was obtained for genetic testing including Whole Exome Sequencing (WES). Functional studies such as immunohistochemistry and Western blot using patient-iPSC derived neuronal cells and CRISPR cas9 using Xenopus tropicalis model were performed to confirm pathogenicity.

Results: Three consanguineous families, two afflicted with familial epilepsy and hereditary spastic paraplegia (HSP) are presented here. The ages of onset in the epilepsy families ranged from 6 months to 5 years and symptoms started in both families with hand tremor and included tonic clonic and absence seizures and cognitive decline. The age of onset in the HSP was 8 months, and symptoms were consistent with complicated HSP associating seizures in both patients. Brain MRI showed thinning of the corpus callosum while EEG detected slow background in patients with epilepsy. WES identified homozygous missense variants in two genes, proteasome 20S subunit beta 1 (PSMB1; c.632C>G, p.Ala211Gly) in the epilepsy families and the adaptor protein (AP) complex 2 alpha-2 subunit (AP2A2, p.Ser923Gly) in the HSP family. Families with PSMB1 variant did not report relationship but they are from the same ethnic group and have the same last name. Both variants segregated with the disease phenotype in the families and were not present in SNP databases. While PSMB1 was associated with a severe autosomal recessive neurodevelopmental disorder with microcephaly, hypotonia, and absent language in a Pakistani family, AP2A2 has not been previously associated with disease, but the protein is a member of the AP complex family known to be implicated in other forms of HSP. Western blot analysis and endocytosis of transferrin receptor (TfR) in patient-derived neurons suggested that the AP2A2 variant interferes with endocytosis in neurons. Moreover, tadpoles with AP2A2 knockout showed cerebral oedema and progressive seizures. Functional studies to assess the impact of the PSMB1 variant are ongoing.

Conclusion: This study finds novel genes involved in familial epilepsy and HSP in the Malian population and expands the genetic heterogeneity of these diseases.

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IMPLEMENTING WGS-BASED RARE INHERITED DISEASE DIAGNOSTICS IN THE STOCKHOLM HEALTHCARE REGION

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** On behalf of Genomic Medicine Center Karolinska Rare Diseases*

In healthcare clinical genetics is transitioning to clinical genomics and especially rare disease diagnostics is increasingly done through panel, exome and whole-genome sequencing. At Karolinska we have formed Genomic Medicine Center Karolinska Rare Diseases (GMCK-RD), a joint unit between healthcare and academia, enabling large-scale genome sequencing of patients. GMCK-RD brings together experts from various medical disciplines with clinical geneticists, bioinformaticians and researchers. Through GMCK-RD, over 10,000 individuals have been analyzed by clinical genome sequencing (GS) with an overall yield of 33%, providing a genetic diagnosis to >2,543 individuals. By tight collaboration in 15 multidisciplinary expert teams thousands of patients with various rare diseases have been diagnosed. Our analysis covers detection and interpretation of SNVs, INDELs, uniparental disomy, CNVs, balanced structural variants, and short tandem repeat expansions. Visualization of results for clinical interpretation is carried out in Scout—a custom-developed decision support system. To facilitate the discovery of new disease genes, GMCK-RD is reporting variants to ClinVar and has joined international data sharing initiatives, including UDNI, Beacon, and MatchMaker Exchange. Altogether, we at GMCK-RD have moved healthcare in our region towards precision diagnostics and precision medicine.

Milan Macek[1]

UNDIAGNOSED RARE DISEASES IN THE CZECH REPUBLIC: ACTIVITIES ON THE NATIONAL COORDINATION CENTRE FOR RARE DISEASES AND MULTIDISCIPLINARY NATIONWIDE COLLABORATION

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In the last decade, the system of care for rare diseases has been fully developed in the country. During the 2009 Czech EU Council Presidency the first National Strategy of Rare Diseases (2010-2020) was officially adopted and implemented via three successive National Action Plans. Moreover, the National Coordination Centre for Rare Diseases was established in our department and facilitates domestic and international links, including the latest adoptions in the field of rare diseases and genomic testing. We also closely collaborate with the Czech Society of Medical Genetics and Genomics, which partners with payers and oversees the conduct of rare disease diagnostics according to accreditation standards based on ISO15189 and now even IVD-R. We have been involved in many national and international legislative initiatives in the field of rare diseases comprising the a) formulation of the Genetic Act 373/2011 Coll. §28-30 which builds upon the recommendations of the European Society of Human Genetics, then we introduced the term “rare disease” in the national healthcare legislature for reimbursement purposes (Act 48/1997 Coll.) and fostered international ratification of the Additional Protocol on Genetic Testing to the Oviedo Convention. Finally, we implemented Czech partners in the European Reference Networks (ERN) for rare diseases in the framework of the amendment of Act 372/2011 Coll. §113a). Currently, genetic testing is fully reimbursed by public health insurance and Czechia participates in 22/24 ERNs creating a multidisciplinary and integrated system for rare disease research, diagnostics and specialised medical care. We have also participated in several European Union projects aimed at rare disease research and diagnostics, such as RD-Connect.eu and Solve-RD.eu, and coordinate the national hub of Orphanet. Finally, we are working with our Norwegian partners within the frame of the EEA/Norway grants scheme which is aimed at the Roma minority that has specific population-specific recessive disorders.

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FAILURE TO THRIVE, ICHTHYOSIS, DEAFNESS, AND ENDOCRINOPATHIES IN AN INFANT WITH A NOVEL BIALLELIC AP1B1 MUTATION CAUSING ABNORMAL INTRACELLULAR ATP7A TRAFFICKING

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Introduction: Biallelic pathogenic variants in AP1B1, which encodes for the β subunit of the adaptor protein complex-1 (AP-1), were recently shown to cause an autosomal recessive keratitis-ichthyosis-deafness (KIDAR) syndrome, characterized by failure to thrive, developmental delays, sensorineural hearing loss, keratitis, erythroderma, and ichthyosis. This closely resembles MEDNIK syndrome, caused by mutations in the AP-1 σ subunit (encoded by AP1S1). AP-1 is an important complex of intracellular vesicle sorting responsible for bidirectional transport of clathrin-dependent vesicles between the trans-Golgi network and endosomes. Two of its well-recognized cargo molecules are the copper transporters ATP7A and ATP7B, associated with X-linked Menkes disease and autosomal recessive Wilson's disease, respectively.

Case study: We present an 8-month-old male infant of Palestinian descent who was born prematurely at 32 weeks to consanguineous parents (first-degree relatives) and was admitted for recurrent respiratory infections and vomiting. On physical examination, he presented with marked hypotonia, failure to thrive (Z score -5.2), bilateral profound sensorineural hearing loss, ichthyosis, sparse hair, and wrinkled skin. Laboratory findings included pancytopenia: leukocyte 2,500/mm3 (4,500-11,000), erythrocyte 1.90 million/mm3 (4.3-5.9), and platelet 54,000/mm3 (150,000 - 450,000). Further workup revealed persistent elevations in parathyroid hormone (PTH), in the range of 70.7-132 pg/ml (normal range 14.9-56.9), necessitating phosphorus supplementation (0.5-1mg/kg body weight). He also developed hypoglycemic episodes (27 mg/dL, normal range 70-100 mg/dL), with appropriately elevated cortisol and growth hormone levels and undetectable insulin levels at the time of each event, indicating a physiological response. In addition, elevations in thyroid stimulating hormone (TSH) were seen in the setting of elevated free thyroxine (T4). There was a steady increase in liver transaminases, alkaline phosphatase, and lactate dehydrogenase (LDH).

Results: Whole exome sequencing (WES) demonstrated two homozygous missense variants of uncertain significance (VUS), in AP1B1 (c.496delG, p.Leu166Trp*fsTer38). Urine copper was elevated at 432 microgram/gram creatinine (norm: 0-50), ceruloplasmin levels was 17-19.9 mg/dL (norm: 6-18) supporting abnormal copper metabolism. Immuno-histochemistry (IHC) showed that in the presence of 200μM copper, ATP7A in patient-derived fibroblasts remained in the trans-Golgi network, unlike the normal plasma membrane relocalization of ATP7A seen in control cells. IHC in HEK293T cell line overexpressing ATP7A showed a similar pattern when treated with siRNA against AP1B1, further demonstrating abnormal trafficking.

Conclusion: The triad of hearing loss, failure to thrive, and ichthyosis in infants should raise concerns for defects in the AP-1 complex. Defects in copper transport and other endocrine or metabolic abnormalities may be present concomitantly, reflecting interactions between AP-1 and various transmembrane proteins normally.

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DE NOVO 6Q16.3 MICRODELETION INVOLVING GRIK2: CASE REPORT AND CURRENT LITERATURE EVIDENCE

To date, different size of 6q16 deletions have been associated, with highly variable expressivity, to autism spectrum disorder (ASD), developmental delay, epilepsy, and hyperphagic obesity. We describe a 4 years-old girl, presenting with mild dysmorphic features, ASD, developmental delay, and absent speech, carrying two different chromosomal anomalies. The non-consanguineous couple reported an unremarkable family history, except for the first son of the maternal sister, affected by ASD. The proband was born at term, after an uneventful pregnancy conceived though in vitro fertilization procedure with intracytoplasmatic sperm injection technique. Motor and language delay and the presence of motor stereotypies (hand flapping) were noted at 15 months. Genomic DNA was extracted from peripheral blood of the proband and his unaffected parents and trio-based Single Nucleotide Polymorphism array (SNParray) analysis through CytoSNP-850K platform was performed. SNParray revealed a de novo 6q16.3 microdeletion (spanning approximately 2.8 Mb) occurred in the paternal chromosome. Standard karyotype analysis also detected a de novo insertion: ins(4;2)(q31.3;q23q31) confirmed by FISH whole-chromosome painting probes. Optical Genome Mapping (OGM) technology permitted to better define the chromosomal breakpoints and showed that the 2q22.3q24.3 segment was translocated into the long arm of chromosome 4 (4q28.3) resulting in an inverted insertion, apparently not inducing any gene disruption or chromosomic material loss. Hence, it may not have a primary causative role into the girl's clinical phenotype, although a gene position effect or regulatory anomalies consequences cannot be ruled-out. OGM also confirmed the microdeletion, apparently not structurally associated to the insertion. The 6q16.3 de novo microdeletion is more likely the cause of the neurodevelopmental phenotype and it is one of the smallest microdeletions reported to date. In detail, 6q16.3 region contains GRIK2 (OMIM*138244), a disease-causing gene, predicted as a dosage sensitive gene and described in knock out mice to cause ASD-related phenotypes. Heterozygous Single Nucleotide Variants have been recently associated with NEDLAS (Neurodevelopmental Disorder, Impaired Language and Ataxia and with or without Seizures OMIM #619580), and biallelic loss of function variants with Intellectual Developmental Disorder (OMIM #611092). In addition, the microdeletion also includes SIM1, a RefSeq gene, associated so far to obesity and nutrition disorders. 6q16.3 microdeletion could lead to the haploinsufficiency of GRIK2 and SIM1, possibly predisposing to epilepsy and obesity. Child's growth is currently regular and no abnormalities were evident on the last EEG. An appropriate multidisciplinary follow-up is ongoing, in order to prevent new clinical signs occurrence and to refine the genotype-phenotype correlation.

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CASE REPORT OF GALACTOSEMIA

Patient SB, a male newborn weighing 3100 gr at birth and born at 38 weeks of gestation to consanguineous parents, from a normal pregnancy and delivery. Neonatal period was without complications, started breastfeeding and was discharged on 4th day of life. At the age of 1.5 months the child was admitted to primary healthcare center due to poor feeding, sporadic vomiting, and mild jaundice. The weight gain from after birth was 550 grams. Milk insufficiency was considered, breastfeeding continued and standard formula was added to increase weight gain. The child was readmitted to the hospital after a month as symptoms worsened. Laboratory tests that were conducted at primary level health care facility showed following results: mild anemia, slightly increased total bilirubin level, and normal C reactive protein concentration. Cows milk protein allergy and mother milk jaundice were suspected. So mother was recommended to stop intake of diary products and standard infant formula was changed with partially hydrolyzed formula. At the age of 3.5 months, the baby was admitted to the hospital as his condition did not improve. At the admission infant was undernourished, weight was below -2 standard deviation on weight for age chart, abdomen was descended. Examination reveal developmental delay (infant was not able to fix and follow objects, hold the head, dis not have a social smile, but was reacting on noise), skin was icteric, liver was lightly enlarged. Eye examination revealed cataract. Abdominal ultrasound, routine lab tests, blood biochemistry analyses, infection markers were evaluated that showed mild increase of liver function tests. Based on clinical presentation Galactose level were investigated that was significantly increased - 1048 mg/l (normal range < 100 mg/l), Galactose1phosphate was elevated while GALT level was low (<5 mg/dl , normal range > 20 mg/dl). Genetic testing confirmed the diagnosis of Galactosemia. Following the introduction of a lactose-free formula, the biochemical indicators quickly and completely returned to normal, and the child's development improved. The case serves as a reminder of how crucial it is to consider metabolic diseases when making a differential diagnosis of a patient presenting with non specific symptoms. It would be advised to create short courses that focus on clinical symptoms and presentations when metabolic illnesses can be taken into account to improve early detection and management of these conditions.

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A CASE OF CONGENITAL CNS ANOMALY IN A PATIENT WITH TOMACULAR NEUROPATHY

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Purpose of the study: to evaluate the possibilities of neuroimaging for verification of concomitant congenital disorders of the central nervous system in individuals with hereditary neuropathy with a tendency to paralysis from compression (tomacular neropathy).

Materials and Methods: A review of Russian and foreign literature was carried out, which gives an idea of the typical symptom complex and rare phenotypic manifestations of the disease. A clinical case of tomacular neuropathy verified by molecular genetic methods (deletion of the PMP22, COX10, TEKT3 genes) with a family history (paternal grandfather) in a twenty-five-year-old man is considered. The first signs of the disease were observed during adolescence. Clinically significant disorders began to appear in the second decade of life. At the same time, there were complaints about the feeling of "rotation" in the lying position, discomfort when performing marching movements. On examination, in addition to the typical picture of flaccid paresis of the arm with impaired sensitivity by the type of hypesthesia along the ulnar and median nerves, there were showed the signs of dynamic ataxia, a slight decrease in vibration sensitivity and muscular-articular feeling on the contralateral lower limb. Detected atypical disorders led to the assumption of concomitant pathology of the central nervous system. An MRI study of the brain was performed on a 3 Tesla tomograph. On T1-weighted images of sagittal sections and T2 in axial sections, asymmetry of the hemispheres of the cerebellum and vermis was found due to atrophic changes on the right. Contrast-free angiography revealed no significant deformities, occlusions, or features of the arteries of the circle of Willis.

Results: Careful clinical history taking, assessment of complaints and objective status of a patient with hereditary tomacular neuropathy followed by neuroimaging revealed concomitant CNS congenital pathology in the form of cerebellar hemiatrophy and cerebellar vermis.

Conclusion: It is necessary to inform practitioners about concomitant congenital pathology of the CNS in patients with hereditary neuropathies and the possibility of diagnostic using magnetic resonance imaging.

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MUTATIONS IN THE PROMOTER AND DEEP-INTRON REGIONS OF HBB GENE ARE THE CAUSE OF 11% CASES OF BETA-THALASSEMIA IN RUSSIAN FEDERATION

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Background: Beta-thalassemia OMIM 613985 is a hereditary blood disorder in the beta chain of hemoglobin with autosomal dominant type of inheritance . The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. Variable phenotypes of betta thalassemia rang from severe to moderate anemia. Beta-thalassemia is caused by mutations HBB gene NM_000518.5. Diagnosis of thalassemia is based on hematologic and molecular genetic testing.

Methods: Molecular genetic diagnosis thalassemia betta was delivered by Sanger sequencing for 401 patients with phenotype of betta thalassemia.

Results: 89% of pathogenic variants have been identified in the first and second exons and in the first intron of gene HBB, all of them were previously described in HGMD database. 11% of pathogenic variants has been found in promoter region and in deep-introne region of the second introne. No pathogenic variants were found in 3`UTR region. Only two mutation were identified in the region of the third exon, one of them is new c.331_332insTG. Two mutations c.316-197C>T CS840010 and c316-106C>G CS820005 have been detected in 39 patients. Six different mutations in promoter region have been identified in 6 patients.

Conclusion: Usually, molecular genetic diagnostics includes the study of the coding sequence of a gene, including the regions of exon-intron connections, but mutations in promoter and deep-intronic regions may be the cause of disease in the significant percentage of patients.

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TARGETED PANELS AS THE FIRST STAGE IN THE LABORATORY DIAGNOSIS OF LEUKODYSTROPHIES

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Introduction. Leukodystrophies are genetically determined disorders that primarily affect the white matter of the central nervous system. Genetic mutations affecting the production and maintenance of myelin are the root cause of leukodystrophies. The age of manifestation or onset of leukodystrophy varies significantly depending on the specific type of the disease and the underlying genetic mutation. Symptoms of leukodystrophy also vary extensively depending on the specific type and severity of the condition. Common symptoms include developmental delay, loss of motor skills, vision and hearing problems, and cognitive decline. MRI (Magnetic Resonance Imaging) is a crucial diagnostic tool in the evaluation of leukodystrophies. NGS technologies have been the main diagnostic approach to the establishment of a genetic cause of leukodystrophies.

Methods. A comprehensive examination of 467 Russian patients from unrelated families aged from 1 month to 71 years with signs of leukodystrophies was carried out. The following methods were used: genealogical analysis, clinical examination, neurological examination, radiography, and targeted panel sequencing consisting of 59 genes responsible for the development of hereditary leukodystrophies.

Results. A total of 205 patients were diagnosed (44%). The average age of patients admitted for diagnosis was 12.5 years. Among the patients with the established diagnosis, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (DARS2) prevailed (17%). Metachromatic leukodystrophy (ARSA), Krabbe disease (GALC), and Alexander disease (GFAP) accounted for 14%, 9%, and 7%, respectively. Several rare forms of diseases that were not previously described at the molecular level in the Russian Federation have also been identified: leukodystrophy, hypomyelinating leukodystrophy type 2 (GJC2), combined SAP deficiency (PSAP), and leukoencephalopathy with vanishing white matter (EIF2B1).

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A SYSTEMATIC APPROACH FOR THOUSAND SEVERE UNSOLVED PEDIATRIC CONDITIONS: RESULTS FROM THE TELETHON UNDIAGNOSED DISEASE PROGRAM

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Many sporadic and serious childhood diseases remain undiagnosed despite extensive medical and genetic testing. Diagnosis is critical for prognosis, specific and timely treatment, family planning, and understanding the pathomechanisms of disease.

In Italy, the Telethon Foundation charity created the Telethon Undiagnosed Diseases Program (TUDP) to provide a systematic approach to improve the diagnostic yield and provide an overview of the underlying genetic mechanisms.

All applications (1,232) were submitted together with electronic phenotyping from approximately 60 clinical geneticists from 22 pediatric genetics and clinical centers or via an online platform. Procedures were standardized across centers through regular online meetings to achieve more accurate and reproducible phenotyping. Eligibility criteria were based on severity, complexity, and negative results of complete genetic analysis. Genetic testing was performed at least in trios, and the case reanalysis and matching process was repeated periodically for all still-negative cases. The TUDP has studied 1,063 families selected from 1,232 applications. 897 clinical genetic reports have been provided to date. A definitive diagnosis has been made in 50% of cases, with mutations identified in more than 200 different genes. In addition, about 10% of cases have suspect variants that are used in the matching process to find second cases. The general overview indicates that the vast majority (71%) of the causative variants were de novo, either with autosomal dominant (68%) or X-linked (3%) alleles. Recessive forms (either autosomal or X-linked) explained the remaining 29% of cases, with homozygous mutations identified in only 10% of cases. The high percentage of de novo mutations is similar to other undiagnosed programs in developed countries and may reflect the general postponement of parenthood. This confirms the need for parallel trio testing.

We conclude that a systematic approach can solve about 50% of missed diagnoses due to heterogeneity of genetic causes, while the remaining cases may be due to unique and therefore elusive mechanisms that require extended matching. The multicenter TUDP model is a cost-effective solution that should be transferred to clinical settings to avoid diagnostic delays or misdiagnosis in children.

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IN-SILICO PATHOGENICITY PREDICTOR CLASSIFICATION FOR UNCHARACTERIZED VUS IN RARE AND UNDIAGNOSED DISORDERS

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Genomic variant interpretation is a critical step in diagnostic short-read sequencing. A "supporting" evidence for pathogenicity (PP3) in the ACMG/AMP guideline is defined by the agreement of multiple lines of in-silico evidence assessments. Many in-silico pathogenicity predictors (ISPPs) have been developed in this context. However, as data accumulate in databases such as ClinVar, it has been observed that these ISPPs do not always provide accurate predictions for each gene. Therefore, choosing the ISPP would create a bias, and there should be a standard on which to use in diagnostics. Here, we present an approach that statistically compares the efficiency of 46 different ISPPs in the dbNSFP (v4.4a) dataset for missense variants by using variants reported to ClinVar to ensure correct gene-specific predictor matching, followed by calculating a metascore that assigns pathogenicity to each possible variation in the human genome.

ClinVar variants were chosen based on their clinical significance for reliable pathogenicity assessment when assigning the variants to 3 main groups: Benign (also including Likely benign and Benign/likely benign), Pathogenic (also including likely pathogenic and Pathogenic/Likely pathogenic, and Unknown (including only uncertain significance). Only dbNSFP (v4.4a) ranked scores (0-1) of ISPPs were used for the comparability via variance-based multiple and pairwise comparisons among defined variant groups. Then, ISPPs were listed according to their gene-based statistical significance in predicting a variant's pathogenicity.

Based on gene-specific significance, each gene was assigned a weight for each ISPP available in the analysis, integrating the statistical significance results from comparisons and performance of each ISPP on allocating Benign and Pathogenic variant groups. Essentially, each variation in the human genome was assigned a new score with its located gene's weight for each ISPP and ranked score for that ISPP, which we called the VAMPP-score (Variant Analysis using Multivariate Pathogenicity Predictor-score).

With the VAMPP-score, we propose to upgrade the ACMG/AMP PP3 criterion's strength level to moderate, which can lead to potential re-classification, a possible diagnosis, or vice versa, a downgrade when promoting a variant's benignity - with the potential use of ACMG-BP4 criteria for ISPP assessment. The statistical results are planned to be available soon as an open-access web platform that enables gene-specific ISPP analysis for users. Also, the VAMPP-score is planned to be available as a variant annotator for routine diagnostic variant interpretation for users.

David Pearce[1,2,3]

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THE INTERNATIONAL RARE DISEASE RESEARCH CONSORTIUM (IRDIRC): MAKING RARE DISEASE RESEARCH EFFORTS MORE EFFICIENT AND COLLABORATIVE, AROUND THE WORLD

The International Rare Disease Research Consortium, or IRDiRC, is a global consortium of key stakeholders from different facets of rare disease research that together seek to drive advances in diagnostics, therapeutics, and patient outcomes. The consortium facilitates a global and cross-disciplinary exchange of ideas to tackle key issues in rare diseases through the development of recommendations, data standards, tools, and guidelines that harmonizes research efforts and improves efficiency. While IRDiRC has made significant contributions to the development of new therapies and diagnostics since its founding in 2011, much work remains to alleviate the burden of rare diseases. The consortium has demonstrated its success in providing a global platform to advance rare disease research through collaborative efforts worldwide, continuing to identify and address barriers to health equity for all rare disease patients.

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JUVENILE RECURRENT DVT DUE TO RARE COMBINATION OF PROTEIN C (PC) DEFICIENCY AND FVL MUTATION

Introduction: Protein C deficiency is a rare autosomal dominant disorder with a characteristic of hypercoagulation state and recurrent venous thrombosis. Less attention was focused on PC deficiency so that misdiagnosis is very common. In patients with PC deficiency, starting treatment with oral anticoagulant drugs is associated with a transient hypercoagulable state and clinically overt thromboembolic complications before and even after reaching a full anticoagulant effect. PC deficiency has a morbidity of 0.02-0.5%, and is identified when the PC concentration or activity is below 60-70%. FVL has a high prevalence among symptomatic PC–deficient persons, individuals who are heterozygous for both conditions have a more than twofold risk of thrombosis, compared with family members with protein C deficiency alone.

Case report: 18-year-old male was admitted to our hospital with complaints of painful swelling of his right lower limb. 2 years earlier patient had first episode of DVT in left lower limb. He was a 16-year-old, when he first developed DVT. He received anticoagulants for 1 year and treatment was stopped 10 month prior to recurrent event. Vascular ultrasound confirmed deep venous thrombosis in right lower limb (right common femoral and iliac veins were affected), partial recanalization of left Popliteal, Femoral and Iliac veins. Family history was unremarkable. Both events of DVT were unprovoked. Genetic testing for inherited and acquired thrombophilia was done. According to clinical features, laboratory and image findings, patient was diagnosed as recurrent DVT caused by PC deficiency and heterozygous form of FVL mutation.

Anticoagulation treatment with UFH and Warfarin was started. The clinical manifestation was not relieved. On day 4, the painful swelling of right lower limb dramatically increased. Vascular ultrasound revealed thrombosis of right Popliteal, Femoral and Tibial veins. Warfarin and UFH were stopped and treatment continued with fresh frozen plasma and LMWH. Pain was managed with Opioids. Symptoms of right lower limb was remarkably reduced. He was kept on anticoagulation therapy with LMWH for successive 10 days, continued with NOAC till now. Patient is under physicians' constant observation and does not experience any recurrence.

Conclusions: Unprovoked VTE must be investigated for inherited Thrombophilia. Patients with recurrent DVT, FVL- Heterozygote gene mutations and Protein C deficiency requires anticoagulation therapy for the non-limited time. Our report suggests the importance of early recognition of protein C deficiency and thrombophilia gene mutations in youth with recurrent vascular thrombosis and personalized management should be emphasized.

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PERCC1-ASSOCIATED CONGENITAL ENTEROPATHY: DELINEATING THE NATURAL HISTORY OF A NEW DISORDER OF ENTEROENDOCRINE CELL FUNCTION

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Objective: Congenital diarrheas and enteropathies (CODEs) constitute a heterogeneous group of individually rare disorders, characterized by infantile-onset chronic diarrhea. Recently, biallelic deletions encompassing an unannotated open reading frame termed PERCC1 on chromosome 16, were identified as the cause of an autosomal recessive CODE among families of Iraqi-Jewish descent (previously termed Intractable Diarrhea of Infancy, IDIS). Disruption of PERCC1 was further shown to hamper the function of enteroendocrine cells (EECs) in organoids and in vivo models. We sought to elucidate the natural history of this newly-recognized disorder.

Methods: Clinical data was obtained directly from the patient and/or their parents, via a virtual semi-structured medical interview. When a direct interview was not possible, clinical data was collected by the physician caring for the patient, based on their medical records.

Results: An international cohort of n=11 patients was recruited for the study, 3 of whom were female, at an average age of 18.5 years (range, 2-37). Molecular diagnosis was reached at an average age of 14.8 years (range, 1.5m-36y). TPN was required in all patients, and was successfully weaned off in 9/11, at an average age of 8 years (range, 10m-20y). The PERCC1-related genotype underlying their disease varied between biallelic chromosomal deletions (6/11 patients; 54%); a recently identified stopgain mutation (c.390C>G) shared by unrelated patients of Irish descent (3/11 patients; 27%); a novel c.555C>G point mutation (1/11 patients; 9%); or maternal UPD of chromosome 16 encompassing PERCC1 harboring a novel c.348C>G truncating variant (1/11 patients; 9%).

Conclusions: PERCC1-associated congenital enteropathy is an ultra-rare, underdiagnosed disorder, typically manifesting at early infancy with persistent watery diarrhea and hypernatremic dehydration. Our findings expand the current knowledge regarding both the molecular basis and phenotypic spectrum of this disorder.

Shmuel Prints[1]

A FAMILY CASE OF SEVERE ASTHMA RESPONDED TO MEPOLIZUMAB. ISN'T THERE ANOTHER PATH FOR ENDOTYPE-SPECIFIC THERAPY?

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Introduction: The development of precision medicine indicates that many common diseases appear to be a collection of pathological conditions that differ in pathogenesis and genetics. One of them is bronchial asthma. The individualization of biological therapy for refractory asthma generates growing interest in the epigenetics of this disease.

Case description: A mother with severe steroid-dependent asthma was identified as T2 phenotype and successfully treated with mepolizumab. Her daughter developed severe asthma later. Because the offspring didn't have clear features of the T2 phenotype, she passed several futile trials of different biological medicines. Finally, the mepolizumab treatment led to a dramatic improvement in her disorder.

Conclusion: Current biomarkers do not permit consistent selection of the optimal therapy for an individual patient with severe asthma. The personal clinical-genetical case analysis, originally developed to identify undiagnosed diseases in pediatrics, can be approved in identifying new diseases hidden under the umbrellas of diagnostic blockbusters.

Ratna Dua Puri [1,2]

THE LANDSCAPE WITHIN THE INDIAN UNDIAGNOSED DISEASES PROGRAM: INSIGHTS & CHALLENGES

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The Indian Undiagnosed Diseases program was conceived on the background of the assessed burden of rare disorders in India. With a huge population of over a billion, the system of marriages including consanguinity and endogamy, it is estimated that that more than 56 million individuals are likely to be affected by rare disorders in India. Technological advances including chromosomal microarray, tests for metabolic disorders and exome sequencing are widely available and used in the larger academic centres and hospitals to reach a diagnosis. However, it is estimated that only up to 30% patients receive a diagnosis and at times, in a highly curated cohort, 50%.

Within this landscape, the Indian Undiagnosed Diseases Program (I-UDP) was conceived with the support of the Indian Council of Medical Research as a 3 years multicentric, multidisciplinary research program. Four centres, three clinical sites and one data analysis centre participate in the program. The aims of this program include identification and characterization of causal genetic events underlying unexplained familial syndromes by whole exome and /or genome sequencing, to build collaborative capacity for diagnosis and generate public resources that can be leveraged by the biomedical community to facilitate study in various aspects of rare disorders including pathogenesis and treatment. The idea was conceived and supported through the work of the undiagnosed diseases network international (UDNI).

The program has completed 2 years 7 months till date, 214 patients have been recruited till last analysis at the completion of 2 years. Of these, 142 underwent exome sequencing and 72 underwent genome sequencing. Sixty-nine patients have received a diagnosis to date. The patients recruited in this project have a wide spectrum of phenotypes ranging from neurological including developmental delay and intellectual disability, difficult to control seizures, microcephaly, severe failure to thrive, dysmorphism, multiple malformations, skeletal dysplasia, bone marrow failure syndromes and ophthalmological disorders.

We identified a significant diagnostic yield on reanalysis of existing genomic data that underscores the importance of detailed phenotype to interrogate the data. Enhancement of the inhouse pipeline to capture copy number variants (CNVs), synonymous variants and newly identified genes also contributed to the diagnostic yield. Genome sequencing identified large CNVs, intronic variants, variants in poorly covered exonic regions of the exome.

This program has enabled the recognition of the utility of multiple stakeholders working together towards the diagnostic odyssey of patients with rare disorders. Enhancement of skills, technological advances, cross border collaborations and working together within the UDNI has greatly contributed towards augmenting rare disease diagnosis.

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PHENYLALANINE TREATMENT IN 8-MONTH OLD GIRL WITH MITOCHONDRIAL FARS2 DEFICIENCY

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FARS2 is a nuclear gene encoding mitochondrial phenylalanine tRNA aminoacyl synthetase, responsible for ligating phenylalanine to mitochondrial tRNA. Biallelic mutations in FARS2 gene manifest with either, an early onset epileptic encephalopathy or later onset, spastic paraplegia, seizures and developmental delay. Phenylalanine treatment has already been described as an N1 trial in FARS2 affected 3 years old girl with favorable clinical impact (ref: PMID 36603837).

Here, we describe the clinical course of a 6-month old baby girl who was transferred to Sheba Medical Center, Israel with a clinical picture in keeping with developmental regression, encephalopathy, epilepsy and movement disorder.

Her past medical history includes, hospital admissions in a different medical center, at 3 month of age with encephalopathy and mastication movements treated acutely with benzodiazepines followed by maintenance treatment with Keppra. During admission an extensive work up had been done including metabolic work up, sepsis work-up, head imaging, ophthalmological exam, and urine toxicology which were all normal. Her second admission was at 5 month of age with encephalopathy, myoclonic jerks and hypsarrythmia on EEG. She was started on Vigabatrin and keppra. In view of refractory status epilepticus, she was transferred to the Pediatric ICU, where she was intubated and had loading of Vimpat, hydantoin and luminal with cessation of seizures. Brain CT, CSF analysis including lactate, brain MRI, sepsis and infectious work up were all normal. Plasma amino acids showed low serine levels and and low phenylalanine levels at 23nmol/l (ref:28-80) along with low/borderline phenylalanine levels in CSF. Plasma lactate was normal. She was extubated after a few days. Repeat EEG showed no epileptic activity. Exome testing had been done demonstrating compound heterozygosity for FARS2 gene.

She was transferred to Sheba medical center at 6 month of age with a clinical picture manifesting with encephalopathy, movement disorder involving her limbs and facial muscles and hypotonia. Repeat MRI/MRS showed brain atrophy and lactate peak. She continued therapy with keppra, phenobarbital with an addition of Clonazepam without resolution of her myoclonic jerks. Phenylalanine treatment was started with gradual elevation of the dose up to a target dose of 3 times DRI, followed by the addition of Perampanel with gradual cessation of her myoclonic jerks.

In conclusion, we describe the clinical course of FARS2 affected 6-month old girl with a clinical picture dominating with movement disorder and encephalopathy treated with a combination of antiepileptic treatment and high dose L- phenylalanine.

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THE CASE OF RUBINSTEIN-TAYBI SYNDROME - HUNTING FOR HIDDEN MUTATION

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Rubinstein-Taybi Syndrome (RSTS) is a rare Mendelian disorder of the epigenetic machinery (MDEM), typically caused by mutations in the CREBBP or EP300 genes, which are transcriptional co-factors that play an essential role in regulating gene expression through chromatin modification. RSTS is characterized by neurodevelopmental delay, various congenital malformations and distinctive facial features, making it a clinically recognizable syndromic condition.

We describe an 11-year-old male with clinical features consistent with RSTS. He was born from non-consanguineous parents. At birth he presented with lacrimal duct obstruction, bilateral cryptorchidism, micrognathia and feeding difficulties. Dysmorphic features include downslanting palpebral fissures, arched eyebrows with synophrys, long eyelashes, epicanthus, a prominent and beaked nose, malformed ears, long philtrum, thin upper lip, protruding lower lip, high palate, low anterior and posterior hairline, and grimacing face typical for RSTS. He also has high myopia, hyperextensible joints, hirsutism, prolapse of anterior mitral valve and minor hypertension of the pulmonary artery stem. The boy has moderate neurodevelopmental delay, learning difficulties at school, mild behavioral abnormalities including attention deficit and hyperactivity disorder. He has a friendly and curious character.

Extensive genetic investigations were performed, including karyotype (2014), array CGH (2015), CREBBP and EP300 MLPA (2016), whole genome sequencing trio (2020), gene panel for skeletal dysplasias (2022), long-read exome (2023) — all yielding negative results. Finally, genome-wide DNA methylation analysis EpiSign was performed (2023), which includes 60 conditions (43 genes and 10 chromosomal regions), involved in the regulation of epigenetic machinery. The episignature was consistent with RSTS type 1.

Current case illustrates the importance of methylation studies in patients, whose clinical phenotype is consistent with MDEMs but DNA sequence-based investigations are negative. We speculate that the mutation disrupting CREBBP gene may be located in the non-coding region (promoter or deep intronic region) or there may be a structural variant (SV) or mobile genetic element (ALU or LINE sequence), detection of which are within the limitations of the standard NGS-based technologies. Furthermore, we plan to perform optical genome mapping (OGM) with an attempt to find the hidden mutation.

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EPIGENETICS IN RARE DISEASES: THE ROLE IN CYSTIC FIBROSIS

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Introduction: Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disorder in the Caucasian population with an incidence of about 1:3,000 live births. Chronic airway dysfunction and inflammation are the main causes of morbidity and mortality of CF patients. The variability of clinical manifestations of Cystic Fibrosis even among individuals with the same genotype suggest not only the diversity of mutations in the CFTR gene but that other genetic and environmental factors influence the gene. Aberrant immune responses in Cystic Fibrosis might be explained by abnormal DNA methylation at specific genes that are involved in the chronic inflammation process. The aim of the study was to identify the global DNA methylation levels and the methylation status of the promoters of inflammatory and anti- inflammatory cytokines (IL-8, TNFα, IL-10) in T lymphocytes from CF patients.

Materials and Methods: The study was approved by the ethics committee of Tbilisi State Medical University. Patients were selected according to the CFTR mutations: homozygous for p.F508del or p.Tyr515fs and compound heterozygous for p.F508del/p.Tyr515fs. CD4+ T cells were isolated from CF patients (n=16) and control subjects (n=16) using EasySep™ Direct Human CD4+ T Cell Isolation Kit (Stem Cell Technologies, US). Global DNA Methylation was performed using Combined Bisulfite Restriction Analysis - Polymerase Chain Reaction (COBRA-PCR) of LINE and Alu interspersed repetitive elements (IRE). DNA methylation analysis of cytokine promoters was performed by the methylation-specific polymerase chain reaction. DNA fragments were amplified using specific primers for methylated and unmethylated DNA.

Results: IRE methylation analysis revealed significant hypomethylation of CpG islands in LINE, but not in Alu elements compared to healthy controls in CD4+ T cells. In addition, we found that methylation of IL-8 and TNFα gene promoter regions were significantly hypomethylated, whereas CpG sites of IL-10 gene promoter were hypermethylated in cystic fibrosis patients compared to control individuals.

Conclusions: Identification of disease-modifying epigenetic marks and their association with Cystic Fibrosis may help to find new therapeutic solutions and personalized approaches in the treatment of patients with CF.

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CHANGES IN THE COURSE OF FANCONI ANEMIA AFTER COVID-19 INFECTION

Introduction: Fanconi anemia (FA) is one of the four most frequent among inherited bone marrow failure syndromes. It is a chromosomal instability disorder caused by germline mutations in the DNA repair genes of the FA/BRCA pathway. Proteins encoded by FA genes play important roles in numerous cellular functions, including DNA repair, detoxification of reactive oxygen species and aldehydes, energy metabolism, and both proinflammatory and myelosuppressive cytokine homeostasis. Patients with FA usually develop variable degrees of pancytopenia in childhood and often have specific clinical phenotype. FA is usually diagnosed in childhood, then followed by pediatric and adult hematologists. Covid-19 infection can manifest with a profound inflammatory response, which may cause severe immune damage to the lungs. Coronaviruses are also able to infect bone marrow cells, that is why SARS-CoV2 infection can cause several hematological abnormalities including neutrophilia, lymphopenia, and thrombocytopenia. We report a case of patient with FA after Covid-19 infection.

Case report: A patient was diagnosed with FA at childhood. He manifested with severe anemia and thrombocytopenia, had short stature, low birth weight, microcephaly, micrognathia, and café-au-lait spots. The diagnose was confirmed by increased chromosome breakage in clastogenic assay. The patient started observation in our clinic in April 2019 at the age of 19 y.o. His median hemoglobin level was 68±5 g/L, thrombocyte amount - 30±4x109/L. The patient was transfusion-dependent and required three procedures of red blood cell transfusion monthly. In November 2021 he was diagnosed with moderate Covid-19 infection with polysegmental pneumonia and sinusitis. The patient underwent treatment with Remdesivir in combination with antibiotics. After recovery, his common blood count underwent changes. Since this time till now his hemoglobin level is higher than 100 g/L, thrombocytes are above 85x109/L. From this moment the patient attends clinic to receive hemotransfusion only once every 6 months.

Conclusion: FA as a representative of inherited bone marrow failure syndromes manifests as ineffective and stressed hematopoiesis. The effect of another stress pathogen on stem cells could be unpredictable.

Ahmed Waqas

UNRAVELING A NOVEL HOMOZYGOUS TRUNCATING VARIANT IN PPFIBP1: EXPANDING THE SPECTRUM OF PPFIBP1-ASSOCIATED NEURODEVELOPMENTAL DISORDERS

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Neurodevelopmental disorders (NDDs) are classified as a group of disorders affecting function and development of the brain and having wide clinical variability. Herein, we describe two affected individuals segregating a recessive NDD. The affected individuals exhibited phenotypes such as global developmental delay (GDD), intellectual disability (ID), microcephaly and speech delay. Whole-exome sequencing (WES) followed by bidirectional Sanger sequencing techniques identified a homozygous nonsense variant (c.466C > T; p.Gln156*) in the PPFIBP1 gene (NM_003622.4) that segregated with the disease phenotype. Further, to elucidate the effect of the variant on protein structure, 3D protein modelling was performed for the mutant and normal protein that suggested substantial reduction of the mutant protein. Our data support the evidence that PPFIBP1 has a pivotal role in neurodevelopment in humans, and loss-of-function variants cause clinically variable neurodevelopmental phenotypes.

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CALYPSO AND IOBIO TOOLS IN THE UDN

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Abstract: Patients presenting with complex phenotypes represent some of the most challenging diagnostic cases. Evolving phenotypes, bioinformatic and biological resources demand these cases are regularly monitored to provide a diagnosis at the earliest opportunity. Further, diagnosis requires the combined expertise of large teams comprising treating physicians, genetic counselors, medical geneticists, diagnostic pathologists, bioinformaticians and variant analysts that bring together the patient's family history and clinical presentation; etiology of genetic disease; computational analysis; and variant interpretation to expertly adjudicate the role of candidate variants. Existing software tools typically cater to those with computational expertise and can exclude other critical team members from contributing their full expertise to the diagnostic process.

The University of Utah and Frameshift Labs are collaborating to develop Calypso: a comprehensive software platform to support diagnostic teams in a collaborative web-based environment. Combining a computational backend for analysis tasks; an easy-to-use web-based front-end integrating popular iobio tools; and a communication interface, Calypso will help team-based, longitudinal genome diagnostics become a reality.

Longitudinal analysis will include variant re-analysis and re-annotation pipelines that ensure changes in a patient's phenotypes, or underlying genetic knowledge (e.g. updates to ClinVar) are made available to the diagnostic team as early as possible.

Cohort dashboards allow case information in large projects (e.g the UDN) to be visually interrogated, and variants present in any cases in the cohort to be interrogated.

Case dashboards provide at-a-glance summaries of patient cases, including a visual timeline of a patient case and notifications of outstanding actions. This will include lists of required tasks including reviewing variants that have been flagged by the re-analysis / re-annotation pipelines.

Integrated analysis tools include the popular iobio web-apps, IGV, and a tool to identify phenotypically "similar" patients in the cohort will help all team members leverage all case and cohort data to reach diagnosis for every patient. The bam.iobio tool provides a quick visual assessment of the data quality of a BAM or CRAM file. The gene.iobio tool provides a visual review of variants in dynamically provided lists of genes. Genepanel.iobio allows users to generate lists of genes based on a set of HPO terms, or a clinical note. The University of Utah is additionally building an app for working with RNA-sequencing data.

Calypso is a part of the UDN Phase 3 and aims to provide a network level platform to support a high level of collaboration across sites.

Shinya Yamamoto[1]

FUNCTIONAL STUDIES USING DROSOPHILA SUPPORT CLINICAL DIAGNOSIS AND PHENOTYPIC EXPANSION: BMPR2 IN NEURODEVELOPMENTAL DISORDERS

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Undiagnosed diseases continue to present significant challenges to clinicians, patients, and society. In recent years, the use of model organisms such as the fruit fly Drosophila melanogaster has emerged as a promising approach to gain insights into the underlying genetic and molecular mechanisms of these disorders. Several years ago, we established the Center for Precision Medicine Models (CPMM) in collaboration with clinicians, bioinformaticians, fly, mouse and primate researchers at Baylor College of Medicine to support rare disease diagnosis and research. Here, we provide an overview of this collaborative initiative and present a case from the CPMM. Four individuals with neurodevelopmental symptoms who carry the identical de novo or inherited variant of unknown significance in BMPR2, a gene that have been linked to pulmonary arterial hypertension, were identified by clinicians at Columbia University. We found this variant to behave as a gain-of-function allele using in vivo overexpression experiments in Drosophila. Currently, additional experiments in flies are ongoing to characterize the functional consequences of active BMP signaling in the brain of this model organism and exploring therapeutic pathways. CPMM welcomes submissions from anyone with clinically relevant questions that can be answered using Drosophila or mice (https://bcm.edu/cpmm).

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RAPID WHOLE GENOME SEQUENCING FOR CRITICALLY ILL PEDIATRIC PATIENTS IN TURKEY: AN INAUGURAL PILOT STUDY

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Background: Rare genetic conditions, frequently suspected but often unidentified during intensive care admissions, are major contributors to pediatric mortality and morbidity. While rapid genomic testing in critical care has been adopted globally, this pilot study represents the inaugural effort to evaluate the feasibility and utility of rWGS within the Turkish healthcare context.

Methods: In this pioneering effort, we conducted a prospective trio rapid whole genome sequencing (rWGS) on families with infants (under one year) in an intensive care unit with undiagnosed illnesses at a single Turkish hospital. A multidisciplinary team, consisting of primary care providers, specialists, and bioinformatics experts, was assembled. An in-house pipeline was tailored to focus on phenotype-driven variants in recognized disease-causing genes.

Results: Of the 10 infants subjected to Trio WGS, 3 (30%) received a definitive diagnosis. We identified mutations in the IDH3A, SCO1, and FBN1 genes. rWGS concluded the diagnostic journey for 6 (60%) patients and directly influenced the clinical care of 5 (50%). The average turnaround from sample collection to report was 169 hours (range: 124-240 hours).

Conclusion: WGS emerges as a promising diagnostic tool for critically ill children, crucial for both diagnosis and clinical decision-making. This inaugural study underscores the potential and feasibility of rapid genomics in Turkey, achieved through a collaborative approach. However, its broader integration into the national healthcare system warrants further exploration.

13.5
CME Credits