14th UDNI Conference

Undiagnosed Diseases Network International

October 28-31, 2025
Rio de Janeiro, Brazil

INFORMATION
PROGRAM
ABSTRACTS

Genetics for All Institute

UDNI Undiagnosed Diseases Network INTERNATIONAL

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We appreciate the assistance of the United States National Institutes of Health and of the Wilhelm Foundation in preparing for this conference.

Welcome Address

Dear UDNI 2025 Delegate,

The Undiagnosed Diseases Network International (UDNI), a collaborative initiative that spans multiple countries, was established in 2014. Its primary mission is to improve diagnostic rates for individuals living with undiagnosed conditions. The UDNI brings together clinical and research centers renowned for their expertise in rare diseases. This global network fosters interdisciplinary collaboration, facilitates knowledge sharing, and accelerates the translation of research into clinical practice to improve patient care. Since its inception, the UDNI has already organized 13 successful conferences, serving as a platform for sharing breakthroughs and fostering collaboration.

The 14th UDNI Conference was organized over the last year by a vibrant group of people who worked hard to make this meeting a success. The program, designed by a Scientific Committee with support from a broad group of International Advisors, includes 37 keynote presentations and 12 free communications (selected from over 100 submitted abstracts) spread over 13 sessions. It involves over 60 faculty members with broad global representation. In addition to attending the plenary sessions, delegates are strongly encouraged to explore the poster and commercial exhibitions.

Topics in the program include how Undiagnosed Disease Programs (UDPs) and Hackathons are being organized around the world, discussions of technical innovations and pioneer policy approaches, and the promotion of education in the field. The program will also cover the establishment of genomic standards and population genomics, as well as the necessary translational jump from diagnosis to therapy.

For the first time, the UDNI Conference will take place in the Southern Hemisphere, hosted in Barra da Tijuca, a dynamic and safe neighborhood in Rio de Janeiro, Brazil. This vibrant area is known for its stunning beaches, modern amenities, and welcoming atmosphere, making it an ideal setting for the conference. Rio de Janeiro, Brazil's former capital, is internationally celebrated for its breathtaking natural beauty, iconic landmarks, and rich cultural heritage.

Welcome to Rio de Janeiro and to the 14th Conference of the Undiagnosed Disease Network International!

Roberto Giugliani, on behalf of the Organizing and Scientific Committees

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About the 14th UDNI Conference

CONFERENCE DETAILS

Reception Desk Hours:

- **October 28:** 16:00 - 18:00
- **October 29:** 07:00 - 18:00
- **October 30:** 07:00 - 18:00
- **October 31:** The reception desk will be closed, but hostesses will be on-site to assist participants.

Badges: Please wear your conference badge at all times while attending the 14th UDNI Conference.

Internet: Our **Wi-Fi** network is sponsored by Sanofi.

- **Network:** SANOFI
- **Password:** rarediseases

Recharge Area: A designated space for charging your electronic devices is sponsored by MAIS GENE.

Mobile Phones: We kindly request that you turn off or silence your mobile phone during all sessions.

Certificates: Certificates of attendance will be available online after the conference.

Exhibition Area: The exhibition area will feature five booths from our sponsors: **AstraZeneca, Azafaros, Centogene, Sanofi,** and **Genetics for All Institute/Casa dos Raros.**

Coffee Breaks: Coffee breaks will be served in the commercial exhibition area.

Catering Services: The hotel has a restaurant on the ground floor and a bar on the terrace.

Restaurant Hours:

- **Lunch:** 12:00 - 16:00 / **Dinner:** 19:00 - 22:30

OPTIONAL ACTIVITIES

Welcome Cocktail
Date: October 28 **Time:** 19:00
Venue: Aimoré Room, Second Floor, Hotel Windsor Marapendi
Note: This is an optional activity requiring specific pre-registration. If you are not registered, please check for ticket availability at the Reception Desk.

Networking Evening
Date: October 30 **Time:** 20:00 - 22:00
Venue: Rio Scenarium
Address: Rua do Lavradio, 20, Centro, Rio de Janeiro
English: 20, Lavradio Str., Downtown, Rio de Janeiro
Transportation: Buses will depart from the Hotel Windsor Marapendi at 19:30.
Note: This is an optional activity requiring specific pre-registration. If you are not registered, please check for ticket availability at the Reception Desk.

SCIENTIFIC PROGRAM

Media Desk: All speakers, including platform presenters of abstracts, must upload their presentations at the media desk at least two hours before their scheduled session.

- **Operating Hours:**
  - **October 28:** 16:00 - 18:00
  - **October 29:** 7:00 - 18:00
  - **October 30:** 7:00 - 18:00

Questions: Due to the tight schedule, questions for presenters will preferably be submitted via a WhatsApp number, which will be informed during the conferece.

Poster Exhibition: 100 abstracts were selected for poster presentation. The poster exhibition is organized by topics. You can find the topics' list and an author index in the conference program (pages 28-64). Posters can be mounted on October 28 from 16:00 to 18:00 and on October 29 from 7:00.

SPONSORED SATELLITE SYMPOSIA

October 29 | 12:15 - 12:45 | Sponsored by Ultragenyx

Topic: From Genetic Variant to Clinical Manifestation: How Genotype Drives Phenotype and Guides the Diagnosis of an Intriguing Case

Speaker: ***Dr. Carolina Fischinger*** (Porto Alegre, Brazil)

October 29 | 12:45 - 13:15 | Sponsored by Centogene

Topic: Overcoming Challenges in the Diagnosis of Rare Genetic Disorders

Speaker: ***Dr. Carlos Leprevost*** (Curitiba, Brazil)

October 30 | 12:15 - 13:15 | Sponsored by AstraZeneca

Topic: From Signs and Symptoms to the Diagnosis of Hypophosphatasia – How can the diagnostic process be performed earlier? What could a low alkaline phosphatase result indicate?

Speaker: ***Dr. Têmis Maria Félix*** (Porto Alegre, Brazil)

Committees

LOCAL ORGANIZING COMMITTEE (Brazil)

Roberto Giugliani (Chair)
Dafne Horovitz
Fabrizio Gomes Barbosa
Filippo Pinto e Vairo
Gloria Souza
Izabel Marques de Souza
Vicky Simon

LOCAL SCIENTIFIC COMMITTEE (Brazil)

Roberto Giugliani (Chair)
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Thereza Cavalcanti

UDNI INTERNATIONAL BOARD

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William Gahl (USA) – Chair

PARTNERS AND VENDORS

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PARTNER SOCIETIES AND ORGANIZATIONS

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Estudo Colaborativo Latinoamericano de Malformaciones Congênitas
European Reference Network for Rare or Low Prevalence Complex Diseases
Genetics for All Institute
Iberoamericana Academy of Pediatric Neurology
Sociedade Brasileira de Genética Médica e Genômica
Sociedade Brasileira de Triagem Neonatal Erros Inatos do Metabolismo
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Emil D. Kakkis, M.D., Ph.D.Chief Executive Officer and President

We have an inclusive culture of value and respect.

Ultragenyx brings novel products to those living with rare and ultrarare diseases with a focus on debilitating genetic diseases. Founded in 2010, we have rapidly built a diverse portfolio of approved therapies and products aimed at diseases with a high unmet medical

need for which many have no approved therapies. It takes courage, care, talent, and dedication to make a meaningful impact for those living with rare diseases, their families and the rare disease community.

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For more information: **centogene.com**

Azafaros is developing nizubaglustat, an oral asset to target rare neurometabolic diseases. Its Phase 3 (NAVIGATE) study (which began recruiting in July) will evaluate the efficacy of nizubaglustat in GM1 and GM2 Gangliosidosis, and Niemann-Pick type C (NPC).

Gangliosidosis GM1 and GM2, and NPC are rare diseases. Delayed diagnosis is common as they can be undiagnosed or misdiagnosed due to the heterogeneity of their symptoms.

General Information and Venue

LANGUAGE

The official language of the conference is English, and translation services will not be provided.

While Portuguese is the language spoken in Brazil, some people may understand English, and many understand Spanish.

WEATHER AND CLOTHING

The average temperature in Rio de Janeiro in October is between 21°C (69,8°F) and 27°C (80,6°F). The average precipitation in October is 88 mm. Rio is a very informal city; however, the recommended dress code for the conference is **casual or business casual**. The conference rooms may be cool due to air conditioning, so you may want to bring a light jacket.

GETTING AROUND

Rio has a large fleet of yellow taxis, most of which are air-conditioned. The fare is displayed on the taximeter. Please be aware that most taxis only accept cash. At airports and major shopping centers, you can pay a fixed fare in advance at a taxi company desk.

An easy-to-use metro service is available from Jardim Oceanico station in Barra da Tijuca, located 1.5 km from the Convention Center. This line connects to Ipanema (15 min), Copacabana (20 min), and downtown Rio (35 min). Uber is also a reliable transportation option in Brazil.

MONEY AND EXCHANGE

The local currency is the **Brazilian Real (BRL)**. You can exchange foreign currency at major hotels or withdraw cash from ATMs (an ATM is available at the Windsor Barra Hotel). Credit cards are widely accepted at hotels, restaurants, and shops, but most taxis operate on a cash-only basis.

AUDITORIUM

Auditorium, as seen on the floor plan on page 20, is the main room of the event.

GENERAL INFOMATION

- **Telephone:** The country code for Brazil is +55, and the area code for Rio de Janeiro is 21. To make an international call, dial 00 or + before the country code.
- **Electricity:** The standard voltage in Rio is 110V. However, the Hotel Windsor Marapendi operates on 220V. Travel adapters may be necessary. The standard sockets in Brazil are Type N, but Type C plugs can often be used without an adapter.
- **Gratuities:** A service charge is usually included on hotel bills. A 10% tip is optional for restaurant service. Taxi drivers don't typically expect a tip, but it's common to round up the fare if you're satisfied with the service.
- **Business Hours:** Most offices are open from 9 a.m. to 6 p.m., Monday to Friday. Banks are open from 10 a.m. to 4 p.m., Monday to Friday.
- **Safety:** Barra da Tijuca is a relatively safe area, but always take standard big-city precautions. We recommend leaving passports and other valuables in your hotel, watching your belongings, and avoiding the display of expensive jewelry. For personalized recommendations on destinations and routes, please consult the UDNI staff at the registration desk.
- **Congress Venue:** The conference will be held at the **Windsor Marapendi Hotel**, located at Av. Lúcio Costa, 5400, Barra da Tijuca, Rio de Janeiro - RJ, 22630-012, Brazil. The hotel's phone number is +55 (21) 2195-9900.

About Rio de Janeiro

Undiagnosed Diseases Network International | UDNI 2025 | 14th UDNI Conference Oct 28-31, 2025 Rio de Janeiro, Brazil

Population: 6.211.223

Rio de Janeiro is the capital of the state of Rio de Janeiro, in the Southeastern region of Brazil. Those born in the state are mentioned as “Fluminenses”, while those born in the city are called “Cariocas”. Rio de Janeiro, the cradle of Brazilian history, is a cultural and touristic icon. With its natural and cultural exuberance, it stands out as a global hub. The city hosted the 2014 FIFA World Cup, the 2016 Olympic Games and the 2024 G20 Leaders' Summit.

The city of Rio de Janeiro is known worldwide as the “Marvelous City”. Rio transcends its stunning geography to reveal a rich history, dynamic economy, vibrant culture, unique cuisine and great importance for tourism.

Founded by the Portuguese in 1565, the city was the stage for key moments in Brazilian history, from the Colonial Period to the Proclamation of the Republic. The people of Rio are the result of the miscegenation of native, European and African components. This fusion of races and cultures has shaped the identity that defines the capital.

Carioca culture is a mixture of rhythms, colors and celebrations. From samba to funk, including the samba school parade on Carnival, the city breathes music and dance. Street art, expressed in murals and graffiti, is a form of authenticity that colors the metropolis.

Rio de Janeiro attracts visitors from all over the world. Its iconic beaches, such as Copacabana and Ipanema, are postcard settings.

Main tourist attractions

- Cristo Redentor - Christ the Redeemer
- Pão de Açúcar - Sugarloaf Mountain
- Copacabana and Ipanema beaches
- Botanical Garden
- Maracanã
- Selarón Staircase
- Rodrigo de Freitas Lagoon
- Museu de Arte Moderna (Museum of Modern Art)
- Lage Park

Cristo Redentor (Christ the Redeemer) is located at the top of Corcovado Hill, 709 meters above sea level, overlooking a considerable part of Rio de Janeiro. Made of reinforced concrete and soapstone, the statue is 30 meters high and is one of the symbols of Rio and Brazil. Photo: Lucíola Villela/MTur.

Faculty Members

Alessandra FERLINI
Ferrara, Italy

Alessandra Ferlini, born in Bologna, is a medical geneticists and neurologist, professor in medical genetics, and head of the Medical Genetics Unit at the University Hospital of Ferrara (Italy). She is also Honorary visiting professor at the University College London from 2015. She achieved her PhD in London (1995-1999) at the Imperial College of Medicine and she was back to Italy in 2000 and started her activity as medical geneticists in Ferrara as Unit Director. She coordinated/participated to 12 EU research grants and several Italian Grants (Telethon), she was/is Chair of several Working Groups related to Medical Genetics and Rare Diseases, including ESHG, IRDiRC, ERNs, EMQN, ENMC. She was PI in clinical trials for muscular dystrophy based on RNA therapies. Her research is focused on innovative genetic diagnosis and gene discovery, omics sciences, RNA profiling in rare diseases, and novel therapeutic strategies in muscular dystrophies. She is Chair of the Genetic task across EU ERNs and coordinates the EU-IMI project Screen4care focus on genomic newborn screening and digital health..

Alexandra HEUMBER
Geneva, Switzerland

Alexandra Heumber Perry is the Chief Executive Officer of Rare Diseases International, the global alliance of Persons Living with a Rare Disease. She has dedicated her entire career to improving healthcare policies to benefit people living with diseases, with a particular focus on neglected and vulnerable people. She has over 20 years experience in global health with demonstrated capabilities in patient advocacy and multi-stakeholder partnership. As CEO of RDI, Alexandra sets the strategic direction, drives the organizations goals of raising awareness of rare diseases, improving access to diagnostics, treatments and care, advocating for the rights of patients around the world and representing its members and enhancing their capacities to ultimately improve lives of Persons Living with a Rare Disease.

Andreas LANER
Munich, Germany

I am a molecular biologist by training and have been active in cancer genetics and variant interpretation for more than 20 years; my research interests include hereditary cancer syndromes (especially Lynch/HNPCC syndrome, other hereditary colorectal cancer syndromes and HBOC). My position as Head of Genomics Program at MGZ includes supervision of the complete variant classification, interpretation and curation process in our routine diagnostic lab as well as data sharing, data curationand knowledge transfer initiatives. Active member and biocurator of the InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP for colorectal cancer genes and lead of the HUGO Education Committee subgroup - Variant Interpretation and Genome Databases.

Anna Laura ROSS
Geneva, Switzerland

Anna Laura Ross PhD is the Head of Emerging Technologies, Research Prioritization and Support, in the Research for Health department of the World Health Organization Science Division. In this role, Anna Laura oversees activities related to the use of new and emerging technologies to maximize the benefits for global health, and anticipate and mitigate biorisks. Anna Laura also leads activities to facilitate, support and optimize steps in research and development for health products.

Annick REIN
Ramat Gan, Israel

Annick Rein-Rothschild is a pediatrician-medical geneticist specializing in the care of children with rare diseases. With an M.D. degree from Paris-Sud Faculty of Medicine, she has been instrumental in advancing both clinical and academic research in Israel since 1983. She was the Director of the first Israeli Institute for Rare Diseases at the Sheba Medical Center, and serves as an Associate Professor at The Gray Faculty of Medical & Health Sciences at Tel-Aviv University.

Antoine DAHER
Sao Paulo, Brazil

Businessman, with a degree in Political Sciences, Antoine Daher is the founder and president of Casa Hunter. Since 2019, he has also been president of Febrararas (Brazilian Federation of Rare Disease Associations), an organization with over 90 members spread across all regions of Brazil. He is also a co-founder of Casa dos Raros and, since 2015, has been a member of the Technical Chamber for Rare Diseases of the Federal Council of Medicine in Brazil.

Béla MELEGH
Pecs, Hungary

Béla Melegh, MD, PhD, DSc, is professor of medical genetics at the Department of Medical Genetics, University of Pecs, Hungary, involved in training in 7 faculties,former vice-dean of the Faculty of Medicine. Former board member of ESHG, chairof the BMG EBMG, president of Clinical Genetics in UEMS, and EU Exam in Medical Genetics was launched. Charter member of the UDNI; chairs the Education Committee. He co-authored over 380 peer-reviewed research articles.

Faculty Members

Bibiana OLIVEIRA

Porto Alegre, Brazil

Bibiana Mello de Oliveira is a clinical geneticist with a residency in Medical Genetics from the Hospital de Clínicas de Porto Alegre (HCPA). She holds a Master's degree in Genetics Applied to Medicine and a PhD in Genetics and Molecular Biology from the Federal University of Rio Grande do Sul (UFRGS). Currently, she works as a professor of Clinical genetics at the Federal University of Health Sciences of Porto Alegre (UFCSPA) and conducts research within the Brazilian Rare Diseases Network.

Cesar Augustin CRESPI

La Plata, Argentina

Dr. César Agustín Crespi: Médico Especialista Consultor en Clínica Médica y Hepatología. Docente a cargo de la Asignatura ¨Enfermedades Poco Frecuentes en Medicina¨ - Facultad de Ciencias Médicas - UNLP. Ex - Referente del Programa Provincial de EERR - Ministerio de Salud de la provincia de Buenos Aires. Jefe del Centro de Referencia Clínica en Enfermedades Raras y de Dificultoso Diagnóstico (CERyD) - HIEA y C San Juan de Dios - 27 y 70 - La Plata - Buenos Aires - Argentina. Miembro de la Red Iberoamericana de Salud en Enfermedades Raras -RIBERSER. Miembro de Undiagnosed Diseases Network International (UDNI)

Bruce KORF

Geneva, Switzerland

Dr. Korf is Distinguished Professor Emeritus of Genetics at University of Alabama at Birmingham. His research interests are genomic medicine and the natural history, genetics, and treatment of neurofibromatosis. He served as principal investigator of the Department of Defense funded Neurofibromatosis Clinical Trials Consortium, and as co-PI of the Alabama Genomic Health Initiative. He is co-editor Emery and Rimoin's Principles and Practice of Medical Genetics, and editor-in-chief of the American Journal of Human Genetics.

Claudia GONZAGA-JAUREGUI

Mexico City, Mexico

Claudia Gonzaga-Jauregui is a Mexican human genetics and genomics researcher at the International Laboratory for Human Genome Research of UNAM in Mexico. Her research focuses on the investigation of the molecular genetic causes of rare diseases and the identification of medically relevant variation for precision health implementation, especially in underrepresented populations. Claudia is an advocate for equitable access to genomic sequencing to improve health globally.

Carolina FISCHINGER

Porto Alegre, Brazil

Carolina Fischinger, MD, PhD, is a medical geneticist with a large experience on diagnosis and management of rare genetic diseases. She currently is the Head of the Clinical Research Center or Hospital de Clínicas de Porto Alegre, the Medical Director of Casa dos Raros and the President of the Brazilian Society of Inborn Errors of Metabolism and Neonatal Screening.

Dafne HOROVITZ

Rio de Janeiro, Brazil

Dr. Horovitz, MD, PhD, is a clinical geneticist at the National Institute of Women, Children and Adolescent Health Fernandes Figueira / Fiocruz in Rio de Janeiro, Brazil. Her work involves general medical genetics, genetic counselling, new treatments for genetic diseases, and public health policies in genetics. Dr Horovitz is a consulting member of the Brazilian Ministry of Health for the special policy on rare diseases. She has published and collaborated in research on medical genetics, lysosomal storage disorders, and public health.

Faculty Members

Daniel MacARTHUR

Melbourne, Australia

Daniel MacArthur is the Director of the Centre for Population Genomics, based jointly at the Garvan Institute of Medical Research and the Murdoch Children's Research Institute. He previously ran a research team at the Broad Institute of MIT and Harvard, where he co-led the Broad Center for Mendelian Genomics, and led the development of the Genome Aggregation Database (gnomAD).

Domenica TARUSCIO

Roma, Itália

Domenica Taruscio, MD, former Director of the National Centre Rare Diseases, Istituto Superiore di Sanità. She is a Perm anent Board UDNI Member and a Co-Chair of UDNI Low Middle-Income Countries Working Group. She represented Italy at European Medicinal Agency, 2000-2009, and she contributed to International bodies, such as OECD, the European Commission and IRDiRC. She published several reports and more than 230 papers in PubMed

David ADAMS

Bethesda, USA

Dr. David Adams is a practicing physician and researcher in the intramural National Human Genome Research Institute at the National Institutes of Health in the United States. He co-directs the NIH Undiagnosed Diseases Program (UDP) and has a special interest in informatics and bioinformatics. Other work focuses on rare diseases of pigmentation and inborn errors of metabolism.

Emilio J.A. ROLDAN

Buenos Aires, Argentina

Emilio J.A. Roldan, MD, PhD (UBA, Argentina); Secretary of the Executive Board of ICORD; Member of IRDiRC's Scientific Committee on Therapies; Scientific Coordinator at CERyDH; Member of RIBERSER; Scientific Director at Qualix DoT (Spain).

David PEARCE

Sioux Falls, USA

David A Pearce is the chair of the consortium assembly for the International Rare Diseases Research Consortium (IRDiRC) representing funding agencies, companies, and patient advocate groups from approximately 80 countries. He has published over 120 research papers on Batten disease. He founded an international registry for rare diseases known as CoRDS and served as PI for an X01-Affiliate site for the NIH Undiagnosed Program.

Eric KLEE

Rochester, USA

Eric W. Klee, Ph.D., is a consultant & research in the Division of Computational Biology, Department of Quantitative Health Sciences, at Mayo Clinic in Rochester, Minnesota, with joint appointments in the Department of Clinical Genomics and Department of Laboratory Medicine and Pathology. Dr. Klee is the Science Director of Research Data and Digital Integration for Mayo Clinic. Dr. Klee holds the academic rank of Professor of Biomedical Informatics, Mayo Clinic College of Medicine and Science.

Faculty Members

Fernando GOLDSZTEIN

Porto Alegre, Brazil

Fernando Goldsztein is a Brazilian entrepreneur and board member of Cyrela, one of Latin America's largest real estate developers. After his son's diagnosis with medulloblastoma, he founded The Medulloblastoma Initiative in 2021 to accelerate a global research effort toward a cure for the most common pediatric brain cancer. Fernando devotes his time to mobilizing a global network and supporting cutting-edge research.

Filippo PINTO E VAIRO

Rochester, USA

Dr. Filippo Pinto e Vairo is a clinical geneticist and genomics researcher at Mayo Clinic, specializing in rare and undiagnosed diseases, lysosomal disorders, and genomic variant interpretation. He serves as Medical Director of the Program for Rare and Undiagnosed Diseases, and is a member of the Nephrology Genetics Clinic, advancing individualized genomic medicine and diagnostics.

Fulya TAYLAN

Stockholm, Sweden

Fulya Taylan is a research specialist in the Rare Diseases group at Karolinska Institutet and a docent (associate professor) in medical genetics. She analyzes genome data to help diagnose undiagnosed patients. She previously coordinated the Undiagnosed Disease Network International Diagnostic Working Group and is now a co-chair.

Gabriela REPETTO

Santiago, Chile

Gabriela Repetto, MD, Clinical Geneticist and Professor of Genetics at Facultad de Medicina, Clinica Alemana Universidad del Desarrollo in Santiago, Chile, where she directs the Rare Diseases Program. She was President of the Chilean Society of Genetics and is currently co-chair of the Global Genomic Medicine Consortium (g2mc.org) and member of the Technical Advisory Board on Genetics of the World Health Organization.

Gareth BAYNAM

Perth, Australia

Prof. Gareth Baynam is the Medical Director of the Rare Care Centre at Perth Children's Hospital, Head of the Western Australian Register of Developmental nomalies at King Edward Memorial Hospital, was a Founding Member of the Board of the Undiagnosed Diseases Network International, and is a co-founder of the Global Nursing Network for Rare Disease.

Guilherme BALDO

Porto Alegre, Brazil

Dr. Baldo received his Ph.D. degree in Biochemistry from the Federal Universityof Rio Grande do Sul (UFRGS), Brazil, and is currently an Associate Professor of Physiology at UFRGS. His research work is directed at mechanisms of raredisorders, as well as development of personalized treatments for thesediseases, focusing on gene therapy and gene editing. He is an Investigator ofthe Brazilian National Research Council (CNPq) level 1D and member of theNational Biosafety Committee (CTNBio).

Faculty Members

Helene CEDERROTH

Stockholm, Sweden

Founder and President of Wilhelm Foundation, Swedish-based international organization leading the charge in fostering collaborations dedicated to ending the diagnostic odyssey for People Living with Undiagnosed Diseases (PLWUD) worldwide, Co-founder and board member of the Undiagnosed Diseases Network International (UDNI) and co-founder of the Undiagnosed Diseases Network Foundation (UDNF). Pioneered the international Undiagnosed Hackathons.

Iscia LOPES-CENDES

Campinas, Brazil

Iscia Lopes-Cendes, M.D., Ph.D. Professor of Medical Genetics and Genomic Medicine. Head, Laboratory of Molecular Genetics. Department of Translational Medicine. School of Medical Sciences. University of Campinas - UNICAMP

Ignacio ZARANTE

Bogota, Colombia

IGNACIO ZARANTE MD, MSc, PhD. Medical Geneticist, master´s in biology and PhD in Biological Sciences from the Universidad Javeriana. Full Professor and Director of the Institute of Human Genetics at the Faculty of Medicine of the Pontificia Universidad Javeriana. President of the Colombian Association of Medical Geneticists. Head of the Genetics Department at San Ignacio University Hospital.

Janine LEWIS

Silver Spring, USA

Janine Lewis serves as the Director of Research Operations at the National Organization for Rare Disorders (NORD®), leading an essential part of NORD's mission to serve the more than 30 million Americans living with a rare disease. She is a Certified Genetic Counselor and diplomate with the American Board of Medical Genetics, with a background in genetics and extensive leadership and project management experience in the public sector.

Ipek BALABAN

Istanbul, Turkey

İpek Balaban is a 4th-year medical student at Acibadem University in Istanbul, with a full scholarship, passionate about scientific innovation and research. She has been actively involved with the ALIS International Scientific Student Congress for three years, serving as Secretary General. In the most recent term, fostering collaboration between medical students and renowned experts worldwide.

João BOSCO DE OLIVEIRA FILHO

Recife, Brazil

Physician and Researcher, dedicated to the study of patients with Rare Diseases. Creator and conductor of the largest Brazilian study on the genomics of rare diseases, the Rare Genomes Project. Founder of Genomika Diagnostics, which pioneered the use of next-generation sequencing for clinical genetic diagnosis in Brazil, a company that was sold to the Hospital Israelita Albert Einstein. Founding CEO of Genesis Genomics, a joint venture between the Hospital Israelita Albert Einstein and the Fleury/Pardini Group. Founder of NeoGenomics, a highly complex laboratory specializing in Whole Genome Sequencing for diagnosis, prevention, and treatment.

Faculty Members

Jong Hee CHAE

Seoul, South Korea

Jong Hee Chae, M.D., Ph.D. is a Professor of Genomic Medicine at Seoul National University Hospital, Seoul Korea and Director of the Rare Disease Center. A pediatric neurologist and clinical geneticist, her research focuses on rare diseases, including neuromuscular, neurodevelopmental, and mitochondrial disorders. She led Korea's national Undiagnosed Disease Program and currently serves as President of the Korean Child Neurology Society.

Mary Jane DYKEMAN

Toronto, Canada

Mary Jane Dykeman is a data strategist with a health and data law background. A partner at INQ Law in Toronto, she helps organizations harness, identify and execute opportunities for their data. She works on data de-identification, shared data platforms, privacy, artificial intelligence, and health research, in addition to her health law practice. She is Chair, EpiSign Inc.; Advisory Council member to the Wilhelm Foundation and proud supporter of the Undiagnosed HackathonTM. Mary Jane is also Deputy Chair, Canadian Blood Services Research Ethics Board; advisory/data governance committee member to the Temerty Centre for Artificial Intelligence Research in Education and Medicine (T-CAIREM) at the University of Toronto; and editorial board member to Future Medicine AI.

Manuel POSADA

Madrid, Spain

Manuel Posada de la Paz, MD, PhD, Research Full Professor. RIBERSER Coordinator (IberoAmerican Network of Health Experts in Rare Diseases). Member of the board of the UDNI. Specialist in Internal Medicine and also in Public Health. Rare Diseases Research Institute´s former director (2010-2022). More than 300 publications indexed in Web of Science. Lead editor of two Springer-published books entitled Rare Diseases Epidemiology.

May Christine V MALICDAN

Bethesda, USA

Dr. Malicdan, MD, PhD, directs the Translational Laboratory in the NIH Undiagnosed Diseases Program. She leads efforts in gene discovery, functional genomics, and therapeutic development for rare lysosomal disorders such as Hermansky-Pudlak, Free Sialic Acid Storage, GNE myopathy, and Chediak-Higashi syndromes. Her work bridges collaborations with clinicians, scientists, and advocacy groups, keeping patients at the center of discovery.

Maria Teresa ACOSTA

Bethesda, USA

Dr. Maria T. Acosta is Pediatric Neurologist with more than two decades of experience in clinical research from common conditions like ADHD to rare diseases like GM1 and Undiagnosed diseases. From 20025-2018 she served as clinical director of the Gilbert Family Neurofibromatosis Institute at Children's Health System in Washington DC, designing protocols, overseing patient enrollment and outcome assessments, she also co-lead the NHGRI's Genetic study in ADHD. In 2018, she joined NIH Undiagnosed disease program and the GM1 gene therapy trial. She continues working in the development, design and implementation of methodologies that will advance the field of clinical trials in rare diseases.

Michael ZIMMERMANN

Milwaukee, USA

Dr. Zimmermann's work generates powerful tools that reveal how DNA changes affect proteins, complexes, and cause disease, bridging atomic-level insights with clinical genetics. Driven by their new paradigm of computational structural genomics, the team drives innovative solutions, enhancing diagnostic clarity and accelerating development towards therapeutics by moving from static sequence-based annotation to dynamic, mechanistic interpretation of inter-individual genetic variation.

Faculty Members

Mikk CEDERROTH

Stockholm, Sweden

Im a father of four; three of my children died at 16, 10, and 6 from an undiagnosed disease. As Co-Founder of the Wilhelm Foundation, I work to help other families and lead global efforts like the Undiagnosed Hackathons to solve undiagnosed diseases.

Olaf BODAMER

Boston, USA

Olaf Bodamer MD PhD; Professor of Pediatrics; Director of the NORD rare disease center at BCH; Director of the Roya Kabuki Program Division of Genetics and Genomics; Boston Children´s Hospital/Harvard Medical School.

Nara SOBREIRA

Baltimore, USA

Dr. Sobreira, MD, PhD, received her medical degree and clinical genetics training in Brazil, before joining the graduate program in Human Genetics and clinical genetics fellowship at Johns Hopkins, where she now holds where she holds the position of associate professor. She is board-certified both in Brazil (SBGM) and USA (ACMG). Develops research on enchondromatoses, contributed to the creation of PhenoDB, being one of the founders of GeneMatcher and VariantMatcher.

Oleg KVLIVIDZE

Tbilisi, Georgia

Oleg Kvlividze, MD, PhD, Prof Since 2009, Prof. Oleg Kvlividze has served as the CEO of the Georgian Foundation for Genetic and Rare Diseases (GeRaD). With GeRaD he is engaged in RD policy making, as well as advocacy, research, treatment and educational activities at the national and international level. He is official expert on RD issues with the MOH of Georgia. Represent Georgia in IRDiRC, Orphanet, UDNI, EURORDIS, RDI, UEMS. Since 2024 he is a Principal Representative on the ERDERA Governing Board for Georgia. Member of the Editorial Board of the Rare. Open Research in Rare Diseases, the official journal of the UDNI. Author and co-author of more then 80 scientific papers, and some International and national guidelines on RD, dermatology and STI.

Natan MONSORES

Brasilia, Brazil

General Coordinator of Rare Diseases at the Ministry of Health, Brazil. Professor at the University of Brasília, where he is a supervisor in the Postgraduate Programs in Bioethics and in Public Health. Trained as a Biologista and Technician in Clinical Pathology, is also specialist in Bioethics. Obtained degrees of Master of Health Sciences and PhD in Bioethics/Public Health. Is the Coordinator of the Rare Disease Observatory at the University of Brasília, and Senior Research Associate at Fiocruz Brasília.

Ömer Bahadir KILIÇ

Istanbul, Turkey

Ömer Bahadır Kılıç is a 4th-year medical student at Acibadem University, also pursuing a minor in Biomedical Engineering and a degree in Computer Programming with a full-scholarship in Istanbul, Turkey. In 2025, he served as president of ALIS Congress which hosted 4,250 students and 135 speakers worldwide for 8 years. He is passionate about interdisciplinary learning and social healthcare.

Faculty Members

Pawel BUCZKOWICZ

Toronto, Canada

Dr. Pawel Buczkowicz, a PhD in cancer genetics and molecular pathology from the University of Toronto, is the Co-Founder of PhenoTips, a research and clinical genomic data management software. Besides clinical software, his research interests include utilizing genomics technologies to improve therapies for high-risk childhood cancer, rare disease patients and translational research on paediatric stroke, CNS vasculitis and brain tumours.

Rosa Andrea PARDO

Santiago, Chile

MD, Pediatrician, Clinical Geneticists , and Master Degree in Education. Full Professor, director of the Clinical Genetics Specialization and Chief of Genetics Section at University of Chile. President of the National Clinical Genetics Commission of certification. Co-Director of the National Registry of Congenital Anomalies of Chile. Research lines: prevention, genetic/epigenetic causes spina bifida and orofacial clefts.

Ratna PURI

Delhi, India

Ratna Dua Puri Professor in Genetics & Chairperson, Institute of Medical Genetics & Genomics, Sir Ganga Ram Hospital, New Delhi. She has been working in the field of genetics and genomics for over two decades and received awards including Dr IC Verma Outstanding Researcher Award 2019, Dharam Vira Award of Excellence 2010 and Young Investigators Award, Tokyo, Japan 2006. She initiated the Undiagnosed Diseases Program in India, working towards bridging gaps for patients without a diagnosis.

Salman KIRMANI

Karachi, Pakistan

Dr. Salman Kirmani, a Professor at Aga Khan University, is a Medical Geneticist and Pediatric Endocrinologist. US-trained and board-certified, he previously served at Mayo Clinic and now leads multiple child health programs and academic divisions at AKU since 2014.

Roberto GIUGLIANI

Porto Alegre, Brazil

Roberto Giugliani, Full Professor of Genetics at the Federal University of Rio Grande do Sul, in Brazil, is a medical geneticist who founded the Medical Genetics Service of Hospital de Clinicas of Porto Alegre, co-founded and currently leads Casa dos Raros, and is Head of Rare Diseases at Dasa Genomics. He is also the Editor-in-Chief of the Journal of Inborn Errors of Metabolism and Screening and Member of the Brazilian Academy of Sciences.

Salmo RASKIN

Curitiba, Brazil

Graduated in Medicine from the Federal University of Paraná, where he did his Pediatrics residence training and PhD in Genetics. Fellowship in Medical Genetics at the Division of Genetic at Vanderbilt University, Nashville, Tennessee, USA. Scientific Director of the Brazilian Society of Medical Genetics and Genomics and President of the Scientific Department of Genetics at the Brazilian Society of Pediatrics.

Faculty Members

Tammy McALLISTER

Rochester, USA

Tammy McAllister is an administrator within Mayo Clinic´s Center for Individualized Medicine. As a strategic and operational leader, she has worked to advance integration of -omic medicine at Mayo Clinic, overseeing an expanse of innovative translational/clinical implementation efforts in rare disease diagnostics and therapeutics, large-scale population health projects and genomic education.

Tracy DUDDING-BYTH

Waratah, Australia

Conjoint Professor Tracy Dudding-Byth AM is a Consultant Clinical Geneticist with the NSW Genetics of Learning Disability Service and a clinician-researcher in neurofibromatosis type 1 and rare diseases. She co-founded Rare Voices Australia and developed FaceMatch to improve genetic diagnoses. In 2024, she was appointed a Member of the Order of Australia for her contribution to rare disease patient advocacy.

Thereza CAVALCANTI

Ribeirão Preto, Brazil

Thereza Loureiro is a board-certified medical geneticist. She is a preceptor at the Hospital das Clínicas de Ribeirão Preto, University of São Paulo, and coordinates training programs in genomics at Dasa Genômica. She serves on the steering committee of the Brazilian Undiagnosed Diseases Program (UDP-BR), promoting precision medicine and equitable access to genomic technologies.

Wendy van ZELST-STAMS

Nijmegen, Netherlands

Wendy van Zelst-Stams is head of 2 Dutch departments of Human Genetics. She focuses on implementing new genetic diagnostic tools in daily clinical practice especially in the field of rare and undiagnosed diseases and hosted the 2nd Undiagnosed Hackathon initiated by the Wilhelm Foundation in 2024. She's involved in national and European policymaking in the field of Rare Diseases.

Tinatin TKEMALADZE

Tibilisi,Georgia

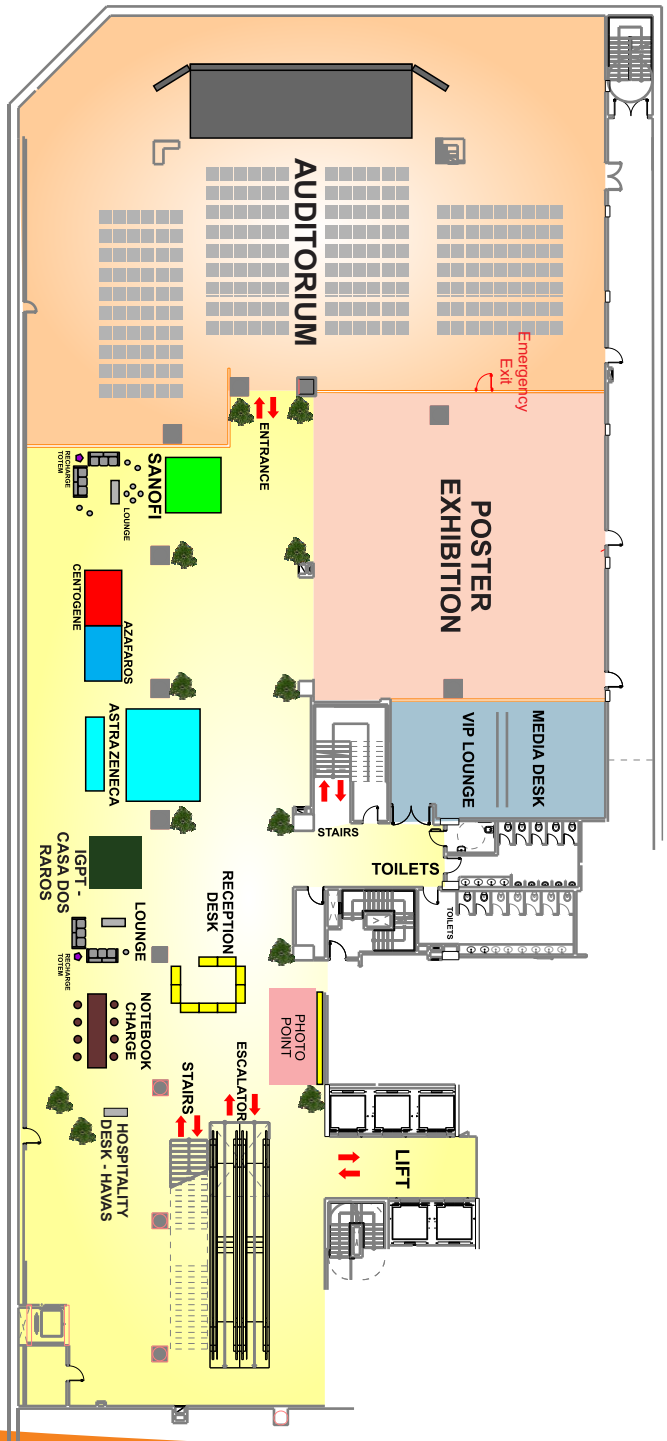
Prof. Tinatin (Tika) Tkemaladze is the head of the Department of Molecular and Medical Genetics at Tbilisi State Medical University (TSMU), the Dean of Medical Faculty at TSMU, as well as consultant clinical geneticist at several major pediatric hospitals in Tbilisi, Georgia. She has special interest in rare and undiagnosed diseases. Despite the challenges related to limited resources in her country, Tika is determined to end the diagnostic odyssey of her patients through active collaboration worldwide.

William GAHL

Bethesda, USA

William A. Gahl graduated from MIT and earned his MD and PhD from the U. of Wisconsin. He is certified in pediatrics and clinical and biochemical genetics. He elucidated the basic defects in cystinosis and Salla disease, published over 650 articles and trained 42 biochemical geneticists. In 2008, he established the NIH Undiagnosed Diseases Program, which made >400 diagnoses and discovered 35 new genetic diseases.

Floor Plan



Basement

Oct 29-30,
14th UDNI International Conference

Ground Floor

Oct 30,
Proficiency Testing
Barás room

2nd Floor

Oct 28,
Welcome Session,
Aimoré room

Oct 31,
Udni Business and Committee Meetings,
Aimoré room

TUESDAY, OCTOBER 28, 2025

19:00 — WELCOME SESSION (SPECIFIC REGISTRATION REQUIRED)

Location: Aimoré room, 2nd floor, Windsor Marapendi Hotel

WEDNESDAY, OCTOBER 29, 2025

08:00 - 09:00 — SESSION 1 - OPENING SESSION

Co-chair: ***Antoine Daher*** (Brazil)

Co-chair: ***Mikk Cederroth*** (Sweden)

Welcome to the 14th UDNI

Roberto Giugliani (Brazil)

The origins of UDNI and lessons learned through the years

Helene Cederroth (Sweden)

From UDPs to Hackathons

Mikk Cederroth (Sweden)

The Undiagnosed Hackathon

Eric Klee (USA)

09:00 - 10:00 — SESSION 2 - PANEL: ONLINE TOOLS TO DIAGNOSE THE UNDIAGNOSED

Co-chair: ***Ignacio Zarante*** (Colombia)

Co-chair: ***Filippo Pinto e Vairo*** (Brazil/USA)

Matchmaking Tools

Nara Sobreira (Brazil/USA)

Modern Clinical Phenotyping

Pawel Buczkowicz (Canada)

FaceMatch Consortium

Tracy Dudding-Byth (Australia)

10:00 - 10:30 — Coffee Break - Poster Viewing

Scientific Program

WEDNESDAY, OCTOBER 29, 2025

10:30 - 12:00 SESSION 3 - PANEL: HIGHLIGHTS OF UDPS AND HACKATHONS WORLDWIDE

Co-chair: ***David Pearce*** (USA)
Co-chair: ***Wendy van Zelst-Stams*** (Netherlands)

Americas
Gabriela Repetto (Chile)

Asia
Salman Kirmani (Pakistan) & ***Ratna Puri*** (India)

Oceania - Recorded
Gareth Baynam (Australia)

UDNI LMIC WG: Aims, Structure and Results
Domenica Taruscio (Italy)

Wrap-Up

12:00 Lunchtime Satellite Symposia (30 min each)

12:15 - 12:45 Genetic Variant to Clinical Manifestation: How Genotype Drives Phenotype and Guides the Diagnosis of an Intriguing Case
Carolina Fischinger (Brazil) - Sponsored by Ultragenyx

12:45 - 13:15 Overcoming Challenges in the Diagnostic of Rare Genetic Disorders
Carlos Leprevost (Brazil) - Sponsored by CentoGene

Poster Viewing

13:30 - 14:30 SESSION 4 - SPOTLIGHT ON EMERGING RESEARCH (ORAL PRESENTATIONS OF 4 SELECTED ABSTRACTS)

Co-chair: ***Eric Klee*** (USA)
Co-chair: ***Guilherme Baldo*** (Brazil)

n.05, p.30 Rare disease diagnostic platform megSAP/GSvar: our experience in processing 10.000 rare disease index short read genomes
Author: ***German Demidov***

n.24, p.37 The Role of RNA Sequencing to Resolve UDN Cases
Author: ***Pinar Bayrak-Toydemir***

n.02, p.29 Diagnosis Ofelia: AI-Based WhatsApp Screening for Rare Disease Risk Stratification in Colombia
Author: ***Ignacio Zarante***

n.81, p.56 Piloting a clinically-integrated undiagnosed disease program: evidence for clinical utility and clinician acceptability
Author: ***Lisa Ewans***

WEDNESDAY, OCTOBER 29, 2025

14:30 - 16:00 SESSION 5 - PANEL: POLICY INNOVATIONS: STRATEGIES TO TACKLE THE UNDIAGNOSED

Co-chair: ***Jong Hee Chae*** (South Korea)
Co-chair: ***Roberto Giugliani*** (Brazil)

- WHO – Genomics and Global Policy - Recorded
  Anna Laura Ross (Switzerland)
- The Role of Rare Diseases International
  Alexandra Heumber (Switzerland)
- The Brazilian MOH approach to rare diseases
  Natan Monsores (Brazil)
- The ERDERA Project
  Oleg Kvlividze (Georgia)
- Wrap-Up

16:00 - 16:30 Coffee Break – Poster Viewing

16:30 - 18:00 SESSION 6 - PANEL: INNOVATIVE APPROACHES FOR UNDIAGNOSED DISEASES

Co-chair: ***Salmo Raskin*** (Brazil)
Co-chair: ***Tinatin Tkemaladze*** (Georgia)

- Computational Structural Genomics: A Transformational Approach for Biology and Medicine
  Michael Zimmermann (USA)
- Unlocking the Power of Epigenetics through Data: EpiSign
  Mary Jane Dykeman (Canada)
- AI in Medical Genetics
  Annick Rein (Israel)
- The Challenge of Genetic and Genomic Newborn Screening: The EU Screen4care Project - Recorded
  Alessandra Ferlini (Italy)
- Wrap-Up

Scientific Program

WEDNESDAY, OCTOBER 29, 2025

18:00 - 19:00 SESSION 7 - CASE REPORTS: PRESENTATION AND DISCUSSION OF 4 SELECTED CASES (2 SOLVED AND 2 UNSOLVED)

Co-chair: ***Dafne Horovitz*** (Brazil)
Co-chair: ***Fulya Taylan*** (Sweden)

1st PLACE BEST ABSTRACT

n.26, p.38 A familiar gene, an unfamiliar story: TCF4 and a new mechanism unearthed after a decade of research
Author: ***Laurence Faivre***

n.37, p.42 Whole genome sequencing in immunodeficiencies: case report of twins with Cartilage hair hypoplasia, Omenn syndrome
Author: ***Istvan Balogh***

n.72, p.53 Undiagnosed syndrome with cleft lip, cleft palate, atrioventricular septal defect, duplication of the hallux
Author: ***Eugenia Ribeiro Valadares***

n.76, p.54 Comprehensive Diagnostic Approach in a Pediatric Patient with Multiple Digestive, Urinary, and Neurological Symptoms.
Author: ***Bárbara Lawlor Sclavo***

THURSDAY, OCTOBER 30, 2025

08:30 - 10:00 SESSION 8 - PANEL: NETWORKS, TRAINING, AND EDUCATION ON UNDIAGNOSED DISEASES

Co-chair: ***Oleg Kvlidze*** (Georgia)
Co-chair: ***Alexandra Heumber*** (Switzerland)

RIBERSER
Manuel Posada (Spain)

Proficiency Testing and Certification
Béla Melegh (Hungary)

Education in Rare Undiagnosed Diseases
Rosa Andrea Pardo (Chile)

Variant Interpretation Education - Recorded
Andreas Laner (Germany)

Wrap-Up

10:00 - 10:30 Coffee Break – Poster Viewing

THURSDAY, OCTOBER 30, 2025

10:00 - 12:00 PROFICIENCY TEST (For registered applicants only)
Co-chair: ***Béla Melegh*** (Hungary)
Co-chair: ***Tinatin Tkemaladze*** (Georgia)
Location: Barás room, Ground floor, Windsor Marapendi Hotel

10:30 - 12:00 SESSION 9 - PANEL: GENOMIC STANDARDS AND POPULATION GENOMICS
Co-chair: ***Eric Klee*** (USA)
Co-chair: ***Salman Kirmani*** (Pakistan)

Genomics in Admixed Populations
Iscia Lopes-Cendes (Brazil)

Genomic Data in Rare Diseases in Brazil
João Bosco (Brazil)

Building more representative reference datasets of human variation - Recorded
Daniel MacArthur (Australia)

Wrap-Up

12:15 - 13:15 Lunchtime Satellite Symposium (60 min)

Hypophosphatasia: an underrecognized disorder
Têmis Félix (Brazil) - Sponsored by **AstraZeneca**

Poster Viewing

13:30 - 14:30 SESSION 10 - SPOTLIGHT ON EMERGING RESEARCH – ORAL PRESENTATIONS OF 4 SELECTED ABSTRACTS
Co-chair: ***Carolina Fischinger*** (Brazil)
Co-chair: ***Tracy Dudding-Byth*** (Australia)

3rd PLACE BEST ABSTRACT
n.96, p.62
The role of ancestry-aware filtering in rare disease variant interpretation
Author: ***Katalin Sümegi***

2nd PLACE BEST ABSTRACT
n.86, p.58
UDN Sweden: Integrating Short- and Long-Read WGS and RNA-seq to diagnose Undiagnosed Children with Rare Syndromes
Author: ***Fulya Taylan***

n.29, p.39
Germline Variants as Contributors to Focal Cortical Dysplasia: Insights from Whole-Exome Sequencing
Author: ***Flávia Paniza Marcone***

n.85, p.58
Romanian UDP: Building a National Framework for Rare and Undiagnosed Diseases
Author: ***Elena-Raluca Nicoli***

Scientific Program

THURSDAY, OCTOBER 30, 2025

14:30 - 16:00 SESSION 11 - PANEL: HOW TO CREATE, STRUCTURE, AND FUND AN INSTITUTIONAL UDP PROGRAM

Co-chair: ***Filippo Pinto e Vairo*** (Brazil/USA)
Co-chair: ***Ratna Puri*** (India)

United States - Recorded
Tammy McAllister (USA)

Europe
Wendy van Zelst-Stams (Netherlands)

Latin America
Thereza Cavalcanti (Brazil) and ***Guilherme Baldo*** (Brazil)

Asia
Jong Hee Chae (South Korea)

Wrap-Up

16:00 - 16:30 Coffee Break - Poster Viewing

16:30 - 18:00 SESSION 12 - PANEL: FROM DIAGNOSES TO THERAPIES

Co-chair: ***Bibiana Oliveira*** (Brazil)
Co-chair: ***David Pearce*** (USA)

Methodology in clinical trials in rare diseases
Silvia Zaragoza (Spain)

Drug Repurposing and IRDiRC
Emilio Roldan (Argentina)

A Global approach to rare and undiagnosed diseases
David Pearce (USA)

Building International Collaborative Efforts to Advance in Therapies
Fernando Goldsztein (Brazil)

Wrap-Up

THURSDAY, OCTOBER 30, 2025

18:00 - 19:00 SESSION 13 - CLOSING SESSION

Co-chair: ***Roberto Giugliani*** (Brazil)
Co-chair: ***Helene Cederroth*** (Sweden)

Next-Gen Leaders: Voices of the Future in Rare Disease
Ömer Bahadir Kiliç (Turkey) & ***Ipek Balaban*** (Turkey)

Abstract Prize
To be announced

Introduction to Next UDNI Conference
To be announced

Closing
Helene Cederroth (Sweden) and ***Roberto Giugliani*** (Brazil)

19:30 Buses depart to Network Evening (specific registration required)

FRIDAY, OCTOBER 31, 2025

09:00 - 13:00 UDNI BUSINESS AND COMMITTEE MEETINGS (open to UDNI members and non-members)

Location: Aimoré II Room, 2nd floor, Windsor Marapendi Hotel

Posters Exhibition

TOPIC INDEX

The abstracts with titles in red will be also presented orally

01 - Adoption of a Chilean Diagnostic Support Application for Rare Diseases: Usability, Acceptability and Perceived Barriers

Nicole Nakousi-Capurro *(Paediatrics Unit, Hospital Carlos Van Buren, Valparaíso, Chile),* **Jean Paul Maidana** *(Facultad de Ingeniería, Universidad Andrés Bello, Viña del Mar, Chile),* **David Araya** *(Instituto de Tecnología para la Innovación en Salud y Bienestar (ITiSB), Universidad Andrés Bello, Viña del Mar, Chile),* **Carla Taramasco** *(Instituto de Tecnología para la Innovación en Salud y Bienestar (ITiSB), Universidad Andrés Bello, Viña del Mar, Chile)*

The implementation of digital diagnostic technologies for rare diseases faces distinct challenges in resource-limited settings. We examine factors influencing the adoption of DIAGEN, an artificial intelligenceenabled clinical decision support application designed for Child Neurologists (CN) in public hospitals to aid the identification of features of neurogenetic conditions before referrals to a clinical geneticist. Its predictive Bayesian model was developed by us, incorporating information from public databases, local clinical expertise and literature revisions. It incorporates a natural language processing model for HPO detection and suggests other evaluations to aid phenotyping and differential diagnosis workup. DIAGEN is currently being tested by CNs at Valparaíso's hospital for evidence of streamlined referrals to the single medical genetics provider, but interim analysis shows low usage rates despite initial acceptance. We administered a structured, mixed-format questionnaire to platform users, combining the System Usability Scale (SUS) to assess usability with the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM). Additionally, items informed by Hennrich and Hua's models of AI technology adoption probed perceived burden, trust, AI literacy, workflow integration, and organizational readiness. Preliminary findings indicate that, although physicians recognize the tool's potential, several barriers hinder effective use: high workload; difficulties identifying and documenting phenotypic characteristics; technically dense language; and insufficient training. Adoption is further constrained by the low frequency of patients with suspected genetic conditions and long intervals between follow-up visits, which reduce opportunities to embed the application into routine practice. Reported facilitators included the perceived added value of the tool and a generally positive orientation toward new technologies, contingent on the availability of training and ongoing support. In conclusion, the adoption of DIAGEN depends not only on its technical capabilities but also on contextual and organizational determinants. Standardized assessment of user experience can surface key barriers and enablers to guide targeted training, workflow redesign, and iterative application improvement, with the aim of enhancing usefulness, acceptability, and sustainability in clinical practice.

02 - Diagnosis Ofelia: AI-Based WhatsApp Screening for Rare Disease Risk Stratification in Colombia

Kelly Joane Leon Torres *(Pontificia Universidad Javeriana),* **Ignacio Manuel Zarante Montoya** *(Pontificia Universidad Javeriana),* **Ana Maria Urueña Serrano** *(Secretaria Distrital de Salud Bogotá)*

Background: Rare diseases (RDs) affect an estimated 3 million people in Colombia. However, fewer than 3% have received a confirmed diagnosis, and diagnostic delays often extend beyond five years, particularly in underserved populations. This prolonged "diagnostic odyssey" leads to avoidable morbidity, reduced quality of life, and delayed access to targeted therapies. Objective: Diagnosis Ofelia is a Colombian innovation that leverages artificial intelligence (AI) to screen individuals at risk of RDs using an accessible, freeof-charge WhatsApp chatbot. The system stratifies users into low, medium, or high risk categories, aiming to reduce time to specialized evaluation and support early clinical suspicion. Methods: Ofelia integrates a generative AI-powered interface with a structured clinical questionnaire covering 10 organ systems, family history, multispecialist consultations, and congenital features. The algorithm was co-designed by medical geneticists and public health experts and is supported by a secure web platform that enables clinician follow-up and risk verification. Ofelia is available via WhatsApp and a web-based interface for health professionals. Results: Since its public launch in February 2025, 298 users have completed the screening. Of these, 74 were successfully risk-stratified, with ~20% of medium/high-risk users having already received virtual or in-person genetic consultations. The tool has shown usability across urban and rural regions, and international reach with 47 users connecting from outside Colombia. Preliminary findings suggest frequent neurological, skeletal, and multisystem involvement among high-risk users. Clinician feedback has informed refinements in risk thresholds and language accessibility. Conclusion: Diagnosis Ofelia demonstrates a novel and scalable approach to digital pre-diagnostic triage in rare diseases. It improves early case identification, facilitates specialist referral, and has been well-received by both patients and providers. Its integration of AI, public health equity, and clinical validation positions it as a model for digital RD screening in low-resource and high-barrier settings.

03 - IA Tools

Abdul Rauf Brenya *(International Association for Impact Assessment),* ***Abdul Rauf Brenya*** *(International Association for Impact Assessment (IAIA))*

Artificial Intelligence and Nanotechnology are two fields that have been instrumental in realizing the goal of precision Medicine-tailoring the best treatment for each Cancer treatment. Recent conversion between these two fields is enabling better patient data acquisition and improved design of nano-materials for precision cancer Medicine Diagnostic nano-materials are used to assemble patient-specific disease profile, which is then leveraged through a set of therapeutic Nanotechnology to improve the treatment outcome. AI is been less acknowledged in African Schools to admit which would enhance to achieve better scientific implementation globally. However, high intra-tumor and inter patient heterogeneity make the rational design of diagnostic and therapeutic platforms and analysis of their output extremely difficult.

04 - Improving age-at-onset estimation in Huntington's disease using a machine learning model

Julio Marchiori *(LUMC)*, **Kasper van der Zwaan** *(LUMC)*, **Stephanie Feleus** *(LUMC)*, **Marco Roos** *(LUMC)*, **Willeke van Roon-Mom** *(LUMC)*, **Susanne de Bot** *(LUMC)*, **Katy Wolstencroft** *(AUMC)*, **Eleni Mina** *(LUMC)*

Huntington's disease (HD) is a rare neurodegenerative disorder that is inherited in a dominant manner and is caused by a prolonged CAG repeat in the huntingtin gene. HD is characterised by motor, behavioural and cognitive abnormalities. Age-at-onset (AAO) in HD refers to the time when symptoms first appear. HD is an incurable condition, which makes the determination of AAO crucial in identifying factors that can modify it, and in developing and evaluating therapies aimed at delaying its onset. The AAO is inversely correlated with the number of CAG repeats representing the most significant factor in estimating the AAO. Current models for AAO prediction are based on the length of the CAG repeat as the primary predictor variable. However, the CAG repeat accounts for about 60% of the variation in the HD population, indicating that there should be more factors influencing the AAO. In this study, we developed machine learning (ML) models to improve the current estimation of the AAO as well as models that can provide estimations for individual symptom onset. To achieve this we used the Enroll-HD dataset which collects observational data (baseline and follow-up) from multiple study sites, in both manifest and premanifest stages of the disease. Study population was defined as

patients enrolled as pre-manifest and those up to 3 years after symptom onset. In addition to the CAG repeat, we included lifestyle factors as well as comorbidities and (non) pharmacological interventions. We performed feature selection to select the most critical variables for our prediction model. Results indicated that, ML model in conjunction with Enroll-HD, generated more accurate predictions of HD AAO, outperforming the current used method. ML model achieved a performance of 77% with an average error of 4.4 years, compared to the 60% performance of the Langbehn formula (used as a baseline model). We also developed additional ML models to predict various symptom onsets such as motor, apathy, and cognitive impairment. The study also examined the relative importance of the various variables that influence these onset domains on an individual basis, highlighting factors such as marital status, education level or the use of certain medications (such as cardiovascular). This is very important for prognosis and patient stratification in clinical trials that focus on neuroprotective treatments. Timely treatments can result in a better quality of life for HD patients and their caregivers.stic and therapeutic platforms and analysis of their output extremely difficult.

05 - Rare disease diagnostic platform megSAP/GSvar: our experience in processing 10.000 rare disease index short read genomes

German Demidov, Marc Sturm, Dominic Boceck, Joohyun Park, Leon Schütz, Alexander Ott, Kilian Ilius, Jakob Admard, Alexandr Chernov, Caspar Gross, Axel Gschwind, Olaf Riess, Tobias Haack, Stephan Ossowski *(Universitätsklinikum Tübingen - Institut für Medizinische Genetik und angewandte Genomik, Tübingen, Germany)*

Genome sequencing is a widely used diagnostic tool for the detection of genetic disease variants. Genome sequencing (GS) is rapidly replacing exome sequencing (ES) for clinical diagnostics of rare disease (RD), due to its ability to detect variants in intronic and regulatory regions. Long read genome sequencing (lrGS) has become an irreplaceable tool for diagnostics of RD patients due to its strongly improved SV and repeat expansion detection, the ability to analyse variants in duplicated genes, and the direct analysis of DNA methylation e.g. for imprinting diseases. However, variant interpretation and the identification of causal variants in RD patients is still challenging and time-consuming and requires trained experts. Hence, there is a need for clinical decision support systems that assist clinical experts in identifying causal variants. Here we describe the freely available, open source genome diagnostics platform, developed at the Institute of Medical Genetics and Applied Genomics, Tuebingen, Germany, which consists of: 1) ngs-bits, a fast and versatile toolset for sequencing data analysis (https://github.com/imgag/ngs-bits/); 2) megSAP (https://github.com/imgag/megSAP), a clinical NGS analysis pipeline for exomes, as well as short and long read genomes; 3) Gsvar (https://github.com/imgag/ngs-bits/blob/master/doc/GSvar/index.md), an AI-assisted clinical decision support system, which allows analysis of single cases, trios and more complex RD family structures; 4) NGSD - a database for clinical NGS data, facilitating rare disease diagnostics and research such as novel gene discovery. We describe our experience in RD diagnostics using this software platform in more than 10 thousand srGS and 200 lrGS samples. We mainly focus on the genetic variants, traditionally challenging for diagnostic exome sequencing, such as structural variants (simple copy-number changes, copy-number neutral events such as inversions, mobile element insertions, repeat expansions). We also present our recent developments such as AI-assisted interpretation of small variants in the context of patients phenotypes. Our freely available diagnostics platform and experience we share in the series of publications can be an invaluable tool for RD diagnostics, especially in developing countries.

06 - AnDDI-Rares network: Coordinated Actions to Diagnose the Undiagnosed in Rare Developmental Disorders in France

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Purpose of research: France has established a national rare disease (RD) strategy through successive plans, with Plan Maladies Rares (PNMR)4 currently underway. AnDDI-Rares, one of 23 national RD networks, focuses on rare malformative and neurodevelopmental disorders, where many patients remain undiagnosed despite extensive workup. The network connects over 40 centers and collaborates with research, patient organizations, and the national Genomic Medicine Plan (PFMG 2025) ensuring equitable access to genome sequencing across all university hospitals. Methods: To address the diagnostic challenges of these heterogeneous disorders, AnDDI-Rares has implemented multiple coordinated actions at national and regional levels, supported by the creation of an "Undiagnosed" committee. Key results or findings: AnDDI-Rares have developed tools to enhance data sharing to improve the diagnostic process. The AnDDI-Rares Diagnostic Observatory was launched to monitor and improve diagnostic pathways through three work packages: (Wp1) analyzing changes in diagnostic strategies between 2012 and 2022, (WP2) re-evaluating de novo CNVs of uncertain significance >1Mb, and (WP3) Omics analyses in patients with established clinical diagnoses but negative genetic tests. Educational tools were designed, including a national protocol for communicating ultrarare results, a publicly accessible FAQ-based information booklet, and an infographic illustrating the diagnostic odyssey. For patients and families, AnDDI-Rares supported the creation of the association "Sans Diagnostic et Unique" and co-organized family-centered events with clinicians and researchers. A partnership with Maladies Rares Info Services enabled the development of moderated online discussion forums. In 2024, a national awareness campaign was launched to inform families and healthcare professionals about the opportunity to revisit undiagnosed cases in light of scientific advances. An exploratory study was conducted to understand how diagnostic uncertainty impacts the medico-social pathways of families of undiagnosed children. Main Results and Conclusions: Through these actions, AnDDI-Rares contributes to reducing diagnostic odysseys, fostering translational research, and strengthening national cohesion in the management of undiagnosed rare developmental disorders. The French model highlights the importance of integrated networks to address the complex challenges of undiagnosed rare diseases.

07 - Brazilian Undiagnosed Diseases Program: First year experience of a collaborative diagnostic initiative

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Background and objective: Timely access to genetic diagnosis remains a major challenge for patients with rare and complex diseases. In September 2024, the Brazilian Undiagnosed Diseases Program was launched as a collaborative initiative between Casa dos Raros and Dasa Genomics. The program provides advanced genomic testing, multidisciplinary review, and systematic case prioritization at no cost, aligned with international undiagnosed disease networks. This study reports the program's initial outcomes from September 2024 to August 2025. Methods: Cases were submitted through a standardized electronic platform and reviewed by a board of clinical geneticists and laboratory specialists. Eligibility criteria included rare, severe, or atypical presentations without a confirmed genetic diagnosis and without prior exome sequencing (WES). Accepted cases underwent WES with copy number variation analysis; complementary tests were recommended when appropriate. Results: Thirty-six cases were submitted, of which 23 met eligibility criteria. Twenty-one WES analyses were performed: 10 yielded a conclusive diagnosis, while 11 remained unsolved, including 7 with variants of uncertain significance requiring further investigation. Additional clinical data or complementary tests were requested in 10 cases. Most accepted patients originated from the South region of Brazil, with no submissions from the North region. The most frequent phenotypes, based on Human Phenotype Ontology terms, were seizures, abnormal facial shape, hypotonia, pain, and microcephaly. Among previously performed investigations, 63.9% had undergone another type of genetic test, and 19.4% had already received WES. Regarding referring physicians, 55.6% of submissions were made by residents in training, and 83.3% originated from the medical genetics specialty. Conclusions: The first year of the Brazilian Undiagnosed Diseases Program demonstrates the feasibility and clinical relevance of a structured national initiative for rare disease diagnostics. Early findings reveal regional disparities in access and emphasize the need for program expansion, international collaboration, and continuous integration of emerging genomic technologies. As an initial phase, the program focused on establishing its implementation framework. Future perspectives include broader dissemination and the strengthening of this national strategy.

08 - Building a Brazilian network to improve genetic diagnosis and research of Autism: Focus on Phelan-McDermid Syndrome

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Autism Spectrum Disorder (ASD) is an early-onset neuropsychiatric condition characterized by social communication impairments, restricted interests, and repetitive behaviors. With a global prevalence of 1-2.4%, ASD exhibits significant phenotypic heterogeneity. In Brazil, the 2022 census reported 2.4 million individuals with ASD (1.2% of the population). Approximately 10-25% of ASD cases are linked to rare, high-impact de novo variants, many following a monogenic inheritance pattern. Phelan-McDermid Syndrome (PMS), a 22q13.3 deletion syndrome, is a key example caused by haploinsufficiency of the SHANK3 gene, whose encoded protein is critical for synaptic function and cortical development. PMS is frequently identified in ASD and intellectual disability (ID) cohorts but remains underdiagnosed due to limited access to genetic testing. The objective of this work is to establish a collaborative Brazilian network to improve genetic diagnosis and research of PMS and syndromic ASD. The proposed initiative involves academic institutions, healthcare professionals, and patient advocacy groups working together to expand access to genomic testing. Individuals with level 2-3 ASD/ID across Brazil will be screened in partnership with Associação PMS Brasil, using exome sequencing as the primary diagnostic tool. Preliminary data highlight the magnitude of the diagnostic gap. The first Brazilian genetic study on PMS identified a 22q13.3 deletion in 0.6% of individuals with ASD and 0.61% of those with ID. PMS prevalence is estimated at 1 in 30,000 live births; however, only ~200 Brazilian individuals are currently diagnosed, far below expectations. Furthermore, data from Associação PMS Brasil show that exome sequencing accounted for nearly 20% of confirmed diagnoses over the last decade, with an average of 19 new families diagnosed per year. We expect that the establishment of this network will significantly increase the identification of individuals with PMS and other monogenic forms of ASD, bridging the current diagnostic gap. Ultimately, the network aims to foster earlier interventions, improve patient care, and stimulate new avenues of research on the genetic architecture of ASD in diverse populations.

09 - Characterization of undiagnosed patients in Brazil: Data from the Brazilian Rare Diseases Network

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Introduction: Accurate and early rare disease diagnosis is essential for management, prevention of complications and genetic counseling, improving quality of life of patients and families. These individuals often face a long diagnostic odyssey, with extensive investigations, however many remain without diagnosis.Objectives: To explore clinical characteristics of undiagnosed individuals assisted in Brazil. Methodology: Data were obtained from the Brazilian Rare Disease Network (RARAS), a nationwide epidemiological survey conducted across 40 centers. All undiagnosed individuals were included, with retrospective data collected between 2018-2019 and prospective data gathered from Apr/2022 to Jul/2025 using a standardized form on the REDCap platform. Resultados: From 19,059 participants in the RARAS survey, 3,321 (17.4%) remained undiagnosed; 54.3% were male, with mean age at last record 14.0 years (median 9.4; range 0–91.3). Most self-identified as White (44.4%) or Admixed (44.2%), with cases mainly from the Northeast (42.4%) and Southeast (32.0%) regions. Low-income groups predominated. Among 2,804 with data on clinical onset, mean age at first symptoms was 3.4 years (median: 0.3), indicating early-onset predominance. Mean ongoing diagnostic odyssey lasted 12.2 years (median: 8.8). Most frequent HPO reported were global developmental delay (n=722), seizures, intellectual disability, and hypotonia. A comparative analysis of the ten most frequent HPO terms in the undiagnosed group versus the remaining participants showed all ten to be significantly different (adjusted proportion differences, $p < 0.01$). Overall, 57.5% reported management, mainly pharmacological (n=1,268), rehabilitation (n=776), and psychological support (n=121). Hospitalization was reported in

35.6% (mean 0.7 previous hospitalizations/patient; range 0-41), and mortality rate was 0.24%. Conclusion: This analysis highlights the magnitude and complexity of unresolved rare disease cases in Brazil, with undiagnosed rates higher than those reported in high-income countries. Data emphasize the predominance of early-onset neurological and developmental phenotypes and the persistence of long diagnostic odysseys, often exceeding a decade, even in specialized centers. These insights underscore the importance of collaborative efforts such as RARAS and reinforce the urgent need for expanded genomic testing, systematic referral pathways, and equitable resource distribution to accelerate diagnosis.

10 - Defining the undefined: A scoping review of undiagnosed diseases

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Introduction: Undiagnosed diseases (UD) pose a clinical challenge, often linked to rare and complex conditions. The lack of consensus on their definition hinders diagnostic standardization and guideline development. Objective: To map and synthesize the literature on UD, focusing on definitions, classification criteria, and clinical guidelines or recommendations. Methods: Scoping systematic review, registered on Open Science Framework and conducted according to PRISMA guidelines, with searches from 2005 to 2025 in PubMed and Embase. The descriptors "Undiagnosed Diseases", "Definition", "Criteria" and equivalents were used. Studies with clear definitions, classification criteria, or guidelines were included. Studies without defined criteria and those focused solely on time to diagnosis were excluded. Screening was performed independently by two reviewers with a third adjudicator, and data extraction was based on full-text review. Results: A total of 316 studies were identified, of which 11 met the inclusion criteria. Three were international multicenter studies, and eight were conducted in specific countries, most frequently in the United States (37.5%; n=3) and South Korea (25%; n=2). The majority were observational studies (54.5%; n=6), including four cohort and two cross-sectional studies, followed by narrative reviews (36.4%; n=4). Publications ranged from 2017 to 2025. All studies provided some characterization of UD, with most (81.8%; n=9) describing them as clinical conditions with objective signs and no defined etiology despite specialized evaluation and the use of advanced diagnostic tests. A subset (27.3%; n=3) broadened the definition to include rare diseases, atypical phenotypes, conditions with unknown molecular basis, or environmental factors confounded with hereditary disorders. One study highlighted the most widely accepted definition, proposed by the UDNI, which considers UD as cases with a unique phenotype, extensively investigated, with obvious diagnoses excluded. Some centers also established temporal criteria, such as a diagnostic "odyssey" exceeding five years in adults. Conclusion: The diversity of definitions highlight a gap beyond diagnosis, affecting patient access to specialized care, research, and health policies, while hindering guideline development. International collaboration is crucial to align definitions and criteria, strengthen health policies, and improve diagnostic strategies for individuals with UD.

11 - Diagnostic Odyssey of Rare Diseases in Brazil: Data from the Brazilian Rare Diseases Network

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Objective: To describe the diagnostic odyssey for rare diseases (RDs) in Brazil using data from the Brazilian Rare Diseases Network (RARAS). Methods: This descriptive cross-sectional study used data from the RARAS project, including retrospective (2018-2019) and prospective (2022-2025) phases. The primary variable was the diagnostic interval, derived by converting age at symptom onset into date format and subtracting it from the recorded date of diagnosis. Analyses were stratified by age group, the ten most frequent RDs, and region of residence. Results: Of the 18,625 records in the database, 5,984 were eligible for analysis of the diagnostic odyssey. The overall mean time from symptom onset to diagnosis was 6.21 years (±8.41). When stratified by age at symptom onset, the mean diagnostic delays varied: 5.12 years for symptoms beginning before age 1; 7.42 years for ages 1-5; 9.55 years for ages 6-12; 9.87 years for ages 13-19; and 4.79 years for symptom onset at age 20 or older. Among the diseases analyzed, the longest diagnostic delays were observed in hereditary angioedema (16.40 years), osteogenesis imperfecta type 1 (11.73 years), and Marfan syndrome (10.28 years). The shortest delays were seen in phenylketonuria (1.19 years) and achondroplasia (2.01 years). Regional comparisons revealed significantly longer diagnostic delays in the Southeast (7.80 years), followed by the South (6.54 years), Northeast (5.67 years), North (4.73 years), and Central-West (3.85 years) regions. On average, individuals consulted 5.32 physicians and 3.14 healthcare services during their diagnostic journey; 14.53% visited five or more services, and 16.68% consulted five or more physicians. Conclusion: This is the first study of the diagnostic odyssey for overall RD in Brazil, showing similar time as other studies worldwide. Such delays contribute to emotional distress, family burden, and increased healthcare costs. The high number of consultations and healthcare services accessed underscores the need for improved professional training and a more structured healthcare network. These pioneering data shed light on the diagnostic journey of RDs in Brazil, emphasizing the urgency of strategies such as expanding access to genetic testing, reference centers, and clinical screening tools to reduce patient burden and optimize resource use

12 - Epidemiological panorama of Undiagnosed Rare Diseases in a Brazilian Public Reference Service

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In Brazil, the undiagnosed rare diseases is marked by structural, epidemiological, and assistive challenges, despite recent advances in public policies and infrastructure. The Public Rare Disease Reference Services (RDSR) aim to reduce the mean time for diagnosis (the 'diagnostic odyssey') through access to advanced technology; facilitate access to specialized services and professional training. Despite all these efforts, undiagnosed rare diseases are still numerous. The study describes the epidemiological profile of undiagnosed rare diseases belonging to the National Registry of Rare Diseases of the RDSR of HU-UFJF/Ebserh. This is part of a prospective study conducted by Rare Diseases Registry Section of Juiz de Fora Federal University Hospital/Ebserh (HU-UFJF/Ebserh), a RSRD (Portaria GM/MS, n 1.890 de 10/08/2021). The research, approved by the institutional ethics committee (CAAE: 33970820.0.3104.5133), analyzed data spanning ongoing since July/2024. Data collected includes demographic information (gender, age, residence city, human phenotype ontology (HPO), Genetic analysis). All data were systematically managed and securely stored on the REDCap platform to ensure the clinical and the genetic information integrities. Results/ Discussion: The initial cohort included 358 pacients, 45.25% (n=162) males, 48.6% live in JF/MG and 51.4% from other cities around. The mean age was 26.36 y (0-85 y; median= 19y), with 44.97% affecting children ≤14y (n=161). Diagnostic investigation was conclusive in 43.85% (n=157) (molecular=131; cytogenetic=18; biochemical test=2). Undiagnosed rare disease is still in 19.55% (n=70), even after diagnostic tests in 1.67 (n=6). Our cohort is caracterized by patients with heart disease as a inclusion factor. The prevalence of undiagnosed disease is lower than what is commonly described on studies (about 50%)1. Despite the organizational advances of reference service, a considerable portion of patients remains undiagnosed. The support from diagnostic pharmaceutical programs and research projects such as the Brazil Genome Map facilitate patients diagnosis; however other technologies such as multi-omic tests, and long-read sequencing are still not available. In the near future we hope that these tools help us to reduce the undiagnosed rare diseases prevalence. Strengthening the reference network, expanding access to specific tests, and epidemiological data are essential to improving this scenario.

13 - Krabbe Disease in a 13-Year-Old Adolescent: Case Report and Diagnostic Approach

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Introduction: Krabbe disease is a rare autosomal recessive lysosomal storage disorder caused by mutations in the GALC gene, leading to a deficiency of the galactocerebrosidasa enzyme. This results in the accumulation of toxic metabolites such as psychosine, causing progressive demyelination of the central and peripheral nervous systems. Although most cases present in early infancy with rapid progression, late-onset forms with variable progression have been described. This case describes the clinical evolution of a patient whose diagnosis was confirmed in the United States during childhood and who is currently 13 years old. Objectives: To describe the long-term clinical course of an adolescent with a confirmed diagnosis of Krabbe disease in childhood and to analyze diagnostic, therapeutic, and prognostic aspects in juvenile-onset forms. Materials and Methods: A retrospective review of the patient's clinical, biochemical, neuroimaging, and genetic data was conducted. The patient is a 13-year-old female, diagnosed at the age of 8 in the United States through genetic testing that confirmed pathogenic mutations in the GALC gene. Serial neurological evaluations, brain MRIs, functional assessment scales, supportive treatments, physical rehabilitation, and overall clinical evolution were reviewed. Results: The patient showed a slow progression of the disease. Initial symptoms included irritability, developmental delay, and hypertonia. Over time, she developed moderate motor and cognitive impairment, requiring mobility aids and specialized educational support. Brain MRI revealed diffuse leukodystrophy with periventricular and cerebellar involvement. Epileptic seizures were controlled with antiepileptic drugs. She was not a candidate for hematopoietic stem cell transplantation due to late diagnosis. Currently, she maintains a moderately preserved quality of life with multidisciplinary palliative care. Conclusions: This case highlights the phenotypic variability of Krabbe disease and underscores the importance of early diagnosis through newborn screening. Although there is no curative treatment at symptomatic stages, supportive interventions can improve function and quality of life. Gene therapy and enzyme replacement are promising future alternatives, particularly if applied during presymptomatic phases.

14 - Mexican Network for Rare Diseases: Facilitating access to genomic diagnostics and raising awareness about rare diseases

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Advances in genomic sequencing technologies have revolutionized the study and diagnosis of rare diseases. Exome sequencing has become a first-line diagnostic test for most patients with congenital anomalies and suspected genetic disorders in high-income countries. Similarly, whole-genome sequencing is being implemented in research settings for the study of genetic diseases with complex etiologies and is increasingly being considered in clinical settings for early and rapid diagnosis. However, these advances are not benefiting patients equally worldwide, increasing health disparities between those living in high-income countries and those living in resource-limited countries. It is estimated that at least 10 million people in Mexico are living with a rare disease, most of whom do not have a molecular diagnosis for their condition and, in most cases, have not even been evaluated by a geneticist. The Mexican Network of Rare Diseases is a collaborative network of clinicians, researchers, and patient organizations that aims to increase the awareness and implementation of molecular and genomic diagnostics for the research and diagnosis of rare and undiagnosed genetic diseases in Mexican patients. We perform trio exome sequencing in patients with suspected genetic diseases to facilitate access to these technologies for patients with limited resources that cannot pay for these tests commercially. To date, a third of patients have received a definitive molecular diagnosis, while another third are being followed-up through research, investigating novel genes and variants. Additionally, in 2022, we began the Mexican Rare Disease Patient Registry to investigate the number and challenges of people living with rare diseases in Mexico through an open registry of patients living with these conditions in the country. Data from this registry illustrate the time it takes in Mexico to obtain an accurate diagnosis for patients living with a rare or infrequent disease, the low referral rate to geneticists, and the low percentage of patients in the country who have a definitive and accurate molecular diagnosis. We also conduct outreach and education activities about genetic diseases and the importance and benefits of achieving an accurate and timely molecular diagnosis for patients and families living with suspected genetic diseases.

15 - The European long read innovation network (ELRIN)

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ELRIN is dedicated to advancing ONT-based long-read genome sequencing as an

innovative approach to first-line genomic diagnostics in healthcare. While we started as a European network of human genetics experts, partners from all over the world are joining us to systematically explore the potential of ONT-based lrGS in diagnostics in different cohorts of RD and of familial cancer (advantages, disadvantages, diagnostic sensitivity compared to srGS), to revolutionize reporting of repeat expansion composition together with exact sizes and with haplotyping of affected alleles preparing patients for ASO treatment studies, and to bring genome wide epigenomic analysis into routine diagnostics. The network of currently more than 30 partners is closely interacting with ERDERA (https://erdera.org/) which is focusing on the unsolved rare disease patients and with the Genomes of Europe consortium (https://genomeofeurope.eu/) which is as part of the 1+MG initiative working on providing data of more than 100T reference genomes.

16 - Understanding rare diseases in Brazil: Evidence from the Brazilian Rare Diseases Network

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Rare diseases (RD) affect up to 16 million Brazilians. The National Policy for Comprehensive Care for People with Rare Diseases was established in 2014, however national data remain fragmented and limited to isolated conditions. In order to generate structured epidemiological evidence, the Brazilian Rare Diseases Network (RARAS Network) was launched in 2020. This multicenter ambispective survey integrates 40 specialized centers, including university hospitals, Rare Disease Reference Services, and Newborn Screening Reference Services, across all five regions of Brazil. The aim of this study is to present the structuring of the network and its preliminary findings. Data collection included a retrospective phase (2018-2019, registered between 2020-2021) and an ongoing prospective phase (since 2022). Standardized forms hosted on REDCap capture demographic, clinical, and genetic data, including Human Phenotype Ontology terms, diagnostic methods, treatments, hospitalizations, and comorbidities. Each participant is assigned a unique identifier for longitudinal follow-up. Ethics approval was obtained from all participating centers. As of June 2025, 19,059 participants were enrolled. Median age was 13.2 years (mean 19.8; SD 18.5); 51.2% were female. Most participants lived in the Northeast (37.5%) and Southeast (31.9%) regions. Consanguinity occurred in 8.3% (12.3% in the Northeast). Among all cases, 65.6% were confirmed, 17.8% suspected, and 16.6% remained undiagnosed. Of confirmed diagnoses, 63.6% had etiological confirmation (42.4% molecular, 32.4% biochemical, 13.6% cytogenetic, 7.6% anatomopathological), while 31.7% were clinical only. Familial recurrence was reported in 26.3%. The mean diagnostic odyssey lasted 6.3 years, with an average delay of 1.9 years between first specialized consultation and diagnosis. In the retrospective phase, 44.5% of patients had $\geq$1 hospitalization; in the prospective phase, 39.8%. Median hospitalization lasted 12 days. The RARAS Network represents the first coordinated national effort to systematically document RD in Brazil. Findings highlight persistent diagnostic delays, especially in undiagnosed and suspected cases, strongly influenced by late referral to specialized centers and regional inequities. Expanding early access strategies and integrating genomic tools are crucial to reduce the diagnostic odyssey and improve outcomes for people living with rare and undiagnosed diseases.

17 - Methylmalonic Acidemia and Homocystinuria By Epimutation: Case Report

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INTRODUCTION: Methylmalonic acidemia and homocystinuria cobalamin C type (cblC disease) is most commoninherited disorder of cobalamin metabolism; increased methylmalonic acid and homocysteine ??are characteristic and it is associated with multisystem involvement and high morbidity and mortality rates, especially in the early-onset form. Clinical evolution and treatment outcome are variable, with prognosis worsening especially in those who receive inadequate or late treatment. cblC deficiency is caused by biallelic MMACHC genetics variants. In recent years, compound heterozygous patients with digenic variants have been reported: pathogenic variants in MMACHC and in PRDX1; the latter is considered an epimutation, since it leads to a hypermethylated sequence that encompasses the promoter and first exon of the MMACHC. This disorder has been named epi-cblC. OBJECTIVE: The aim is to report PRDX1:c.*2C>T variant as a probable cause of epi-cblC. METHOD: diagnosis of cblC disease was made clinically, biochemically and molecularly by whole exome sequencing (WES). CASE REPORT: We report a 6 years old male patient, of normal second pregnancy and non-consanguineous parents, with adequate weight and height, he had jaundice during the first month of life, had normal development until 3.5 months and then regressed. He was referred for evaluation at 5 month of age, on examination he was lethargic, with microcephaly, was hospitalized, had persistent metabolic acidosis, and was treated for sepsis. He remained hospitalized for 5 months, had hospital-acquired pneumonia, COVID, required mechanical ventilation, tracheostomy, optic nerve compromise, and multiple thrombotic events that deteriorate him. Increased methylmalonic acid in urine and homocysteine in blood were detected. Currently, receives vitamin B12, Betaine anhydrous, multivitamins and normoprotein diet. Methylmalonic acid and homocysteine have decreased markedly. The patient has sequelae but has improved significantly. RESULTS WES identified a heterozygous pathogenic variant in the MMACHC:c.394C>T and a heterozygous variant of uncertain significance in the PRDX1:c.*2C>T gene. CONCLUSIONS: Probably, several PRDX1 mutations cause epimutations in MMACHC. Diagnostic molecular panels for this condition, should include the PRDX1. cblC disease is a serious disorder, its early diagnosis and treatment are promising for these patients.

18 - DNA methylation profile of the GSTM3 gene in nasal epithelial cells of Georgian cystic fibrosis patients

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Introduction: Clinical heterogeneity in cystic fibrosis (CF) is well documented, with patients sharing identical CFTR genotypes often exhibiting markedly different disease severities and clinical outcomes. This variability highlights the significant influence of genetic modifier genes, genes other than CFTR that modulate the expression and severity of CF phenotypes. Both modifier genes and epigenetic

alterations can impact various aspects of the disease, contributing to the observed clinical variability. In the present study, we analyzed the DNA methylation pattern of the Glutathione S-Transferase M3 (GSTM3) gene promoter in Georgian CF patients carrying the rare c.1545_1546delTA (1677delTA) mutation. Materials and Methods: The study was approved by the Ethics Committee of Tbilisi State Medical University. Written informed consent was obtained from the parents of all participating patients. A total of 18 CF patients were enrolled, including individuals homozygous for the 1677delTA mutation or compound heterozygous for 1677delTA and either p.Phe508del or another null mutation. Ten age-matched healthy individuals served as controls. Nasal epithelial cells (NECs) were collected from the inferior turbinate of both nostrils using nasal curettes and pooled in 1 mL of RNase-free phosphate-buffered saline (PBS), pH 7.4. Methylation of the GSTM3 promoter was assessed using methylation-specific PCR (MSP). Results: No statistically significant difference in GSTM3 promoter methylation levels was observed between CF patients and healthy controls. However, in our previous study, we identified hypomethylation of LINE-1 mobile elements in CF patients, and a positive correlation was observed between GSTM3 and LINE-1 methylation status. Conclusions: Our study did not reveal a statistically significant difference in GSTM3 promoter DNA methylation between Georgian cystic fibrosis patients carrying the rare 1677delTA mutation and healthy controls. However, the observed correlation between GSTM3 methylation and LINE-1 methylation suggests that epigenetic modifications of modifier genes may contribute to the complex regulation of disease phenotype in CF. These findings highlight the need for larger cohort studies and more comprehensive epigenetic profiling to better understand the role of DNA methylation in CF pathogenesis and clinical variability.

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19 - Evolving diagnostic capacity for rare diseases in Brazil: Insights from the RARAS Network

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Introduction: The decade following the publication of Brazil's Policy for Comprehensive Care for People with Rare Diseases (PNAIPDR, 2014) has seen important advances in structuring rare disease (RD) care. In 2020, the Brazilian RD Network (RARAS) was established, encompassing 37 institutions across the country, including Reference Services for RD, Newborn Screening Services, and University Hospitals. Objectives: This study aimed to map the availability and distribution of diagnostic tests recommended by PNAIPDR within the Brazilian Unified Health System (SUS), based on data from RARAS centers. Methods: A REDCap questionnaire was administered, focusing on the provision of diagnostic procedures. Data collection took place in 2023 with 24 responding centers and was compared to data collected in 2020-2021 and published previously by Oliveira et al. (2023). Ethical approval was obtained from all participating institutions. Results: In 2023, 79.2% of RARAS centers reported access to at least one investigated diagnostic test. Cytogenetic testing was the most widely available group (75.0%), with two-thirds of karyotyping performed in-house. Inborn errors of metabolism (IEM) methods were present in only 41.7% of centers, despite continued availability of basic assays for amino acids, organic acids, and acylcarnitines. Molecular diagnostics were reported in 54.2% of centers, with some methods (Sanger sequencing, MLPA) mostly internalized. Exome sequencing was available in only 4 of the 24 centers (16.7%): 1 in-house and 3 outsourced. Nevertheless, 20.8% of centers had no access to any of the evaluated tests. Laboratory infrastructure was more consolidated, with pathology, clinical pathology, and imaging reported in 75-79% of centers. Compared to 2020 data, overall diagnostic availability rose modestly (73.0% to 79.2%), with cytogenetics expanding (62.2% to 75.0%), molecular testing remaining stable (54.0% vs. 54.2%), and metabolic diagnostics declining (59.5% to 41.7%). Discussion and conclusion:These findings represent the first nationwide data on RD diagnostic test availability after PNAIPDR. Molecular testing remains stagnant and metabolic testing has regressed, exposing inequities and reliance on outsourcing. By excluding experimental or research-only assays, this study reflects routine clinical practice and highlights critical gaps. Results provide evidence to guide public policies, resource allocation, and equity in access to RD diagnostics in Brazil.

20 - Genomic meetings at Casa dos Raros: Clinical integration, diagnostic impact and team development

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Casa dos Raros (CDR) initiated clinical care in June 2023 and, since March 2024, has organized weekly genomic meetings. The main objective is to review all genomic tests available for patients that contain uncertain or causative findings. When necessary, raw data are requested for in-depth reanalysis. The methodology consists of systematic discussion integrating reports, clinical data, and literature review to support variant interpretation. The aim of this study is to report the structuring of this experience and its partial results. Up to August 2025, a total of 154 cases were systematically reviewed during 49 weekly hybrid genomic meetings held at Casa dos Raros, with the participation of clinical geneticists and a biologist. All available genetic test reports, whether from the institution or external laboratories, were critically evaluated, and in selected cases, raw data were requested for in-depth reanalysis. This structured review enabled refinement of variant interpretation and clinical correlation. Among the 154 patients assessed in this period, 12 achieved a definitive diagnosis based solely on case discussion, phenotype, and literature review during the meetings, without the need for additional testing. An additional 16 diagnoses followed reclassification of uncertain variants, supported by segregation and phenotypic reassessment. These preliminary results highlight the role of systematic genomic review in resolving complex cases. In some cases, errors in molecular reports were detected, prompting direct communication with genetic laboratories and re-issuance of corrected results. Additionally, misinterpreted previous external diagnoses were revised and excluded after critical correlation. Moreover, the meetings have contributed to strengthening the correlation between genomic findings and clinical phenotypes, validating or refuting suspected diagnoses, and improving patient management. This process has also fostered continuous learning within the team, enhancing the qualification of clinicians in applied genomics and consolidating multidisciplinary expertise. Beyond diagnostics, these meetings strengthened genetic counseling, professional development, and collaborative learning. The continuous cycle of discussion, critical appraisal, and clinical validation highlights the potential of institutional genomic boards to improve diagnostic accuracy, reduce uncertainty, and promote capacity building in rare disease care.

21 - Misdiagnosed or underdiagnosed? ENPP1 and ABCC6 deficiency carrier frequency in a cohort of Brazilian patients

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Background: Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) is a transmembrane protein responsible for cleaving ectonucleotides, predominantly adenosine triphosphate (ATP), to generate adenosine monophosphate (AMP) and pyrophosphate (PPi). ENPP1 Deficiency can result in two main phenotypes: Generalized Arterial Calcification of Infancy (GACI) which is characterized by ectopic mineralization, particularly along the internal elastic lamina of large and medium-sized arteries, as well as periarticular calcification; and Autosomal Recessive Hypophosphatemic Rickets Type 2 in those who survive GACI, or in individuals who never had clinical cardiovascular manifestations. In 9% of cases, GACI results from biallelic inactivating variants in ABCC6, which encodes a plasma membrane transporter highly expressed in the liver; biallelic variants in ABCC6 typically cause pseudoxanthoma elasticum (PXE), a disorder characterized by calcification and fragmentation of elastic fibers in the skin, retina and cardiovascular system. Methods: Retrospective cohort study of 1254 patients referred to a National Center for Rare Connective Disorders. All patients underwent genetic tests with two customized Next Generation Sequencing (NGS) panels for skeletal dysplasias and genetic connective diseases. Results: Overall, pathogenic variants were detected in 6% patients, no difference in ABCC6 prevalence for male or female, although the variants in ENPP1 deficiency were only found in male patients. A carrier frequency for ENPP1 1 in 440 individuals with suspicion of bone/connective disease and for ABCC6 1 in 89 individuals submitted for NGS studies. Different from other studies performed in a non-selected population, our study had phocus in evaluating a targeted cohort of Brazilian patients with features of a connective/metabolic bone disorder Conclusions: Previously tudies showed a carrier frequency for ENPP1 1 in 312 people, with disease frequency predicted to be about 1 in 200,000 individuals. More recently, a new study showed variants associated with ENPP1 Deficiency estimated to be 1 in 509 to 1 in 127 in the general population which corresponds to a genetic prevalence of 1 in 1,033,927 to 1 in 64,035 pregnancies, 212% higher than the initial studies, suggesting that many patients are missed or misdiagnosed. Our study is the first frequency analysis of GACI and PXE gene variants in Brazilian population, suggesting frequency may be higher than anticipated.

22 - RNU6ATAC minor spliceopathy: -Omics orthogonal approaches to solving complex phenotypes in the Undiagnosed Diseases Netw

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The US NIH Undiagnosed Diseases Network (UDN) has assembled a large cohort of bioinformatic "-omics" data, including genomes and transcriptomes from affected individuals and their unaffected relatives. While the traditional diagnostic approach emphasizes phenotyping informing genotyping, our cohort also enables novel "-omics first" strategies that can uncover complex disease mechanisms independent of precise phenotype matches. Such approaches are particularly valuable when phenotypic variability complicates recognition of shared underlying genetic causes. As part of its mission, the UDN trials various innovative bioinformatics pipelines using our dataset. Here, we highlight such an effort by which the Stanford UDN used the FRASER tool (Find RAre Splicing Events in RNA-seq) to detect abnormal intron retention in transcriptome data, particularly in genes that utilize the minor spliceosome (minor intron-containing genes, MIGs). When applied across a cohort of UDN and GREGOR (Genomics Research to Elucidate the Genetics of Rare diseases) consortium patients, this pipeline identified two unrelated patients as outliers with extensive intron retention specifically in a subset of genes known to be MIGs. Despite minimal phenotypic overlap, both patients exhibited compound heterozygous variants in RNU6ATAC, a small nuclear RNA essential to the minor spliceosome complex. The two patients had been seen for phenotyping at two separate UDN sites by different physicians, years apart. No phenotype match was suspected until use of the FRASER tool prompted re-analysis of their family genome data with a focus on genes comprising the minor spliceosome. These findings represent the first cases of RNU6ATAC-associated spliceopathy. Retrospective review of clinical features revealed shared elements of developmental growth dysfunction and immune dysregulation, consistent with deficiencies in MIG function. This work illustrates how unbiased "-omics first" approaches, empowered by a large UDN dataset, can reveal novel genetic mechanisms underlying rare and complex syndromes, especially in conditions with variable presentation. Ongoing collaborations with bioinformatics partners continue to expand the scope of analytic pipelines, advancing the diagnosis of patients with previously unexplained conditions.

23 - Single-nuclei multiomics of mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy

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Mild malformations of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE) represent recently characterized brain lesions associated with focal epilepsy, distinguished by increased oligodendroglial density, zones of hypomyelination, and presence of heterotopic neurons within the white matter. While previous studies have examined the histopathological and genetic features of these lesions, the cellular and molecular mechanisms underlying MOGHE pathogenesis remain unknown. To address this, we performed paired single-nucleus RNA (snRNA-seq) and assay for transposase accessible chromatin (snATAC-seq) sequencing of gray and white matter regions of MOGHE lesions to

obtain gene expression and chromatin accessibility profiles of over 31,000 nuclei and compared with publicly available control datasets. Our findings revealed significant cellular composition alterations in MOGHE, notably an expansion of oligodendrocytes and the presence of heterotopic neurons in the subcortical white matter. We identified a MOGHE-specific oligodendrocyte subpopulation exhibiting upregulation of synaptic regulation, immune response, disrupted myelination, and epilepsy-related pathways. Signature analyses indicated that these oligodendrocytes share molecular features with those implicated in other neurological disorders involving white matter abnormalities. Moreover, cellular communication analyses revealed that MOGHE-specific oligodendrocytes have enhanced neuronal communication, suggesting a role in synaptic support and neuron-glia interactions. Additionally, heterotopic neurons exhibited upregulation of genes involved in neuronal migration and the Wnt signaling pathway. Consistently, motif analysis based on snATAC-seq profiles identified FOX-family transcription factors, regulators of Wnt signaling pathway, among the most highly enriched motifs in this neuronal population, suggesting a potential mechanism underlying their atypical localization. In conclusion, this study presents the first high-resolution cellular atlas of MOGHE lesions, identifying affected neuronal and glial populations and providing novel insights into the pathophysiological mechanisms of MOGHE.

24 - The Role of RNA Sequencing to Resolve UDN Cases

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The Utah Penelope Program and the UDN focus on addressing the diagnostic complexities of individuals with rare diseases. RNA-seq has become an essential tool in clinical genetics, providing critical insights into gene expression and alternative splicing. Combined DNA and RNA sequencing analysis was performed on 30 patients with diverse clinical presentations. The cohort included two main categories of cases (1) patients with candidate splice altering variants identified by prior genome or exome sequencing where the molecular findings had partial or uncertain clinical overlaps with the reported phenotype, and (2) patients without any diagnostic candidate variants but with a high suspicion of an underlying monogenic disorder based on clinical evaluation. RNA was extracted from whole blood and skin fibroblasts. Gene level quantification was performed using the featureCounts function from Rsubread package, strand specific, paired-end setting. Count matrices were generated using Genomics Features and GenomicAlignments R packages. Outlier analysis was performed using OUTRIDER. Splicing analysis was manually performed using the Sashimi plot function in IGV. RNA-seq analysis provided functional data that helped confirm diagnoses or identify likely diagnoses in ten cases (30%), and a likely resolution of one additional case (37%). Among diagnosed cases, variant resolution was achieved using fibroblast-derived RNA in 3 of 11 cases (27%), blood-derived RNA in 6 of 11 cases (55%), and both tissues in 2 of 11 cases (18%). There are 13 variants identified in 11 cases. The molecular mechanisms for each variant (N=13) assessed were exon skipping (6), intron retention (2), cryptic splice-site activation (1), positional enrichment (2), and multiple splice effects (2). Notably, RNA sequencing enabled resolution on a significantly shorter timescale than traditional workflows, supporting its used as a reflex or concurrent test. This study underscores the value of RNA-seq in unraveling complex diagnostic cases, particularly for intronic variants of uncertain significance. By integrating RNA-seq with genome sequencing, we have enhanced our ability to identify elusive genetic causes of disease. This combined approach proves crucial for resolving diagnostic challenges, establishing RNA-seq and DNA sequencing as indispensable tools in clinical genetics for rare and undiagnosed diseases.

25 - Whole-genome sequencing and analysis of newborns admitted to NICU in the State of Paraná, Brazil.

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Numerous newborns admitted to Neonatal Intensive Care Units (NICUs) suffer from genetic conditions. Rare genetic diseases with early onset often manifest phenotypes linked to high rates of morbidity and mortality. Whole-genome sequencing (WGS) and its analysis have the potential to shorten the diagnostic odyssey, improving quality and life expectancy. Our project engaged eight public hospitals in the state of Paraná, with the aim of demonstrating the feasibility of implementing WGS in the Brazilian Unified Health System (SUS) using the Precision Public Health Center (CSPP) infrastructure. Our main objective is to generate and analyze WGS data from 2,000 newborns displaying indicative phenotypes of genetic diseases, all of whom are admitted to NICUs dedicated exclusively to patients served by the SUS. WGS was carried out using a PCR-free WGS protocol on Illumina Novaseq 6000 sequencer. Raw data and variant calling were processed using the DRAGEN server with GRCh38 as the reference genome sequence. All information regarding participants (sequencing and clinical) was handled and stored using the REDCap platform, with controlled access to each researcher, including a case report, which will be delivered in the shortest possible time to the physician, and following the ACMG guidelines. We started our project by producing and analyzing WGS from ten trios, achieving an average coverage of 36.7x, with the lowest mean coverage at 25.1x. Among these, four cases were conclusive, carrying pathogenic variants in the FLNC, PHOX2B, FANNC, and CHD7 genes. One case presented a partial deletion on chromosome 14, which could not be definitively reported as conclusive due to the lack of CNV validation. Additionally, we identified a maternal case with trisomy of the X chromosome. As anticipated by other efforts worldwide, WGS of newborns admitted to NICUs holds the potential to improve comprehension of genetic diseases, facilitating advancements in the quality of genetic counseling and personalized care, while also mitigating costs to the SUS by addressing preventable complications through targeted treatments. Furthermore, this project will foster the identification of novel genes and genetic variants linked to diseases, offering unprecedented insights into both established Mendelian genetic disorders and previously unknown conditions in the State of Paraná, Brazil. Funding: INOVA Fiocruz Program, Fundação

Araucária, and Ministry of Health of Brazil.

26 - A familiar gene, an unfamiliar story: TCF4 and a new mechanism unearthed after a decade of research

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Purpose of research: TCF4 loss-of-function variants cause Pitt-Hopkins syndrome (PTHS), associating intellectual disability (ID), wide mouth, distinctive facial features, and intermittent hyperventilation followed by apnea. Pathogenic missense variants are primarily clustered within the C-terminal HLH domain required for dimerization and DNA binding. Variants located elsewhere may be associated with mild non-syndromic ID. Methods: Using exome sequencing, we identified de novo missense variants in TCF4 in three individuals who did not show typical PTHS hallmarks. The variants affect ultra-conserved amino acids within or close to the C-terminal HLH domain. In order to study in vivo the role of the de novo TCF4 missense variants, we are exploiting two vertebrate model systems: Xenopus and zebrafish. Furthermore, we are also performing in silico modeling prediction as well as genome-wide DNA methylation, chromatin immuno-precipitation and mRNA sequencing in patient-derived samples. Key results or findings. These individuals showed consistent phenotypic features associating severe cranio-facial features, limb anomalies and growth failure without ID. The main facial characteristics include an abnormal skull shape, wide forehead, sparse eyebrows, epicanthus, anteverted nares, short columella, micrognathia, low-set ears with external ear malformation. All individuals have lacrymal duct obstruction. Limbs malformations include camptodactyly of the fingers and toes, clinodactyly of the 5th finger, syndactyly and nail hypo/dysplasia. In two individuals, growth failure required growth hormone therapy. Neurological examination and psychometric assessment were normal. We firstly confirmed the conservation of the gene expression profile of tcf4 in Xenopus and zebrafish craniofacial development. Preliminary results in Xenopus embryos of the wild-type and the mutated forms of TCF4 indicate an effect on cartilage development. Conclusions and their significance: Overall, we report a new clinical entity associated with suspected gain-of-function variants in TCF4, distinct from PTHS, with facial and limb dysmorphism, growth failure and no ID. The description of other individuals will help to further delineate the phenotypic description.

27 - Biallelic PSTK variants cause generalized selenoprotein deficiency and progressive neurodegeneration

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Selenoproteins, which incorporate the amino acid selenocysteine (Sec), are essential for antioxidant defense, redox regulation, and thyroid hormone metabolism. Their biosynthesis requires a dedicated pathway, including phosphoseryl-tRNA[Ser]Sec kinase (PSTK), which phosphorylates seryl-tRNA[Ser]Sec to enable Sec incorporation at the ribosome. While defects in other pathway components such as SECISBP2, TRU-TCA-1, and SEPSECS have been linked to human disease, no disorder has previously been associated with PSTK. We identified compound heterozygous PSTK variants in a 3-year-old proband who presented with hypotonia, global developmental delay with regression, acquired microcephaly, refractory seizures, sensorineural hearing loss, cortical visual impairment, and progressive encephalopathy with brain atrophy. Biochemical evaluation revealed low circulating selenium, abnormal thyroid hormone levels, absent glutathione peroxidase activity, and undetectable selenoprotein P, consistent with global selenoprotein deficiency. Patient fibroblasts demonstrated absent glutathione peroxidase 4 expression, increased lipid peroxidation, and poor survival unless supplemented with high-dose vitamin E, indicating susceptibility to ferroptosis. These findings establish PSTK deficiency as a novel inborn error of selenoprotein biosynthesis with a pleiotropic and severe neurodegenerative phenotype. The cellular evidence implicates ferroptotic cell death as a key contributor to the pathology. Based on these insights, we are exploring antioxidant-based therapies, including vitamin E and a novel lipoxygenase inhibitor, as potential interventions. This first report of biallelic PSTK variants highlights the essential role of PSTK in selenium homeostasis and underscores the importance of selenoproteins in human neurological function.

28 - Expanding the clinical and genetic spectrum of GLUL-related developmental and epileptic encephalopathy

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The GLUL gene encodes glutamine synthetase (GS), which plays a crucial role in glutamine/glutamate homeostasis. Both loss-of-function and gain-of-function variants of GLUL are known to cause genetic disorders in humans. Biallelic loss-of-function variants cause congenital glutamine deficiency, leading to developmental and epileptic encephalopathy (DEE) in an autosomal recessive manner. In contrast, certain variants of GLUL that lead to the loss of the N-terminal degron exert a gain-of-function effect, causing an autosomal dominant DEE. Only six autosomal recessive cases and ten autosomal dominant cases have been reported to date, and knowledge about GLUL-related DEE remains limited. In this study, we identified three unrelated patients with DEE carrying heterozygous de novo GLUL variants. One patient carried a variant that had been reported previously in two patients (c.-13-2A>G), and the other two patients carried novel candidate variants (c.-13-1G>C and c.604T>C). An alternative splicing event causing loss of the N-degron of GS was confirmed by RNA sequencing in a patient carrying c.-13-1G>C variant. A comparison of our patients with previously reported cases revealed common symptoms, including epilepsy and global developmental delay. However, our patients exhibited additional phenotypes, such as hypertonia, cerebral atrophy, and T2 hyperintensity in deep grey matters, which had not been described in patients with autosomal dominant GLUL-related DEE. The seizure patterns and responses to antiseizure medications varied among patients, reflecting their diverse phenotypic spectrum. Similarly, biochemical analyses of plasma and cerebrospinal fluid showed heterogeneous profiles. We

presented analyses of the GLUL-related DEE with detailed clinical descriptions and identified novel causal variants. Comparative analysis of genotypes and phenotypes revealed the diverse nature of the disease, expanding our knowledge about the genetic and clinical spectrum of GLUL-related DEE.

29 - Germline Variants as Contributors to Focal Cortical Dysplasia: Insights from Whole-Exome Sequencing

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Malformations of cortical development (MCD) arise when one or more fundamental processes of cortical formation -proliferation, migration, or organization- are disrupted. Focal Cortical Dysplasia (FCD), a localized MCD, is among the most frequent causes of drug-resistant epilepsy, often requiring surgical treatment. Diagnosis relies on the integration of clinical and imaging findings, such as MRI, histopathology, and, increasingly, genetic testing. Current literature links FCD primarily to somatic variants in genes encoding components of the mTOR signaling pathway. While the role of somatic variants in driving focal dysplastic lesions is well established, germline variants have also been implicated, either as "first hits" requiring a subsequent somatic event, or as independent contributors to the phenotype.

This study aimed to identify germline variants potentially associated with the FCD phenotype. We analyzed patients who underwent resective surgery for the control of seizures and received both clinical and histopathological confirmation of FCD. DNA from blood samples underwent whole-exome sequencing followed by bioinformatic processing to generate variant call files (VCFs). VCFs were interrogated using the Franklin by Genoox platform. Variants were filtered based on frequency, classification, and confidence, as well as through two gene panels: one encompassing known FCD-related genes and another including epilepsy-associated neurodevelopmental genes. Variants in genes already reported in the literature were prioritized in the initial step, followed by an expanded analysis without gene panel restrictions to explore novel findings. Candidate variants were classified according to ACMG guidelines. We identified 22 germline candidate variants in 18 patients with FCD, including one classified as likely pathogenic and 21 as variants of uncertain significance. Five variants occurred in genes belonging to the mTOR pathway. Although further studies are needed to confirm these variants' pathogenic role, our findings underscore the importance of studying the germline genetic background of patients with FCD, so that the interaction between somatic and germline variants can be further explored. Furthermore, our results highlight the complex and heterogeneous genetic architecture of FCD, suggesting that its etiology may extend beyond somatic variants confined to the mTOR pathway.

30 - Rare and Ultra-Rare Diseases in Ethnic Minorities from Georgia - Time for New Gene Discovery?

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Introduction: Genetic isolates offer invaluable insights into novel disease gene discovery, especially when there is high rate of consanguinity. Georgia is a small country with a population of around 3.7 mln. Historically, several Azerbaijani tribes were settled in the Southern part of Georgia in the 16th century. Today, Azerbaijanis represent the largest ethnic minority in Georgia, and have remained relatively isolated till today. Limited literature exists on rare diseases in this community, and our previous publications highlighted MSMO1, ELOVL1 and Alport syndrome cases. Subjects/methods: Retrospective data collection from hospital records between January 2019 and August 2024 included patients of Azerbaijani descent with homozygous disease-causing variants identified through genetic testing. There were total of 65 patients from 60 families, majority from rural villages in Southern Georgia. Results: Identified variants implicated 35 recessive disease-causing genes, spanning neurodevelopmental, neuromuscular, metabolic, renal, and immunodeficiency conditions. Notably, 25/35 (70 %) of detected alleles represented novel variants. For example, homozygous COL4A3, c.765G>A, p.((=)) was observed in three apparently unrelated families from the same small village Algeti, suggesting a founder effect. Two children from distal cities had homozygous ADA, c.44A>T p.(His15Leu), suggesting increased carrier frequency of ADA variant in this subpopulation. Two newborn siblings died from anotia and Hirschsprung disease where WES/WGS in each of them was negative, suggesting there might be a new yet unknown disease-causing gene. A 5 yo boy with developmental delay and resistant epilepsy was revealed to have homozygous IQSEC3, c.2999del, p.(Lys1000ArgfsTer115), a candidate gene specifically expressed at GABAergic synapses and its loss causes seizures in mice. Conclusions: Our study unveils a cohort of Georgia's ethnic Azerbaijani patients with rare, ultra-rare and potentially novel diseases, shedding light on the unique genetic landscape and founder effects. The presence of a substantial number of novel variants underscores the genetic distinctiveness. Importantly, over 60% of identified diseases are clinically actionable, emphasizing the urgent need for early diagnosis, treatment, and counseling. Ongoing investigations aim to further explore this distinctive genetic tapestry.

31 - TERT Gene Mutation Associated with Combined Immunodeficiency: A Pediatric Case Report

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Objective: To report a pediatric patient presenting with recurrent respiratory infections and combined immunodeficiency associated with a heterozygous variant of the TERT gene, not fitting previously described phenotypes. Methods: Descriptive case report based on review of electronic medical records, caregiver interview, and literature review. Results: A 5-year-old female presented with recurrent respiratory infections, selective IgA deficiency, mild IgG deficiency, persistent leukopenia, and cutaneous lesions. She had a history of failure to thrive, premature graying hair, and learning delay. Lymphocyte immunophenotyping revealed reduced CD4+ T cells. Skin biopsy showed granulomas with caseous necrosis, negative for mycobacteria and fungi, raising suspicion of cellular and humoral immunodeficiency. Whole exome sequencing revealed a heterozygous variant of uncertain significance (VUS) in the TERT gene, not compatible with known dyskeratosis congenita subtypes. At age 6, she developed progressive

headache and hemiplegia. Brain MRI revealed a right parietal mass, initially treated as presumptive CNS tuberculosis without improvement. Partial surgical resection diagnosed primary CNS lymphoma. Despite multiple chemotherapy regimens, the tumor progressed, and the patient developed severe chemotherapy-related complications, including mucositis, acute kidney injury, and persistent bone marrow aplasia. Palliative care was instituted, and she died at age 7. Conclusion: This case illustrates a possible link between TERT gene mutations and combined immunodeficiency, highlighting the importance of genetic evaluation in atypical immunodeficiency presentations. Even without classical dyskeratosis congenita phenotype, TERT variants may predispose to severe infections, immune dysregulation, and malignancies. Early multidisciplinary follow-up is essential for optimizing management and anticipating complications.

32 - The PALB2 truncated variant in a Panamanian patient associated with a high risk of hereditary colorectal cancer

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Introduction: PALB2 is a high-penetrance gene mainly associated with breast, ovarian, pancreatic, and prostate cancer. However, recent evidence suggests an emerging role in hereditary colorectal oncogenesis. We present the case of a 44-year-old Panamanian woman diagnosed with colorectal cancer between the ages of 31 and 35, with a significant family history. The patient was referred for genetic testing to identify germline variants associated with hereditary cancer susceptibility. Methods: Next-generation sequencing (NGS) was performed on peripheral blood DNA using the TruSight Hereditary panel (Illumina®; 113 genes). The variant was interpreted following ACMG/AMP guidelines, using VarSome, Franklin, ClinVar, and CADD, and its frequency was verified in gnomAD and LOVD. The structural impact was assessed by comparing three-dimensional models of the full-length and truncated protein generated with AlphaFold and visualized in PyMOL. Possible transcript degradation was predicted using positional criteria and NMD algorithms (VarSome, Ensembl VEP). Results: A heterozygous nonsense germline variant in PALB2 (c.1675_1676delCAinsTG; p.Gln559Ter) was identified and classified as pathogenic (PVS1, PS4, PM2; CADD=29.5). The truncation resulted in the loss of the C-terminal WD40 domain, essential for interaction with BRCA2, and likely activation of premature termination codon-mediated degradation. Conclusions: This finding supports a severe functional loss of PALB2, consistent with the clinical phenotype and familial aggregation, and reinforces its potential role in predisposition to hereditary colorectal cancer. Its detection has relevant clinical implications for genetic counseling and cancer surveillance in carriers.

33 - A Rare INS Intronic Splicing Variant in a Case of Neonatal Diabetes: Importance of Early Genetic Diagnosis

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Neonatal diabetes mellitus (NDM) is a rare monogenic condition, with a reported prevalence ranging from 1 in 90,000 to 1 in 260,000 live births. It is characterized by severe hyperglycemia during the first year of life and may present in either permanent or transient forms. In transient cases, clinical symptoms regress spontaneously, with or without later recurrence. Due to its low incidence, NDM remains underreported and is frequently misdiagnosed as type 1 diabetes mellitus. One of the principal genetic causes of this condition is variants in the insulin gene (INS). In such cases, neonates present with normal pancreatic morphology; however, insulin production is impaired, leading to hyperglycemia. This form of NDM generally follows an autosomal dominant inheritance pattern, with a high frequency of de novo mutations. Accordingly, molecular genetic testing is essential for accurate diagnosis and for guiding targeted and effective treatment. Here, we describe the case of a Brazilian male patient, currently five years of age, with clinical features consistent with NDM. Whole-exome sequencing was performed using the Illumina NovaSeq X platform, and data were analyzed with a targeted panel comprising seven genes previously associated with monogenic diabetes, using the Franklin by Genoox platform. A heterozygous variant in the INS gene, c.188-31G>A, located in intron 2, was identified. This variant is deposited in dbSNP (rs797045623) and classified as pathogenic in ClinVar. It was absent from the gnomAD and ABraOM population databases and was interpreted by the Franklin platform as likely pathogenic, in accordance with ACMG criteria (PS2; PM2), based on automated analysis. This variant has previously been associated with cases of permanent NDM. The patient received a clinical diagnosis at nine months of age and initiated insulin therapy at 15 months. Regarding family history, the proband's mother was diagnosed with NDM at 11 months of age and has remained on insulin therapy since then. In addition, the proband's maternal aunt was diagnosed at nine months, following episodes of diabetic ketoacidosis, and likewise remains insulin dependent. This case underscores the importance of early molecular diagnosis in patients with NDM, both to ensure optimized disease management and to accurately identify the underlying genetic cause, which directly informs therapeutic decision-making for the patient and their family members.

34 - Assessing the clinical relevance of processed pseudogenes in rare genetic disorders

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Background: Processed pseudogenes (PPGs) are genomic elements generated by retrotransposition of mRNA molecules. They lack introns and often retain poly-A tails, reflecting their origin from reverse-transcribed RNA. Although often considered non-functional, PPGs can have pathogenic consequences - either by disrupting the expression of host genes or by increasing the dosage of their

parental gene. Several disease-associated PPG insertions have been reported, resulting in splicing alterations and host-gene loss of function. However, they can be easily overlooked in routine bioinformatics analyses. Materials and Methods: We analyzed 5,745 whole-genome sequences from probands with suspected Mendelian diseases and their relatives, representing 3,237 families (1,818 mono, 438 duo, 886 trio, 82 quadro, 13 penta). Among these, 1,342 families had no confirmed molecular diagnosis at the time of analysis. WGS data were processed using in-house pipelines.Results: All events classified as multiple intron deletions in Manta CNV calls were considered potential pseudogenes. We detected 48 possible variants that could represent PPGs absent from the GRCh38 reference genome, identified by manual inspection in IGV. After validation, 44 processed pseudogenes were confirmed, including 32 novel ones. Among these, 24 were located within introns of protein-coding genes and 20 in intergenic regions. Most processed pseudogenes had low allele frequency (37 events occurred at $<0.5\%$ in our dataset, with allele counts calculated per individual rather than per family). After mapping the precise integration sites and orientations of PPGs, we analyzed parental genes for triplosensitivity, evaluated haploinsufficiency of host genes, and searched for secondary variants in patient WGS data where biallelic changes could lead to disease. We also used AlphaGenome to predict functional consequences of large insertions at integration sites. However, none provided evidence for unresolved cases, although two novel PPGs may have functional relevance in autosomal recessive disorders. Conclusion: Processed pseudogenes are relatively rare genomic events, and our findings suggest that the proportion of pathogenic PPG insertions is low, at fewer than 1.1 per 1,000 WGS cases (Clopper/Pearson 95% CI: 0/0.11%). Analysis in larger cohorts will be essential to clarify the contribution of PPGs to unsolved Mendelian disease.

35 - Duchenne muscular dystrophy in a female patient

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Background: Duchenne muscular dystrophy (DMD) patients are characterized by muscle weakness, gross motor delay, and elevated serum CK levels. The disease is caused by mutations in the DMD gene located on the X chromosome. DMD most commonly affects males, with a typical age at diagnosis being between 3-5 years. Here we present an ultra-rare manifestation of DMD in a female patient. Patient and methods: The female patient was born as the first child of healthy parents. Motor development was delayed. Unsteady gait and imbalance were described at the age of 3 years, and later poor coordination at age 6. Highly elevated serum CK levels were measured. EMG/ENG (Electromyography/Electroneurography) studies showed a dominant neurogenic pattern with myogenic lesions. At age 13, gradual deterioration of muscle strength was observed with hypotrophic muscles. Serum CK was 1868 U/L. Cytogenetic testing was performed at the age of 7 years. MLPA performed at the age of 8 years showed no copy number variations in the DMD gene. At age 13, targeted next-generation sequencing (NGS) of the DMD gene showed no pathogenic mutations. Finally, whole genome sequencing (WGS) was performed, and the raw data was used for breakpoint analysis. Results: Cytogenetic examination revealed a t(X;10)(p21.1;p12.1) translocation, which turned out to affect the DMD gene with one of the breakpoints located in exon 54 (detected by whole genome sequencing). X chromosome inactivation test revealed skewed X-inactivation (ratio99:1). Muscle histology and dystrophin immunohistochemistry showed severe dystrophic changes and highly reduced dystrophin expression. These results, in accordance with the clinical presentation of the patient led to the diagnosis of DMD. Conclusion: Although in very rare cases, DMD can manifest in female patients as well. In this case, a balanced X-autosome reciprocal translocation disrupts the DMD gene and skewed X-inactivation leads to the manifestation of the DMD phenotype.

36 - First case of NSD2 deletion from Georgia - ending the diagnostic odyssey

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Background: Wolf-Hirschhorn syndrome (WHS) is a one of the most common and well-recognized microdeletion syndromes caused by deletions in 4p16.3 region. The condition is characterized distinct facial features, microcephaly, developmental delay, growth restriction, seizures, and congenital heart defects. Loss-of-function (LOF) variants in NSD2 gene, which lies within this region, is associated with distinct, rather mild phenotype partially overlapping with WHS. Up to date about 30 cases with NSD2 LOF variants have been described in medical literature. Case report: We describe a 13 yo female patient with developmental delay and short stature and chacteristic facial features: microcephaly, bird like face, downturned corners of the mouth, microretrognathia, high palate, misaligned and extra teeth, arched eyebrows, she was born on 36 weeks, with BW - 1700gr, BL - 45cm (SGA). She had mild feeding difficulties at birth which resolved spontaneously after several months. Her motor development was age appropriate, speech was delayed and she still continues to have speech-articulation difficulties. She attends the school and requires special education program. She is not able to read, write or calculate, however her verbal communication skills are very good and she has friendly and cheerful character. There is bilateral renal hypoplasia on renal ultrasound and ECG showed slight aortic and mitral valve insufficiency. Brain MRI did nor reveal any structural anomalies. Her weight, height and head circumference are below 3rd centile. Short term treatment with growth hormone was not successful. Initial karyotyping in 2018 was normal (46,XX). Short read exome sequencing (ES) in 2021 was negative. Long read ES in 2024 revealed deletion of NSD2 gene, confirming the diagnosis of Rauch-Steindl syndrome. Discussion and Conclusion: Current case illustrates the superiority of long read ES over short read ES in patients with unexplained developmental delay, especially

those presenting with dysmorphic features and short stature. Negative ES may be explained by limitations of the performed methodology and urges clinicians to continue seeking the diagnosis in ES-negative patients, whose clinical symptoms remain unexplained. Obtaining the diagnosis is important for reproductive decision-making, as well as optimized health supervision and clinical decision-making.

37 - Whole genome sequencing in immunodeficiencies: case report of twins with Cartilage hair hypoplasia, Omenn syndrome

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Background: Primary immunodeficiency diseases (PIDs) are clinically and genetically heterogeneous disorders caused by variations in ~500 genes. Genetic diagnosis is challenging, whole exome sequencing (WES) diagnostic efficiency is 20-30%. Patients and Methods: Based on clinical symptoms and immunological parameters (lymphadenopathy, eosinophilia, dysmorphic appearance, low nasal bridge, shortening of tubular bones, generalized erythrodermia) the proband and her twin sister were suspected to have Omenn syndrome. First WES analysis and array CGH were performed with negative result. As the final possible test, whole genome sequencing (WGS) was performed in the deceased twin pair and in their parents. Results: WGS identified compound heterozygosity for two previously reported pathogenic variants (LRG_163(t1):n.1-22_1-3dup and LRG_163(t1):n.147G>A) in the nonprotein-coding RMRP gene. Based on the genetic findings and the clinical presentation, the diagnosis of Cartilage-hair hypoplasia with Omenn syndrome was established in the siblings. Conclusion: The diagnostic efficiency of WES in case of primary immunodeficiency is very low (20-30%). In the case of negative WES result, whole genome sequencing can be a significant aid in the establishment of a genetic diagnosis as it covers mitochondrial genome, non-coding regions, promoters, enhancers, introns, regulatory elements and can detect CNVs and other structural variants more readily. In our cases, WES by definition could not identify the causative variations as they are located in a non protein-coding gene. As the genetic background is identified, prenatal or pre-implantation testing are offered.

38 - Social Media and Rare Diseases: experiences of brazilian parents in a qualitative study

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Rare diseases affect approximately 13 million Brazilians and pose significant challenges to families, including limited information, social stigma, caregiving burden, and barriers to accessing healthcare services. Within this context, social media has emerged as a strategic space for support, visibility, and advocacy. This study aimed to explore how social media shapes the lived experiences of parents raising children with rare diseases in Brazil. A qualitative, exploratory design was adopted, involving ten parents (nine mothers and one father) who manage digital profiles dedicated to their journey with rare diseases. Semi-structured interviews were conducted online via Google Meet, recorded, transcribed verbatim, and analyzed using Bardin's Content Analysis. The study followed the ethical principles outlined in Resolution 466/2012, and all participants provided informed consent. Three major thematic categories emerged: (1) social media as a tool for visibility and advocacy, amplifying awareness of rare diseases, giving caregivers a public voice, and influencing policymakers and industry stakeholders; (2) digital platforms as spaces of support, empathy, and belonging, fostering connections among families facing similar challenges and reducing social isolation; and (3) networks as instruments for financial and logistical coping, enabling fundraising campaigns, resource mobilization, and negotiations for access to high-cost therapies. Overall, social media plays a multifaceted role in the daily lives of these families, functioning as a source of emotional, social, and material support. Beyond facilitating the exchange of experiences and building communities of belonging, it serves as a vehicle for political and social mobilization, transforming individual pain into collective action. The findings highlight the need to recognize and integrate these digital practices into public health policies, and to promote further research on their impact on psychosocial support and the strengthening of care for individuals living with rare diseases.

39 - Bridging the Gap: Digital Navigation of Undiagnosed Rare Disease Journeys in Latin America

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Background: Rarus Health is a digital platform co-designed with patients and families to empower those affected by rare diseases across Latin America. Our mission is to support individuals often left behind by traditional healthcare systems including undiagnosed patients and their caregivers who struggle to navigate a complex, fragmented landscape. Objective: To illustrate the lived experience of families seeking answers for undiagnosed rare diseases and identify key systemic and psychosocial gaps, based on a real-world case from Chile. Methods: We present a case study of a family from a remote region of Chile who, after receiving inconclusive next-generation sequencing (NGS) results, reached out via the Rarus Health platform. Leveraging our connections within the Undiagnosed Diseases Network International (UDNI), we facilitated collaboration with the Departments of Pediatrics-Neurology at Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute (Texas Children's Hospital), enabling the family's inclusion in ongoing research. Results: Key findings from this journey include: Persistent stigma: Extended family members remain unaware of the suspected genetic condition, reflecting deep-rooted stigma surrounding genetic diagnoses. Ethical and psychological hurdles: Absence of genetic counseling exacerbates parental guilt, which is sometimes reinforced by healthcare providers. Expectation gap: Families frequently conflate research participation with access to immediate treatment, maintaining hope for a "cure" that may not exist. Quality of life disconnect: Concepts of quality of life and patient empowerment are novel and poorly understood in many emerging-market contexts. Conclusions: Our experience demonstrates that digital platforms like Rarus Health can play a transformative role in supporting families through the uncertain and emotional journey of rare disease diagnosis. By connecting families to international research networks and providing psychosocial support, we address gaps that go far beyond the biomedical. There is an urgent need for integrated digital tools that guide, educate, and empower families addressing not only clinical needs but also stigma, expectations, and emotional well-being.

40 - Diagnosis and management of the patient with complete androgen insensitivity syndrome (CAIS)

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Context: Complete Androgen Insensitivity Syndrome (CAIS), a form of androgen receptor disorder, affects 1 in 20,000 to live births. Individuals with CAIS have normal-appearing external female genitalia, but their gonads are undescended testes. The syndrome results from mutations in the AR gene, leading to defective androgen receptor function. This causes resistance to testosterone and other androgens, while the individual's body develops female secondary sexual characteristics under the influence of estrogen. Case Presentation: A 15-year-old patient, phenotypically female, with primary amenorrhea and sparse pubic and axillary hair. External genitalia of developed female type, labia minora and majora hypoplastic, vagina short 4-5 cm, Breasts are normally developed, Physical development: height 178 cm, weight 61 kg, the build is masculine. Ultrasound examination revealed no uterus or ovaries, A magnetic resonance imaging scan of the pelvic cavity was performed, where the uterus and ovaries could not be seen. Laterally, the distal part of the external iliac vessels showed an irregular-oval-shaped, clearly contoured, moderately contrasting tissue structure measuring 23/11/28.5 mm on the right; 19.5/10.5/24 mm on the left. Hormonal status: elevated testosterone and gonadotropins (FSH, LH), low estrogen and AMH levels, By cytogenetic examination: Karyotype 46 XY, with whole exome sequencing: AR gene NM_000044.6:c.2668G>A , p.Val890Met pathogenic variant was detected. The patient is on estrogen replacement therapy after gonadectomy. Conclusion: Complete Androgen Insensitivity Syndrome (CAIS) is an important condition to consider in the evaluation of primary amenorrhea. Early diagnosis, appropriate management including gonadectomy and estrogen replacement, and psychological support are crucial for ensuring the best outcomes for affected individuals. CAIS emphasizes the need for a multidisciplinary approach, including genetic counseling, endocrinology, gynecology, and mental health support.

41 - A 25-year diagnostic odyssey in Antley-Bixler syndrome type 2: Implications for a treatable disease

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Male twin patient born to consanguineous parents, began his diagnostic odyssey at 15 days of life when referred to medical genetics evaluation due to multiple malformations and dysmorphic features. In the neonatal period, he presented with biventricular dilation, dorsal kyphosis, bone demineralization, cerebral ventricular dilation, forearm diaphyseal thinning, thoracolumbar spina bifida, right-sided hearing loss, congenital clubfoot, short stature (p3%) and metatarsal anomalies. Craniofacial dysmorphisms included mandibular prognathism, maxillary atresia, downward-slanting palpebral fissures, saddle nose with short columella, and malar hypoplasia. Due to perinatal complications requiring transfer, newborn screening was not performed. The patient was followed until 18 years with a presumptive diagnosis of skeletal dysplasia, but molecular confirmation was not accessible. Karyotyping yielded normal results. He underwent multiple orthopedic surgeries, including correction of talocalcaneal synostosis. Following his discharge from the pediatric care at age 18, there was a gap in specialized follow-up. Clinical reassessment was resumed at age 25. Physical examination revealed gynecomastia, shawl scrotum, hyperpigmented macules, rhizomelic shortening, sloped shoulders, flat occiput, use of palatal and maxillary distractors, and reduced testicular volume. Whole exome sequencing identified a pathogenic homozygous variant in the POR gene [c.850G>C p.(Ala284Pro)], establishing the diagnosis of Antley-Bixler syndrome type 2 with genital anomalies and disordered steroidogenesis. The molecular diagnosis ended a 25 years-long journey, enabling proper care and underscoring the critical role of early access to genetic testing in rare disease evaluation. Hormonal evaluation showed markedly elevated adrenal precursors (17-OHP>1500 ng/dL; progesterone 7.08 ng/mL). Corticotropic axis was presumed intact given stable cortisol and absence of adrenal crises. Testosterone was borderline on two occasions and is under evaluation for replacement. This case illustrates a 25-year diagnostic delay due to absent newborn screening and restricted access to molecular testing, resulting in significant morbidity. Early recognition of POR-related Antley-Bixler syndrome, a rare but potentially treatable condition, could have enabled timely hormonal management and improved outcomes.

42 - A novel NSD2 variant associated with Rausch-Steindl syndrome: Insights from a prolonged diagnostic odyssey

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Introduction and objective: The present study reports a case of Rauch-Steindl syndrome (RAUST), a rare genetic disorder with autosomal dominant inheritance characterized by intrauterine and postnatal growth restriction, neuropsychomotor developmental delay, craniofacial dysmorphisms, and distinctive behavioral traits. We describe a RAUST case caused by a novel NSD2 variant, emphasizing diagnostic challenges. Methods: Case report. Results: At two years old, the patient was referred to the clinical genetics service, due to pre- and postnatal growth restriction, language acquisition delays and craniofacial dysmorphisms (micrognathia, ocular hypertelorism), in addition to articular dimples, gait asymmetry, and inward deviation of the left foot She was born by elective cesarean section, from non-consanguineous parents (father aged 37 years and mother aged 40 years), with a family history of attention deficit/Hyperactivity disorder, autism spectrum disorder and giftedness. Given the clinical presentation, Silver-Russell syndrome was initially suspected. Exams were carried out, the urinary organic acid analysis, conventional karyotyping, and methylation testing for Silver-Russell were all normal, microarray demonstrated loss of heterozygosity on chromosome 2. With Silver-Russell syndrome ruled out, whole exome sequencing (WES) was indicated but delayed >1 year due to insurance issues. It detected a heterozygous missense variant (c.2519G>A (p.Gly840Glu) in NSD2 gene, not previously described. In silico predictive tools suggested a deleterious effect. Correlating this information with the patient's phenotype, a high suspicion of RAUST was raised. Therefore, parental genotyping was requested. Due to an initial refusal, the test was only performed three years later. Segregation analysis confirmed a de novo variant, supporting the reclassification as likely pathogenic and establishing diagnosis. Conclusion: After a long diagnostic journey, a novel NSD2 variant was confirmed to be the cause of RAUST in this case. This delay, among other factors, illustrates persistent barriers to timely genetic diagnosis and reinforces that access to diagnostic techniques and parental segregation remains limited and time-consuming, which imposes additional burden on affected families.

43 - Diagnostic Barriers in 22q11.2 Deletion Syndrome: Lessons from a Delayed Case in a Middle-Income Country

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Introduction and Objectives: Timely recognition of DiGeorge syndrome remains challenging in low- and middle-income countries (LMIC) due to phenotypic variability, overlapping features with other disorders, and limited access to molecular diagnostics. Early detection is crucial for guiding targeted interventions and improving outcomes. We present a case illustrating how these barriers contributed to a delayed diagnosis, underscoring the need for sustained clinical suspicion, even in atypical presentations. Methods: We reviewed the medical history of a 22-year-old man diagnosed with 22q11.2 deletion, at age 14. Since birth, he had recurrent respiratory infections, a structural heart defect, persistent neonatal hypocalcemia, and immunological abnormalities, which were misattributed to other syndromes, delaying referral for genetic testing. Results: The patient was born preterm (29 weeks) with cardiopulmonary complications and underwent surgical repair of a double aortic arch at age 3. He exhibited persistent hypocalcemia, hypothyroidism, neurocognitive impairment, recurrent bronchial obstruction, CD4+ lymphopenia, and hypogammaglobulinemia. Initial suspicion for velocardiofacial syndrome at age 9 prompted chromosomal microarray analysis, revealing a heterozygous 2.6 Mb deletion at 22q11.21. Limited awareness among healthcare providers and restricted access to genetic testing contributed to a 14-year diagnostic delay. Conclusions: In LMIC, restricted molecular diagnostic availability and insufficient recognition of syndromic patterns can lead to prolonged diagnostic odysseys in 22q11.2 deletion syndrome. Strengthening clinician awareness and expanding access to genetic testing are essential to reduce delays, optimizing care, and improving prognostic outcomes in rare diseases.

44 - Generalized Lymphadenopathy Caused by a Rare Disease and its Rare Complication - A Case Report of a 4-Year-Old Child

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Background and aims: Generalized lymphadenomegaly can be associated with rare disorders. Our aim was to establish the diagnosis and optimal treatment of a female child, who has been admitted because of progressive generalized lymphadenopathy. Methods: The 4.5-year-old child underwent evaluation since December 2023. Extensive imaging and laboratory tests were performed. Peripheral blood and bone marrow samples were analyzed and followed-up by flow cytometry. Bone marrow, lymph node and skin biopsy samples were examined. Cytogenetic analysis, whole exome sequencing and chromosome fragility test were carried out. Results: Our patient was 2.5-year-old when she presented with generalized lymphadenopathy, followed by skin rashes five months later. Peripheral blood and bone marrow examinations revealed significant T-cell activation (71%) by flow cytometry, monoclonality was not detected and initial immunohistochemical tests did not confirm an immunoblastic background. That time, oral prednisolone therapy was effective, lymph nodes showed regression. In May 2024, she presented with a significant progression, flow cytometry results raised the suspicion of Autoimmune Lymphoproliferative Syndrome and detected 13% CD3+/CD4-/CD8- TCRab+ cells in the bone marrow, with over 99% being TRBC1 negative, indicating clonality. Further diagnostic tests were initiated, and immunosuppression was administered together with intravenous immunoglobulin therapy. This therapy achieved significant regression of lymph node enlargement, and her skin symptoms showed marked improvement. The result of the exome sequencing confirmed the diagnosis of ataxia-telangiectasia (ATM:NM000051.3) c.1564_1565delGA, p.(Glu522Ilefs*43) paternal origin and c.7274delG, p.(Gly2425Valfs*15 maternal origin. Because of clinical progression histopathology was repeated, results confirmed T-cell prolymphocytic lymphoma (T-PLL), nodal infiltrate. Chemotherapy was started according to LBL 2018 protocol with a reduced methotrexate dose. Treatment course was uneventful until May 2025, when she had a severe septicemia and pseudomembranous colitis, caused by Clostridium difficile infection. Conclusions: Ataxia telangiectasia is a rare, autosomal recessive disorder, which predisposes for T-cell neoplasms, including T-PLL. Follow-up of parents, who are heterozygous for ATM mutation is important because of an increased risk of developing certain malignancies.

45 - MYH3, LTBP3, and CNOT1 Gene Variants in a Patient with Skeletal Malformation

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Congenital arthrogryposis is a severe, progressive disorder that can affect the skeletal system. We describe a patient presenting with congenital and hereditary arthrogryposis. The patient exhibits low-set, posteriorly rotated ears; downslanting palpebral fissures; mild facial asymmetry; downturned mouth corners; clinodactyly of the fifth finger; camptodactyly; and bilateral foot deformities. Genetic testing was performed to establish a diagnosis, assess prognosis, and evaluate reproductive risks. Family history revealed muscle atrophy in the patient's mother, maternal uncle, and maternal grandfather. Given the familial pattern and absence of consanguinity, an autosomal dominant inheritance was initially considered. Whole exome sequencing identified three heterozygous variants likely contributing to the phenotype:MYH3 gene: Exon 4, c.245C>G (p.Pro82Arg) - likely pathogenic; , LTBP3 gene: Exon 13, c.1860C>A (p.Cys620*) - likely pathogenic; CNOT1 gene: Intron 45, c.6604-2del - likely pathogenic. The MYH3 variant is presumed to be the primary contributor, associated with Contractures, Pterygia, and Spondylocarpotarsal Fusion Syndrome 1A (OMIM: 178110), inherited in an autosomal dominant manner. The LTBP3 variant may also contribute to the phenotype and is linked to Geleophysic

Dysplasia 3 (OMIM: 617809), another autosomal dominant disorder affecting skeletal development. The CNOT1 variant is associated with CNOT1-Related Disorder (OMIM: 604917), which can involve skeletal abnormalities. However, the patient does not exhibit the neurological or behavioral features typically seen in CNOT1-related conditions. This case highlights a complex genetic etiology underlying congenital arthrogryposis and skeletal malformations, with three heterozygous variants identified in the MYH3, LTBP3, and CNOT1 genes. The MYH3 variant is likely the primary contributor, consistent with an autosomal dominant inheritance pattern. Additional variants in LTBP3 and CNOT1 may modulate the phenotype, although the absence of neurological symptoms suggests limited expression of CNOT1-related features. These findings underscore the importance of comprehensive genetic analysis in diagnosing and understanding hereditary skeletal disorders.

46 - Undiagnosed Case with Distal 16p11.2 Deletion Involving ATXN2L and SH2B1: Expanding the Phenotypic Spectrum

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Background: A significant proportion of children with syndromic neurodevelopmental delay remain undiagnosed. Distal 16p11.2 deletions are rare CNVs linked to developmental delay, macrocephaly, intellectual disability, micro-penis and obesity. ATXN2L has been proposed as a candidate gene for neurodevelopmental delay with macrocephaly, whereas SH2B1 contributes to metabolic dysregulation. Methods: A 6-year-old boy from Panama was evaluated in a genetics clinic for unresolved neurodevelopmental disorder. Clinical assessment included physical examination, anthropometry, neurodevelopmental evaluation, and basic metabolic screening. Genetic testing with whole-exome sequencing in duo (patient and mother) was performed, with CNV analysis. Results: The patient presented global developmental delay, intellectual disability, severe language impairment, macrocephaly (+2 SD), obesity, micro-penis, and behavioral dysregulation with aggressiveness. Laboratory workup (thyroid, electrolytes, acid-base balance, neonatal screening) was normal. Exome CNV analysis revealed a heterozygous 16.05 kb deletion spanning chr16:28.8-28.9 Mb (GRCh38), involving ATXN2L exons 1-12 and multiple genes including SH2B1. The mother was wild-type; paternal sample was unavailable, suggesting a likely de novo event. Discussion: This case remained undiagnosed under standard clinical evaluation. The molecular finding integrates the neurodevelopmental and macrocephalic phenotype (likely driven by ATXN2L haploinsufficiency) with metabolic and endocrine features (obesity, micro-penis, related to SH2B1). Compared with the previously reported single ATXN2L case, our patient broadens the phenotype to include endocrine and behavioral traits, supporting a dual-gene contribution within the distal 16p11.2 locus. Conclusion: We present an undiagnosed case explained by distal 16p11.2 deletion involving ATXN2L and SH2B1, expanding the recognized phenotype to obesity, micro-penis, and aggressive behavior. This highlights the importance of exome-based CNV detection in rare neurodevelopmental disorders and adds to the international effort to characterize undiagnosed patients within UDNI.

47 - Estimation of Direct and Indirect Costs in the Patient Journey for Rare Diseases Using TDABC

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This study aimed to estimate the direct and indirect costs of the care journey for patients with rare diseases, using real-world data from Casa dos Raros (March 2024 to April 2025) and the TDABC (Time-Driven Activity-Based Costing) methodology. The analysis was structured in stages, organizing data from 820 patients registered in the GERCON system (Specialized Consultation Regulation System of SUS). Patients were classified according to the type of consultation: 1,961 multidisciplinary, 18 specialized, and 1,143 genetic consultations. A cost simulation was conducted for consultations across three value scenarios (low, intermediate, and high), based on market research and unit costs per type of care. The average estimated cost per patient for consultations alone was: USD 215.71 (low), USD 295.72 (intermediate), and USD 455.75 (high). When clinical, laboratory, and genetic tests were included, the average total costs per patient reached USD 511.71, USD 875.72, and USD 1,719.75, respectively. The conversion rate the values from Brazilian reais (R$) to US dollars (US$), based on an average exchange rate of R$ 5.00 = US$ 1.00. Service time was measured using average time estimates per stage (registration, reception, consultations, report issuance, and discharge), simulating three total duration scenarios: short (24.4h), medium (30.5h), and long (36.6h). Preliminary analysis revealed significant cost variability among patients, influenced by clinical complexity and diagnostic needs. A direct relationship was observed between the number of consultations, journey duration, and cost intensity. The TDABC approach enabled precise cost detailing, identification of operational bottlenecks, and more efficient planning of specialized services. The proposed model offers a solid foundation for public policy decision-making and resource allocation for rare diseases. Its adaptability allows integration with health technology assessment (HTA) models and cost-effectiveness studies.

48 - Integrating Biologists in Genetic Counseling: an untapped workforce.

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Brazil faces a critical shortage of clinical geneticists, severely limiting access to genetic counseling (GC). This bottleneck prolongs the diagnostic odyssey for families with rare undiagnosed diseases. In contrast, countries like the United States and France utilize highly trained non-physician genetic counselors to expand service reach. This article argues for the formal integration of trained biologists (Master's/PhD level) into GC teams in Brazil, working in partnership with physicians to improve patient access and outcomes. We conducted a narrative review of international models of GC (US, UK, France) and analyzed Brazilian workforce data from the Medical Demography in Brazil, Brazilian Ministry of Health and the Brazilian Society of Medical Genetics (SBGM). Legislation and training pathways for non-physician GC were examined. The US has over 5,000 certified genetic counselors, a recognized profession since the 1980s. France's "conseillers en génétique" perform autonomous counseling. Brazil's normative instruction (Ordinance 81/2009) considers that genetic counseling is the central pillar of health care in clinical genetics and must be guaranteed to all individuals and families at risk of congenital anomaly or genetic disease, but with Medical Genetics having the fewest registered physicians among all specialties, there is a long wait for appointments. The Federal Council of Biology (CFBio) regulates the work of biologists in this area through resolution 692/2024, which defines the activities and requirements for the professional. Biologists with a Master Degree or PhD level in human genetics possess deep genomic knowledge ideal for pre-test counseling and result explanation, and can increase the workforce in the field. The integration of biologists into GC is a feasible and necessary strategy to address Brazil's genetic services gap. This multidisciplinary partnership can reduce waiting times, enhance patient understanding, and allow clinical geneticists to focus on complex diagnostics and management. This model provides a pragmatic solution to a systemic healthcare access problem, aligning Brazil with successful

international practices and ultimately improving care for families with rare diseases.

49 - Mapping Costs in Stiff Person Syndrome: A Patient-Centered Journey Using the ABC Classification Approach

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Objective: To describe the clinical and economic journey of patients diagnosed with Stiff Person Syndrome (SPS), a rare autoimmune neurological disorder, and to identify key cost drivers using the ABC cost classification methodology. Methods: A patient-centered approach was employed using a detailed case report to map the healthcare journey of an individual with SPS. A visual flowchart was developed based on real-life steps experienced by the patient, capturing the clinical and logistical progression from symptom onset to long-term care. The mapped stages included: 1. Unexpected symptoms (mainly cerebellar ataxia); 2. Initial fear and confusion; 3. Symptom investigation; 4. Symptom recognition; 5. Misdiagnosis (e.g., labyrinthitis); 6. Initial medical consultation; 7. First round of exams; 8. New clinical suspicion; 9. Specialist consultations; 10. Advanced diagnostic testing; 11. Confirmed diagnosis; 12. Treatment initiation; 13. Continuous monitoring; 14. Specialized consultations; 15. Multidisciplinary support; 16. Search for potential cure to be tested via participation in clinical trials. A structured questionnaire was applied to estimate direct and indirect costs associated with each stage. The ABC methodology was used to classify costs into: - A - High-cost (e.g., IVIG, immunosuppressants, hospitalization, loss of productivity) - B - Medium-cost (e.g., consultations, rehab therapies, adaptive equipment, legal fees for judicialization of the access to therapies) - C - Low-cost (e.g., transportation, non-specialist visits) Results: The case revealed diagnostic delays of several months and repeated referrals before identification of anti-GAD65 antibodies and clinical confirmation. The most burdensome costs emerged during treatment and follow-up stages, especially in patients requiring chronic immunotherapy and multidisciplinary care. Cognitive, psychiatric, respiratory, loss of mobility, worsening of eyesight and gastrointestinal symptoms also contributed to the complexity and costs of care. Conclusions: Mapping a real SPS case allowed detailed visualization of the clinical journey and associated financial challenges. The ABC framework proved effective in cost stratification and highlights opportunities for earlier diagnosis, integrated care, and targeted public policy in rare disease management.

ractices and ultimately improving care for families with rare diseases.

50 - Rare diseases in Brazil: educational videos as a strategy to train healthcare professionals

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Background: Rare diseases (RDs) represent a heterogeneous group of conditions with prevalence of up to 65 per 100,000 individuals. In Brazil, an estimated 13 million people live with an RD, mostly genetic, with 6,000-8,000 disorders described. The diagnostic process is often lengthy and complex, hindered by the wide variability of signs and symptoms. This scenario highlights the urgency of public health policies that strengthen early detection, train healthcare professionals, and expand access to specialized services within the Brazilian Unified Health System. This project integrates a professional master's program in Brazil, supported for improving practical knowledge and producing outputs for the Unified Health System. Objective: To develop and evaluate educational videos on rare diseases aimed at healthcare professionals. Methods: This methodological study applies a technological production approach guided by the Analysis, Design, Development, Implementation, and Evaluation (ADDIE) framework. Content planning will incorporate the perspectives of rare disease experts, health education specialists, and patients. The subsequent phases of design and production will ensure clear, concise language and accessible audiovisual resources to guarantee usability and self-instruction. The script and the video will be evaluated by 5 to 8 specialists. The project will be submitted to the ethics and research committee. Preliminary results: The literature review highlighted recurrent barriers in RD care, including limited professional awareness, fragmented diagnostic pathways, unequal access to specialized services, and a scarcity of educational materials available in Portuguese. These findings support the selection of core topics to be addressed in the planned videos, such as early recognition of warning signs, integration of genetic knowledge in clinical practice, and the importance of an interdisciplinary team. Raise awareness among healthcare professionals about considering a genetic disease in changes that may be common to other diseases. Expected results: Once produced, the educational videos are expected to enhance knowledge and awareness of RDs among healthcare providers, stimulate continuous learning in genetics and rare diseases, and promote equitable access to information. The final product will be freely available, replicable, and adaptable by other institutions, expanding its reach across Brazil.

51 - 15q11.2 BP1-BP2 Microdeletion Mimicking Prader-Willi Syndrome: A Case from a Middle-Income Country

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Introduction and Objectives: Accurate differentiation between Prader-Willi syndrome (PWS) and phenotypically similar disorders remains a diagnostic challenge, particularly in low- and middle-income countries (LMIC) where access to advanced molecular testing is limited. PWS is classically caused by the loss of paternal gene expression in the 15q11-q13 region and manifests with neonatal hypotonia, feeding difficulties, hyperphagia, obesity, hypogonadism, and cognitive-behavioral impairments. Molecular confirmation is achieved through methylation analysis of SNRPN. However, overlapping syndromes such as 15q11.2 BP1-BP2 microdeletion can mimic certain PWS features, leading to misclassification. We report an adult patient initially diagnosed with PWS whose final genetic evaluation revealed a 15q11.2 BP1-BP2 microdeletion, underscoring the need to refine diagnostic algorithms. Methods: A 29-year-old man with developmental delay, early hypotonia, behavioral disturbances and hypopituitarism was clinically diagnosed with PWS during childhood. Despite this, he maintained a normal body mass index (BMI) and never developed hyperphagia. Standard methylation testing for SNRPN and NDN genes was negative. Due to the atypical clinical course, chromosomal microarray analysis was performed. Results: Genetic testing revealed a homozygous deletion in NIPA1 and a heterozygous deletion in TUBGCP5, both located within the 15q11.2 BP1-BP2

region. These findings confirmed 15q11.2 BP1-BP2 microdeletion syndrome rather than PWS. Clinical reassessment corroborated the absence of hallmark PWS features such as obesity and hyperphagia. The patient and family received targeted genetic counseling focused on prognosis, recurrence risk, and long-term management. Conclusions: This case illustrates how 15q11.2 BP1-BP2 microdeletion syndrome can mimic PWS, particularly when only clinical criteria are considered. In LMIC settings, restricted access to molecular diagnostics increases the likelihood of delayed or inaccurate diagnoses, affecting both medical management and genetic counseling. Expanding diagnostic strategies to include microarray testing when methylation results are negative is essential to avoid misclassification, optimize care, and contribute to a more accurate global understanding of rare neurogenetic disorders.

52 - A case of MIRAGE syndrome in Chile: clinical diagnosis beyond negative exome findings

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Case presentation: This is the case of the second daughter of a non-consanguineous couple. The pregnancy was characterized by early intrauterine growth restriction and oligohydramnios. Due to abnormal fetal monitoring, an emergency cesarean section was performed at 28 weeks, and she was born severely small for gestational age. She developed complications due to her prematurity, anemia, thrombocytopenia and recurrent infections. During her course, she experienced hyponatremia and hypoglycemia, associated with low cortisol and abnormal renin and ACTH studies, leading to a diagnosis of adrenal insufficiency. A gynecological ultrasound highlighted a small retroverted uterus. The myometrium appeared homogeneous, and a linear image suggestive of a 1 mm endometrium was observed. Gonads were not visualized intra-abdominally or in the inguinal canals. Given the suspicion of MIRAGE syndrome, due to the history of prenatal and postnatal growth restriction, developmental delay, thrombocytopenia, anemia, adrenal insufficiency, and recurrent infections, a karyotype was requested. The karyotype showed 46,XY with the presence of female genitalia, confirming the clinical diagnosis of MIRAGE syndrome. Clinical exome sequencing was performed to search for alterations in the SAMD9 gene. Genetic study and discussion: Whole-exome sequencing of peripheral blood and hair follicles identified two SAMD9 variants. The first, c.3040G>A (p.Glu1014Lys), was classified as a VUS based on low population frequency, although in silico predictors and available evidence do not support pathogenicity. The second, c.460C>T (p.Gln154), is a truncating variant considered likely pathogenic, but inconsistent with the gain-of-function mechanism of MIRAGE and observed in our internal database in unrelated phenotypes. Hair follicle analysis was performed to account for clonal elimination of pathogenic alleles in hematopoietic tissue, as previously reported in SAMD9 disorders. No additional variants were detected in other genes explaining the phenotype. Conclusions: This case underscores the critical role of clinical diagnosis in MIRAGE syndrome, where molecular confirmation may be hindered by mechanisms such as clonal elimination and variant detection challenges.

53 - A case of MIRAGE syndrome in Chile: clinical diagnosis beyond negative exome findings

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(Hospital Dr Luis Calvo Mackenna)

Objective: To report a Chilean patient with clinical features consistent with MIRAGE syndrome, in whom the diagnosis could not be genetically confirmed despite comprehensive testing. Case presentation: Second child of a non-consanguineous couple; the mother had treated cervical carcinoma. Pregnancy was high risk due to early intrauterine growth restriction and oligohydramnios. Due to abnormal fetal monitoring, an emergency cesarean section was performed at 28 weeks, and she was born severely small for gestational age. At birth, she presented with apnea requiring positive-pressure ventilation. The neonatal course included respiratory distress evolving to bronchopulmonary dysplasia, grade III intraventricular hemorrhage with parietal infarction, secondary epilepsy, and severe post-hemorrhagic hydrocephalus requiring ventriculoperitoneal shunting, complicated by ventriculitis due to R. planticola and S. epidermidis. Cytopenias included thrombocytopenia and anemia. Endocrine evaluation revealed recurrent hyponatremia and hypoglycemia with hypocortisolism and abnormal renin/ACTH, confirming primary adrenal insufficiency. Pelvic ultrasonography showed a hypoplastic retro-uterine uterus; gonads were not visualized. Testosterone was low and anti-Müllerian hormone markedly reduced, consistent with complete gonadal dysgenesis. Karyotype: 46,XY. Physical examination: hyperpigmented skin, hirsutism, macrocephaly with wide fontanelle, low nasal bridge and female external genitalia without clitoromegaly. The combination of growth restriction, developmental delay, adrenal insufficiency, gonadal dysgenesis, cytopenias, infections, dysmorphic features, and 46,XY karyotype supported MIRAGE diagnosis. Genetic study and discussion: Whole-exome sequencing of periferal blood and hair follicles identified two SAMD9 variants. c.3040G>A (p.Glu1014Lys) was a VUS, extremely rare but without aditional supportive pathogenic evidence. c.460C>T (p.Gln154*) is truncating, classified as likely pathogenic, but inconsistent with the known gain-of-function mechanism and also found in unrelated phenotypes in our database. Hair follicle analysis was performed to assess clonal elimination, previously described in SAMD9 disorders. No additional variants of interest were identified. Conclusions: This case highlights the central role of clinical diagnosis in MIRAGE syndrome, where molecular confirmation may be limited by clonal elimination and variant interpretation challenges.

54 - A Clinical Case Whose Phenotype is Compatible With a Progeroid Syndrome, and the Difficulties in it's Genetic Diagnosis

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This case corresponds to a 3 years old girl, daughter of non-consanguineous healthy parents. She was a full-term newborn, growth was appropriate for gestational age, she was vigorous and without dysmorphia. After 6 months of life weight loss began and diagnosis of chronic malnutrition was made at 9 months of life. She added hyperpigmented lesions scattered on the skin, ankylosis of the 3rd and 4th fingers of both hands, fractures of teeth, hair discoloration and loss of eyebrows and eyelashes. She maintained adequate neuropsychological development. She was admitted to hospital for nutritional repair and thorough study. On physical examination she shows: senile appearance, sharp voice, scarce and light hair, scarce eyebrows and eyelashes, enophthalmos, gray sclera, thin lips, small mouth, fractured lower teeth and pits in the upper ones, tense skin with scattered hyperpigmented lesions involving dorsal region and the face, ankylosis of 4th and 5th fingers of both hands, signs of chronic malnutrition, and ankylosis of both ankles. The following complementary exams were performed: brain magnetic resonance, renal function, liver function test, glycemia, complete blood count, proteinogram, immunoglobulin dosage, dosage of vitamins D and B, thyroid profile, ACTH and basal cortisol quantification, lipid profile, HIV test, and Holter monitoring for 24 hours. Of these significant findings were: discrete eosinophilia, inversion of the A/G ratio, hypergammaglobulinemia of polyclonal appearance, decreased vitamin D, hypertriglyceridemia and decreased variability in the heart rate. There is no etiological or mechanistic orientation to explain the clinical evolution. We proposed as a probable diagnosis a Progeroid syndrome but

no firm clinical oriented diagnosis was evident, so we performed exome sequencing as first evaluation. No pathogenic or likely pathogenic variants related to the phenotype were found. We decided to perform complete genome sequencing but again no candidate variants were detected. Given that the cost of these studies was covered by the family and were made in a commercial laboratory the strategy of trio sequencing could not be proposed, and it was not possible to access the data for reanalysis yet. In summary our patient is a preschool girl with a probable progeroid syndrome, in whom genetic diagnosis was not obtained with the mentioned techniques, this making difficult a correct treatment and family counseling.

55 - A Complex Neurodevelopmental Disorder Characterized by Sensory Processing Disorder, Hypotonia, and Subtle Dysmorphisms.

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Introduction: We report on a 6-year-old male with a complex neurodevelopmental phenotype whose extensive diagnostic evaluation yielded no definitive etiology. This case highlights the clinical challenges in diagnosing children with unique constellations of sensory dysfunction, motor delays, and subtle dysmorphisms that fall outside recognized syndromes. Case Presentation: The patient's history is marked by early-onset hypotonia, motor and speech delays, and feeding difficulties. His pregnancy and birth were uneventful, with normal weight, stature and head circumference. As a baby he had reflux and vomiting, despite anti reflux medication and dietary modifications. Motor development was slightly delayed, having sat without aid at 13 months and walked without support at 18 months; speech development was also slow, but at 2 years 11 months he began to speak well. Core diagnoses include Developmental Coordination Disorder (DCD) and a severe Sensory Processing Disorder (SPD) predominantly affecting the vestibular and proprioceptive systems. His cognitive profile reveals a notable discrepancy between high emotional intelligence (97th percentile) and impaired visuospatial processing (9th percentile), slow processing speed, and executive dysfunction requiring individualized academic support. Physical examination discloses peculiar and triangular facies, different from the rest of the family, relative macrocephaly (weight and stature on 10th centile, head circumference on 50-75th centile), retrognathia, a congenitally absent lower central incisor, a prominent coccyx, and persistent rhinorrhea; there are no pigment abnormalities or asymetries. Comprehensive investigations, including karyotype, SNP-array, metilation studies for Silver-Russell syndrome, whole exome investigation and brain MRI revealed no abnormalities. Conclusion: This case exemplifies the diagnostic odyssey faced by patients with likely neurogenetic disorders that remain unresolved by standard exome sequencing. The patient's unique phenotype suggests a pathogenic mechanism involving variants in non-coding or regulatory regions not captured by current methods. We underscore the necessity of a multidisciplinary management approach and advocate for periodic reanalysis of genomic data as technologies and knowledge advance.

56 - An Ultra-Rare and Unprecedented Case of Syndromic Cognitive and Developmental Delay

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A 26-year-old female patient, born at term by vaginal delivery, presented with an initial APGAR score of 4. The delivery was complicated by a nuchal cord and was followed by early feeding difficulties. The neonate was discharged after three days of hospitalization. Family history was notable for paternal consanguinity, a maternal half sister with syndromic phenotype who died in the neonatal period, and a paternal half brother with delayed motor development. Her neurodevelopmental assessment doctors raised suspicions of autism spectrum disorder, attention-deficit/hyperactivity disorder, dyslexia, and learning disabilities. The patient attended regular school until the age of 9, when she began to show progressive cognitive impairment. By the age of 15, she had confirmed a diagnosis of progressive cognitive decline associated with speech and writing difficulties. Phenotypically, she exhibited syndromic craniofacial features similar to Kabuki syndrome (latter excluded), such as epicanthus inversus, blepharophimosis, long eyelashes, arched eyebrows, retrognathia, thick lips, gingival changes, micrognathia and dental abnormalities. Given the clinical complexity, the patient underwent extensive genetic testing. Conventional karyotyping was normal. CGH array identified 3 heterozygous microduplications. Exome sequencing detected 4 variants of uncertain significance and 2 likely pathogenic: SPTAN (NM_001130438.2, c.5664A>C, p.Glu1888Asp) TOGARAM (NM_001308120.1, c.3549_3553del, p.Lys1186fs), PTEN (NM_001304717.2, c.1408G>T, p.Asp470Tyr), MYMK (NM_001080483.2, c.271C>A, p.Pro91Thr), MED13L (NM_015335.4, c.469G>A, p.Val157Ile) and MYCBP2 (NM_015057.4, c. 11552T>C, p.Ile3851Thr). Among these, MYMK and TOGARAM1 variants were classified as likely pathogenic; however, they do not fully explain the patient's phenotype. Notably, the TOGARAM1, MED13L, and PTEN variants have not been previously reported in the literature. Variant c.1408G>T, p.Asp470Tyr in PTEN involves the substitution of amino acids with distinct biochemical properties, which may affect protein function, although its contribution to the clinical manifestations remains unclear.

57 - Challenges in Molecular Diagnosis of Genodermatoses: Insights from the Argentine CEDIGEA Experience

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Genodermatoses are rare inherited skin disorders, most with prevalences ranging from 1 to 9 per million. They represent a major diagnostic and therapeutic challenge, particularly in pediatrics, where syndromic forms often first manifest in the skin. Our main objective was to implement molecular diagnosis to improve clinical management and enable early recognition. The limited knowledge of the genetic background in our population represents an additional difficulty in assessing the pathogenicity of the variants identified in our patients. The Molecular Diagnostic Laboratory at the Center for Research in Genodermatoses and Epidermolysis Bullosa (CEDIGEA), Faculty of Medicine, University of Buenos Aires, analyzed samples from 1,120 patients in 801 families, referred through a dermatology network across Argentina and parts of Bolivia and Paraguay. Molecular testing was performed by Sanger sequencing and next-generation sequencing (NGS). A molecular diagnosis was established in 815 patients (72.7%), identifying variants in 65 genes across 70 genodermatosis groups. We detected 419 distinct pathogenic/likely pathogenic variants, 176 (42.0%) of them novel. This enabled precise classification and the creation of a variant-ancestry database to optimize diagnostic strategies. Despite this high yield, 291 patients from 253 families remain without a molecular diagnosis, even after NGS testing in

112 of them. The largest unresolved groups correspond to ichthyosis (47), epidermolysis bullosa (32), incontinentia pigmenti (26), and ectodermal dysplasia (21). Smaller groups included palmoplantar keratoderma (16), Ehlers-Danlos syndrome (15), CARD14-associated papulosquamous eruption (14), RASopathies (12), atopic dermatitis (11), and erythrokeratodermias (11). The remaining 86 patients presented with diverse suspected genetic disorders across 34 clinical categories. Molecular diagnosis has transformed the care of patients with genodermatoses in Argentina, reducing diagnostic delays and enabling early interventions. However, a substantial proportion of patients remain undiagnosed, underscoring the need for expanded genomic approaches. With this work, we aim to raise awareness of CEDIGEA and its activities, highlight the large number of unresolved cases, and express our openness to international collaborations to elucidate the causes and mechanisms of these disorders.

58 - Epileptic and Developmental Encephalopathy-57 of Difficult Diagnosis: A Novel Mutation Identified in the KCNT2 Gene

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Epileptic and developmental encephalopathy-57 (EED57) is caused by a heterozygous mutation in the KCNT2 gene on chromosome 1q31. EED57 is characterized by global developmental delay with hypotonia, variable intellectual impairment, and poor or absent language, associated with refractory multifocal seizures in the first days or months of life. The present work describes the case of a Peruvian child with epileptic and developmental encephalopathy-57, who presents a novel heterozygous mutation in the KCNT2 gene. A 7-year-old male patient was referred to the INSN-SB (Lima-Perú) due to difficult-to-manage seizures. He is the only child of a non-consanguineous couple, born by cesarean section due to dysfunctional labor, without complications, at term, and appropriate for gestational age. Since he was 2.5 years old, he showed generalized myoclonic and atonic seizures, refractory to medical treatment. Physical examination revealed poor eye contact, long eyelashes, thick eyebrows, prominent upper lip, hirsutism, delayed psychomotor development, impaired intellectual development, poor speech and language, hypotonia, and autistic features. The EEG was consistent with Lennox-Gastaut syndrome. Genetic diagnosis was performed by NGS using a panel of genes associated with germline epilepsy syndromes. A novel heterozygous mutation c.1554-11T>C chr1:196340581A>G was found in the KCNT2 gene, which, together with the clinical features, was consistent with EED 57. The mutation has not yet been described in patients with EED 57. Our results highlight the importance of considering clinical features, laboratory tests, and family history to establish a diagnosis.

59 - Generalized lipodystrophy under etiological investigation: A pediatric case report

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Lipodystrophies are rare, heterogeneous disorders characterized by partial or generalized loss of adipose tissue, often associated with severe metabolic complications and multisystem involvement. Establishing an etiological diagnosis is essential for personalized management and accurate genetic counseling. We describe a 12-year-old male with generalized lipodystrophy. Growth restriction appeared at age seven, followed by progressive low weight and short stature. He developed severe dyslipidemia (total cholesterol up to 320 mg/dL), requiring continuous simvastatin since age 10. Additional findings included hypogonadism, prediabetes, and encopresis. Malformations and systemic involvement were present, including a horseshoe kidney and right bundle branch block, while neurodevelopment and cognition were preserved. On examination, he showed short stature, low weight, hyperreflexia, reduced skin elasticity, generalized loss of subcutaneous fat, apparent muscle hypertrophy, and thoracic asymmetry. Family history included a brother who died neonatally from pulmonary malformation and several relatives with mild dyslipidemia. No consanguinity was reported. Laboratory evaluation confirmed persistent dyslipidemia and hypogonadism. A targeted hypertriglyceridemia panel was negative, and MLPA for LMNA gene showed no copy number changes. Whole exome sequencing identified a heterozygous de novo frameshift variant in MYOCD (NM_001146312.2: p.Asn125Thrfs*9), absent from population databases, predicted to undergo nonsense-mediated decay, and classified as a variant of uncertain significance. To date, MYOCD has been only associated with congenital megabladder. However, emerging evidence suggests possible roles in smooth muscle biology and lipid metabolism, raising the hypothesis of a novel phenotype. GeneMatcher did not reveal additional cases. This report illustrates the complexity of syndromic lipodystrophy and diagnostic challenges in unresolved presentations. Although a de novo MYOCD variant was identified, its contribution to the phenotype remains uncertain. This underscores that further investigations, together with comprehensive genomic approaches, systematic international data sharing, and cautious genotype-phenotype correlation, will be essential to clarify the underlying etiology and to provide accurate genetic counseling.

60 - Heterozygosity in WNT10A Associated with Congenital Infiltrative Lipomatosis

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Introduction: Infiltrative lipomatoses are rare childhood conditions characterized by abnormal accumulation of adipose tissue with expansive and infiltrative behavior, potentially affecting critical structures and causing chronic pain. The association with variants in the WNT10A gene, which is related to ectodermal dysplasia and rare syndromes, has been scarcely described. Objective: To report a case of congenital infiltrative lipomatosis associated with heterozygosity in WNT10A, presenting with an atypical phenotype and chronic abdominal pain. Methods: A female child, born in 2019, presented with a dorsal mass since birth, later developing non-encapsulated infiltrative fatty lesions in the dorsal, retroperitoneal, and abdominal regions. Multiple imaging exams (ultrasound, CT, MRI) and biopsies were performed, with histopathology compatible with lipoma without atypia. Whole exome sequencing revealed a heterozygous variant in WNT10A. The patient is under multidisciplinary follow-up due to chronic pain, frequent hospitalizations, and continuous need for analgesics. Results: The clinical phenotype includes extensive lipomatous lesions, abdominal pain, and focal muscle hypertrophy, without classic signs of ectodermal dysplasia. The identified WNT10A variant is classified as of uncertain significance but is potentially relevant in the clinical context, suggesting a broader spectrum of associated manifestations. Conclusion: This is a rare case of congenital infiltrative lipomatosis associated with heterozygosity in the WNT10A gene. The finding highlights the importance of genetic investigation in cases with atypical

phenotypes and reinforces the relevance of multidisciplinary follow-up for clinical management and diagnostic clarification.

61 - Hyperammonemic encephalopathy in a male patient from Panama, whose mother and sister have asymptomatic hyperammonemia

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Background: Inborn errors of metabolism are rare causes of intellectual disability and complex neurobehavioral phenotypes. We present a case with biochemical and genomic findings suggestive of a urea cycle disorder but with atypical features and no confirmed diagnosis. Case report: A 17-year-old male presented with global developmental delay, severe intellectual disability, absence of speech, self-injury, and aggressive behavior. Plasma ammonia was persistently elevated (281 μmol/L). Metabolic screening showed increased sarcosine and ethanolamine, abnormal urinary organic acids (arabinose, pyroglutamic, pyruvic and phenylacetic acids elevated; isovaleric acid low), and raised neurotransmitter metabolites (5-HIAA, VMA). The patient's mother and sister were asymptomatic but showed mild hyperammonemia. Whole-exome sequencing revealed a heterozygous variant of uncertain significance (VUS) in NAGS (NM_153006.3:c.1216G>A; p.Asp406Asn), located at 17q21.31. Biallelic mutations in NAGS cause N-acetyl glutamate synthase deficiency (NAGSD), a recessive urea cycle disorder. This missense variant was predicted as damaging by PolyPhen-2, Mutation Taster and LRT, tolerated by SIFT, and showed moderate/uncertain impact by REVEL (0.453) and PrimateAI3D (0.538). Discussion: The phenotype overlaps partially with NAGSD (hyperammonemia, developmental delay, intellectual disability, behavioral issues) but includes atypical features not previously described, such as hypersarcosinemia, elevated ethanolamine, 5-HIAA, and VMA. A single heterozygous variant does not confirm diagnosis, though a second pathogenic allele undetected by exome (deep intronic, structural, or regulatory) remains possible. The finding of asymptomatic relatives with mild hyperammonemia suggests a potential subclinical carrier effect, variable penetrance, or an alternative hereditary mechanism. Further studies such as whole-genome sequencing, RNA analysis, or MLPA are warranted. A therapeutic trial involving sodium benzoate is underway under the supervision of experts. Conclusion: This case illustrates a complex metabolic and neurobehavioral phenotype, partially consistent with NAGSD but currently undiagnosed. The presence of biochemical alterations in asymptomatic relatives highlights the importance of family-based follow-up and the need for broader functional and genomic testing to clarify its molecular basis.

62 - Inconclusive Extensive Genetic Investigation: A Single Center Experience in Brazil

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Rare disorders are often challenging to diagnose, leading to long diagnostic odysseys, misdiagnosis, extensive laboratory testing and burden to the patients and their families. Although the access to Next Generation Sequencing (NGS) improved the diagnostic yield, some patients are still undiagnosed and data from middle/low income countries are scarce. Therefore, we conducted a retrospective analysis to characterize the odyssey of undiagnosed patients who are assisted by a medical genetics team in a brazilian tertiary center. We included patients with non-diagnostic results of Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS), who had at least 1 appointment from January 2024 to July 2025. We identified 17 patients (8 female; 47%), most with congenital-onset symptoms (median age = 0 months), predominantly without familial recurrence (10; 58,8%) and no exposure to teratogens during pregnancy (16; 94,1%). WES was the most common test (16; 94,1%) and took a median of 57 months from the first symptoms to perform the testing (of those, 30 months were to get an appointment with a clinical geneticist). Besides those patients being provided for in a public health service, 5 tests (29,4%) were covered by insurance or by the patients families own expenses and 3 (17,6%) were offered to patients by the State after a judicial order. The central nervous system was the most affected in our cohort - 11 patients suffered from morphological and/or physiological abnormalities, based on the The Human Phenotype Ontology. In 9 cases, at least 1 Variant of Uncertain Significance (VUS) was identified - two patients were misdiagnosed based on misinterpreted VUS by physicians not trained on genetics. In 1 case, a possible diagnosis of a somatic condition was proposed by the pediatric rheumatologist team, but it wasn't possible to provide the proper test. In 10 cases (58,8%), other genetic testing were performed - mostly karyotyping. Therefore, some patients are still undiagnosed even after WES or WGS. In addition, those tests may be inaccessible and can be misinterpreted by non-trained professionals. This can be, at least partially, explained by the long waiting lists, lack of standardized clinical pathway and lack of public policies to disseminate the use of NGS in Brazil.

63 - Infant with Homozygous LRP2 VUS and Donnai-Barrow-like Phenotype: Expanding the Spectrum

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Background: Donnai-Barrow syndrome (DBS) is an autosomal recessive disorder caused by biallelic pathogenic variants in LRP2, encoding the endocytic receptor megalin. DBS typically presents with craniofacial dysmorphism, agenesis of the corpus callosum, developmental delay, epilepsy, neurosensory hearing loss, ocular anomalies, and renal tubular proteinuria. To date, only a limited number of cases have been reported worldwide. Methods: We evaluated a 4-month-old male infant from the Ngäbe-Buglé indigenous group in Panama, presenting with multiple congenital anomalies, global developmental delay, epilepsy, and dysmorphic features. Clinical assessment, neuroimaging, and exome sequencing were performed. Results: Clinical findings included microcephaly (-3 SD), severe growth retardation, hypotonia, seizures, hypertelorism, flat nasal bridge, low-set ears, high-arched palate, micrognathia, and bilateral cryptorchidism. Neurological imaging revealed agenesis of the corpus callosum, hypoplasia of the brainstem and cerebellum, and colpocephaly. Additional anomalies included neurosensory hearing loss, atrial septal defect (sinus venosus type), and generalized hypopigmented macules along Blaschko lines. Exome sequencing identified a homozygous missense variant in LRP2 (c.11890A>G; p.Lys3964Glu), classified as a variant of uncertain significance (VUS) by ACMG criteria (PM2, PP3, BP1). The variant is extremely rare (MAF 0.00000657, gnomAD) and has not been previously reported in association with DBS. A second heterozygous variant in EVI2A/NF1 (c.-2_8del) was also detected but considered incidental. Discussion: The patient's phenotype overlaps with DBS but also includes atypical features not classically reported, namely cutaneous Blaschkoid hypopigmentation, cerebellar and brainstem hypoplasia, and congenital heart disease. These findings suggest a potential expansion of the phenotypic spectrum of LRP2-related disease, although the variant remains classified as a VUS pending further evidence. Conclusion: We

describe an infant with a homozygous VUS in LRP2 presenting with a Donnai-Barrow-like phenotype and novel features, broadening the clinical spectrum associated with LRP2. This case highlights the diagnostic challenges of variants of uncertain significance and underscores the need for international case aggregation to determine their pathogenicity.

64 - Mobile Element Insertion in TTN as a Hidden Cause of Recessive Titinopathy

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Introduction. Recessive titinopathies are rare and clinically heterogeneous neuromuscular disorders. The size and complexity of the TTN gene create substantial diagnostic challenges. Materials and Methods. Written informed consent was obtained. Genomic analyses included a neuromuscular gene panel, whole-genome sequencing (WGS), and long-read Oxford Nanopore Technologies (ONT) sequencing. Data were processed with standard pipelines, with IGV used for visual validation. Results. A 27-year-old male presented with calf asymmetry, pes cavus, and areflexia. Examination showed atrophy of the anterior compartments and left calf. Creatine kinase was elevated (570-1400 U/L). Lower limb muscle MRI revealed selective involvement of the soleus and anterolateral muscles with relative thigh sparing, suggestive of titinopathy. The panel detected two heterozygous TTN variants, c.59588C>A, p.(Ala19863Asp) and c.107850del, p.(Asp35951MetfsTer3). Segregation analysis demonstrated that both variants were inherited from the healthy mother, incompatible with the suspected autosomal recessive inheritance. Therefore, trio WGS was performed as the next diagnostic step. Analysis identified a novel Alu SINE insertion in exon 359 of TTN in trans position with the frameshift variant. ONT sequencing refined the event as a ~280 bp Alu insertion in reverse orientation (NC_000002.12:g.178530060_178530061ins[[NC_000009.12:65653176_65653455;A[(26_32)]]inv;178530043_178530060]), with a 26-32 nt poly-A tail and an 18-nt target-site duplication (NC_000002.12:g.178530043_178530060). The insertion disrupts the reading frame and is predicted to result in truncation or nonsense-mediated decay. Conclusion. A molecular diagnosis of juvenile-onset recessive distal titinopathy was established. This case highlights the value of comprehensive genomic approaches for resolving complex TTN variants and achieving diagnostic certainty in neuromuscular disorders.

65 - Overview of Nutritional Follow-up in Undiagnosed Patients in Brazil: Data from the Brazilian Rare Disease Network

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Introduction: Rare genetic diseases, whether diagnosed or not, pose major challenges for patients and caregivers. Nutritional intervention is essential for managing dysphagia, underweight, obesity, or food selectivity that these patients may present. This support helps prevent complications, promote growth and development, and improve quality of life. Objective: To describe the profile of undiagnosed patients under nutritional follow-up in centers participating in the Brazilian Rare Diseases Network (RARAS). Methods: Descriptive study based on data from the retrospective (2018-2019) and prospective (2020-2025) phases of RARAS. Data were extracted from REDCap and participants included were those with records of nutritional follow-up, undiagnosed or with a suspect diagnosis. Cases with confirmed diagnosis (n=1412), including those later confirmed, were excluded. For patients present in more than one phase, the most recent record was used. Results: Of the 18,605 records in the database, nutritional follow-up was reported in 9.6% of participants. After applying exclusion criteria, 159 (0.8%; n=49 undiagnosed, n=111 suspected diagnosis) were included. Of these, 56.6% were male, with a mean age of 10 years (±11.2) and 51.5% self-identified as mixed race. The majority were born (42.7%) and lived (44.6%) in Northeast Brazil. A total of 84 suspected diagnoses were registered, most frequently Prader-Willi syndrome (n=6), galactosemia (n=5), phenylketonuria (PKU, n=4), Marfan syndrome (n=3), and mitochondrial disorder (n=3). Suspected diagnosis based on abnormal newborn screening (NBS) represented 17.1%. According to Human Phenotype Ontology, main findings were developmental delay (n=22), seizures (n=19), hypotonia (n=12), microcephaly (n=10), and short stature (n=8). The mean age at the beginning of nutritional treatment was 6 years (±11.2). Care was provided mainly by the Brazilian Unified Health System (54%) or paid out-of-pocket (28.9%). Conclusion: Within the suspected diagnoses, PKU and galactosemia have both specific dietary treatments that, when started early, prevent neurological sequelae and improve outcomes. NBS is a strategic tool for early diagnosis and treatment, reinforcing its central role in public health policies. Overall, these findings highlight the importance of integrating nutritional care into multidisciplinary management, ensuring patients benefit from appropriate support even while the diagnosis has not yet been established.

66 - Precision Genetic Diagnosis of Acute Leukemia at Genetics Departament at Instituto Nacional de Salud del Niño San Borja

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Introduction: Acute leukemias account for 30% of cancers in children, with 75% being Acute Lymphoblastic Leukemia (ALL) and 15-25% being Acute Myeloid Leukemia (AML), which has a poorer prognosis. Next-generation sequencing (NGS) detects germline variants with diagnostic, prognostic, and therapeutic implications. Materials and methods: Between 2020 and 2022, a panel of 120 genes was designed with Illumina®, and between 2024 and 2025, a panel of 162 genes was acquired from Sistemas Genómicos. A total of 239 patients (aged between 2 months and 17 years) referred to the INSNSB's Hematology Genetics Department were studied. DNA was extracted from peripheral blood, libraries were prepared, sequencing was performed on MiSeq equipment, and variants were interpreted using the genetic databases OMIM, ClinVar, LOVD, VarSome, and ACMG, followed by VUS. Results: Of the 239 samples analyzed, 23 (9.6%) had pathogenic or likely pathogenic variants; 142 (59.4%) were VUS, and 74 (30.9%) were benign or likely benign variants. In 39.1% of cases, genes associated with

RASpathies (PTPN11, KRAS, NRAS, CBL, KIT, LZTR1) were found, 17.4% were associated with DNA repair genes (ATM, CHEK2, RAD50, PALB2), 13% to mismatch repair genes (MSH2, MSH3), 4.3% to CDKN2A, and 26% to other oncogenes (RET, IFNGR1, MEFV). Conclusions: NGS with customized panels at INSN-SB identified pathogenic variants in 9.6% of patients and a high percentage of VUS, highlighting the need for follow-up for their reclassification. Findings in RASpathway, DNA repair, and hereditary predisposition genes reinforce the value of genetic diagnosis in the prognosis and therapeutic management of pediatric acute leukemias.

67 - Pulmonary valve stenosis and myopathy in a child with 22q11.2 and ORAI1 deletions: Case Report at the Instituto Nacional

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Here, we report the clinical course, phenotype, molecular findings, and diagnostic implications in a 2-year and 3-month-old male with severe congenital pulmonary valve stenosis and progressive neuromuscular involvement. The patient was referred to Genetics after corrective cardiac surgery because of marked motor regression, not being able to speak or move after discharge from PICU. Clinical assessment included motor and language delayed milestones, generalized hypotonia, flaccid quadriparesis with areflexia and independent gait loss. Dysmorphic features: Downslanting palpebral fissures, flat nasal bridge, full lips, low-set ears and micrognathia; additional findings were clinodactyly and bilateral foot anomalies. Complementary studies showed normal serum CPK and brain MRI. Electromyography demonstrated marked denervation with scarce voluntary motor units and early recruitment. Conventional karyotype was 46,XY. Whole-exome sequencing with CNV analysis identified two heterozygous interstitial deletions: a 2.3 Mb deletion at 22q11.21 (Chr22:18906564-21225554), classified as pathogenic and consistent with 22q11.2 deletion syndrome; and a 0.31 kb deletion at 12q24.31 (Chr12:121626742-121627050) involving ORAI1 gene, classified as likely pathogenic and previously associated with tubular aggregate myopathy. The combined genomic findings provide a cohesive explanation for the multisystemic phenotype: the 22q11.2 microdeletion accounts for the congenital cardiac defect and syndromic facial features, while ORAI1 haploinsufficiency accounts for neuromuscular features. Targeted physical therapy, periodic neuromuscular reassessment, periodic cardiac monitoring, immunological evaluation, calcium homeostasis monitoring, and neuropediatric follow-up are recommended. This case highlights the importance of integrating high-resolution CNV detection into exome workflows for complex pediatric phenotypes. Accurate diagnosis enables genetic counseling and personalized treatment. Parental segregation testing is recommended.

68 - Seckel-like phenotype with 19p13.3 and 19q13.42 duplications and a TRIO gene variant of uncertain significance

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Background: Primordial microcephaly and Seckel syndrome are rare genetic disorders characterized by severe growth restriction, bird-like facies, and neurodevelopmental impairment. Despite advances in genomic technologies, many patients remain undiagnosed.Case report: We describe an 8-year-old male, second child of non-consanguineous parents, with intrauterine growth restriction, prematurity (31 weeks), low birth weight (1,130 g), and neonatal ICU admission for congenital pneumonia. A gastrostomy was required at 20 weeks due to swallowing difficulties. Clinical features included severe microcephaly, bird-like facies, prominent ears, epicanthal folds, extreme proportionate short stature, delayed bone age, bilateral flat feet, motor and cognitive delay, and dental anomalies. Additional findings were renal volume reduction, absent scrotal rugae, epilepsy, and hypothyroidism - consistent with a Seckel-like phenotype. Array-CGH detected a 2.3 Mb microduplication at 19p13.3 (81 genes) and a 284 Kb microduplication at 19q13.42 (17 genes). Whole-exome sequencing revealed a heterozygous missense variant of uncertain significance in TRIO (c.6072C>G; p.Asp2024Glu). Microduplications at 19p13.3 have been associated with microcephaly, developmental delay, and nephrotic syndrome, while TRIO variants have been linked to microcephaly and intellectual disability. However, pathogenicity of the identified variant remains unconfirmed. Conclusion: This case illustrates clinical overlap with Seckel syndrome but no definitive molecular diagnosis. The findings highlight the persistent diagnostic uncertainty in rare genetic disorders and reinforce the value of collaborative initiatives such as UDNI for data sharing and VUS reinterpretation.

69 - Sex reversal, gonadal dysgenesis or both entities in a patient with typical male phenotype and 45,X genotype.

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Objective: We aim to describe the follow-up of a child who has typical male phenotype and several complementary tests not considerable enough to determine the etiology of his condition. Methods and results: We present a 12 year old boy who started follow-up with Genetics and Endocrinology at about 3 years old because of a distal hypospadia, short stature and a karyotype test informed 45,X-X,+add(15q?). No internal feminine organs were found and external male organs were normally placed and formed. He underwent several tests to explain the differences between his genotype and phenotype. First of all, a fluorescence in situ hybridization (FISH) test was performed for complete and centromere 15 and Y chromosomes to determine the additional chromosome part informed on karyotype. Both were negative. His clinical exam showed a height of -2.29 SD. Other endocrinological conditions were discharged as laboratory tests were normal. At 5 years old IGFBP3 and IGF1 concentrations were low and his height decreased to -3.6 SD. Later on, SRY gene and Y chromosome metaphase FISH was made as well as an array-comparative genome hybridization (aCGH) test to look for the presence of the causative factors that could explain male phenotype in sexual or autosomal genes respectively. None of them, involved in the internal and external sexual differentiation, were present as the results only re-confirm the X aneuploidy (arr(X)x1). Between 5 and 6 years old, he got a diagnosis for language impairment, intellectual disability and started several therapies. He also started growth hormone (GH) replacement therapy with normalization of laboratory concentrations for IGF1 and IGFBP3 as well as height. Finally, a whole exome sequencing (WES) test was performed and its result was a mosaicism of 45X,46XX with no pathogenic or likely pathogenic variants on autosomal genes involved in sexual differentiation. Conclusions: Nowadays he is 12 years old, his height is between 3-10 SD, he goes to school with teaching support, internal and external genitalia are masculine with normal growth initiation. The etiology for his condition was not yet confirmed as he has normal male phenotype with complete sexual differentiation with little dysmorphic features but his genotype is an X chromosome

aneuploidy one but without any genomic factors found to explain it.

70 - Suspected mitochondrial cytopathy with proximal myopathy: case report with oxidative stress features

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A 14-year-old Cuban female from Marianao was referred for evaluation of a several-month history characterized by proximal muscle weakness in all four limbs, limiting daily activities (e.g., combing hair, climbing stairs, standing up). No gait instability was observed. Muscle strength fluctuated without a clear relationship to exertion. Occasional bilateral distal tremor not associated with specific tasks, with spontaneous improvement. Paresthesias in hands and feet, fronto-orbital headache with nausea and photophobia (especially during sleep and upon awakening). Episodes of non-specific diplopia. Relevant Medical History: Long-standing focal epilepsy, mild intellectual disability. Diagnosed with celiac disease in 2023. Congenital anomalies include bicornuate uterus and spina bifida. Prenatal history includes maternal anemia, preeclampsia, and emergency cesarean section due to fetal distress. Neonatal hypotonia and admission to pediatric ICU. Chronic treatment with antiepileptic drugs. Allergies to penicillin, cephalexin, carbamazepine, and phenytoin. Physical Examination: Proximal muscle strength 4/5 (Daniels scale), positive Gowers- sign, distal lower limb atrophy. Bilateral triceps hyporeflexia; absent biceps, patellar, and Achilles reflexes. No joint range or gross sensory abnormalities. Complementary Studies: Normal EMG and motor evoked potentials. Sensory potentials showed mildly reduced amplitude in lower limb nerves. Brain and cervical MRI: no findings. Abdominal ultrasound: grade I hepatic steatosis. Oxidative stress biomarkers: elevated MDA and PAOP; altered SOD-CAT activity. Serum amino acids: elevated glycine and histidines; decreased valine and lysine; increased Leu/Ala and Arg/Orn ratios. Intermittently elevated blood lactate. Diagnostic Impression: Clinical picture compatible with a suspected mitochondrial cytopathy or inborn metabolic disorder with multisystemic presentation. The combination of proximal weakness, distal atrophy, oxidative dysfunction, and mild electrophysiological changes suggests a predominantly muscular and sensory mitochondrial involvement. We appreciate the opportunity to present this case and kindly request the scientific community's cooperation in defining the etiology and improving the patient's prognosis. Main Diagnostic Hypothesis - MELAS syndrome (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes).

71 - Undiagnosed Case with De Novo SMCHD1 Variant: Expanding the Phenotype Beyond Bosma Arhinia Microphthalmia Syndrome

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Background: Variants in SMCHD1 are classically associated with Bosma arhinia microphthalmia syndrome (BAMS) and facioscapulohumeral muscular dystrophy type 2 (FSHD2). BAMS is characterized by arhinia, ocular malformations, and hypogonadotropic hypogonadism. However, recent reports suggest that SMCHD1 variants may underlie broader and atypical developmental phenotypes, raising the possibility of an expanded disease spectrum. Methods: We evaluated a 2-year-old boy with multiple congenital anomalies and neurodevelopmental delay. Clinical evaluation included neurological, skeletal, craniofacial, and endocrine assessments. Standard metabolic testing, array-CGH, and trio-based whole exome sequencing (WES) were performed. Results: The patient presented global developmental delay, hypotonia, hyporeflexia, agenesis of the corpus callosum with colpocephaly, Blake pouch cyst, craniosynostosis, vertebral anomalies (butterfly vertebra at T5, partial fusion at T2), blue sclerae, cryptorchidism, high-arched palate, low-set ears, and multiple dysmorphic features. Array-CGH was normal. Trio-WES identified a heterozygous de novo splicing variant in SMCHD1 (c.2338+3G>C), absent from gnomAD and parental samples, classified as likely pathogenic. The phenotype did not match BAMS, as the patient had no arhinia or microphthalmia, but included malformations not previously associated with SMCHD1: corpus callosum agenesis, craniosynostosis, vertebral segmentation defects, and blue sclerae. Discussion: This case remained undiagnosed under conventional approaches. The finding suggests a potential expansion of the phenotypic spectrum associated with SMCHD1. While BAMS typically presents with nasal and ocular malformations, this patient displayed central nervous system, skeletal, and craniofacial anomalies without arhinia, indicating pleiotropic roles for SMCHD1 in embryonic development. The involvement of midline brain structures and vertebral anomalies may reflect disrupted epigenetic regulation of developmental pathways. Conclusion: We report an undiagnosed patient with a de novo SMCHD1 variant and multiple congenital anomalies not consistent with classical BAMS. This case supports an expanded SMCHD1-related phenotype that includes agenesis of the corpus callosum, craniosynostosis, and skeletal defects. Further case aggregation is needed to determine whether this represents a novel SMCHD1-associated syndrome.

72 - Undiagnosed syndrome with cleft lip, cleft palate, atrioventricular septal defect, duplication of the hallux

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Female child, 7 years and 3 months old, only child of a consanguineous couple (her paternal grandmother is cousin of her maternal grandfather). She has an undiagnosed syndrome or more than one syndrome. Her phenotype includes: - Bilateral transforaminal cleft lip and palate surgically corrected + facial dimorphisms (elongated face, fan-shaped eyebrows in the medial region, sinofris, flattened nostrils) + cardiopathy (total atrioventricular septal defect surgically corrected) + feet with total duplication of hallux (preaxial polydactyly) + hands with clinodactyly of the 5th fingers and single flexion fold on the 5th finger of the right han;. - Very nasal voice ; - Normal intelligence; - Normal growth and development. The maternal grandmother's brother has unilateral preaxial polydactyly of the hand, with no other malformations. The mother's maternal cousin is 22 years old and was born with lip or labiopalate cleft (?). The mother has 11 siblings, one of whom was born with clubfoot and the others are healthy. A sister of the child's mother has a daughter, who is 10 years old and was born with isolated cleft lip and cleft palate. Her father has 6 healthy siblings. She has an exome without detected variants. The family lives in a rural area. The father became disabled after an accident with cranial trauma.

73 - Wiedemann-Steiner Syndrome - Case Report at the Instituto Nacional de Salud del Niño, San Borja (INSNSB) Lima, Perú

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Wiedemann-Steiner syndrome (WSS) is a rare genetic disorder caused by mutations in the KMT2A gene, which regulates gene expression during development. It is an autosomal dominant condition, mostly due to de novo mutations. Its prevalence is estimated at 1:25,000-40,000 live births, although it may be underestimated due to diagnostic challenges or misclassification with similar syndromes. More than 1,000 cases have been reported worldwide, while in Latin America, only one case has been described in Colombia. Clinical features includes short stature, hypertrichosis, developmental delay, intellectual disability,

hypotonia, among other features. Diagnosis is confirmed by molecular genetic testing identifying pathogenic KMT2A variants, but overlap with Kabuki, Coffin-Siris, Cornelia de Lange, or Rubinstein-Taybi syndromes makes differential diagnosis essential. No specific cure exists; management is multidisciplinary and symptomatic. WSS does not appear to affect life expectancy when adequately managed; functional prognosis depends on the degree of intellectual disability and supportive care.The objective is to describe a case of challenging diagnosis. We report a 21 days old female patient admitted to INSNSB for evaluation of dysmorphic features. She was born at term from a third pregnancy with low birth weight (2,370 g). Father 43 years old, mother 35 years old, non-consanguineous, with two healthy siblings aged 10 and 13 years. Initial evaluation showed broad nasal bridge, short palpebral fissures, epicanthus, anteverted nares, sparse eyebrows, left foot clinodactyly and clubfoot. Pediatric subspecialty assessments identified bilateral hearing loss (tympanometry), craniofacial dysostosis, blepharoptosis, microcephaly, developmental delay (first words at 22m), and limb-predominant hypotonia delaying sitting and walking until 24m. Laboratory results were normal except for, except for hypercalciuria without acidosis, managed with oral hydrochlorothiazide. Imaging revealed right hip dysplasia, left hip subluxation, and horseshoe kidney. Genetic testing: karyotype 46,XX (20); Array CGH: arrGRCh38x2; Whole Exome Sequencing: KMT2A:c.2275_2297del, heterozygous likely pathogenic variant consistent with WSS.The study and follow-up of rare diseases such as WSS are valuable since the phenotype provides the suspicion later correlated with the genotype.

74 - A Novel Case of Neonatal Tonne-Kalscheuer Syndrome Presenting with Atypical Genitalia and a Pathogenic RLIM Mutation

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Objective: To report the clinical, imaging, genetic, and dysmorphic features of a male infant diagnosed with Tonne-Kalscheuer syndrome (TOKAS) due to a pathogenic RLIM variant, highlighting overlapping phenotypes with other syndromes and contributing to the expansion of the TOKAS spectrum. Methods: Prenatal evaluation included obstetric ultrasounds; and postnatal evaluationincluded physical examination, neuroimaging, genetic testing by exome sequencing, and literature review to compare the phenotype with known TOKAS cases. Clinical findings: Male infant, born at term to a healthy primigravida mother. At birth, he presented with hypotonia, hypospadias, partial labioscrotal fusion, and non-palpable gonads bilaterally. Dysmorphic features included broad forehead, short palpebral fissures, telecanthus, anteverted nares, and short columella. Additional anomalies included atrial septal defect (ASD), patent ductus arteriosus (PDA), dilatation of renal calyces, and cystic adenomatoid pulmonary malformation. Neuroimaging revealed corpus callosum dysgenesis and a germinolytic cyst. Genetic results: Whole exome sequencing identified a pathogenic hemizygous variant in RLIM(NM_016120.4):c.1159C>T;p.(Arg387Cys). This missense variant, located in exon 4, is absent in gnomAD, supported by functional studies, and has been reported in multiple affected individuals. In addition, a heterozygous 2.91 Mb duplication at 22q11.21 was detected, classified as pathogenic based on existing ClinVar and OMIM entries. Discussion: The clinical picture is consistent with the evolving phenotype of TOKAS, particularly the presence of disorders of sex development (DSD), central nervous system anomalies and distinct facial dysmorphism. DSD is increasingly recognized in fetal and neonatal presentations of TOKAS, with recent reports describing high rates of genital ambiguity and internal malformations. Although the identified duplication shows some phenotypic overlap with the current case, it is typically associated with a milder clinical presentation. Conclusion: This report documents a neonatal case of TOKAS emphasizes the need to consider TOKAS in the differential diagnosis of congenital DSD and multiorgan anomalies, and the importance of early genetic testing. Genotype-phenotype correlation in RLIM-related conditions remains critical for prognosis and genetic counseling.

75 - A ten-year perspective on Uruguay's genomic program for rare disease diagnosis

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Rare diseases (RD) affect approximately 7% of the global population, yet individual conditions are infrequent, making diagnosis particularly challenging. In Latin America, the underrepresentation of regional populations in global genomic databases further complicates variant interpretation and reduces diagnostic yield. To address this gap, we launched a national medical genomics program to implement next-generation sequencing strategies within the public healthcare system, aiming to shorten the diagnostic odyssey for RD patients while contributing population-specific genomic knowledge. Short-read exome sequencing and whole genome sequencing (WGS) were performed on 400 and 30 patients, respectively. Variant prioritization used established bioinformatics pipelines enhanced with population-specific filters to improve classification accuracy. The overall diagnostic rate was 52%, with WES achieving 57% and WGS 47%. Preliminary stratified yields included 55% for neurological disorders, 60% for cardiovascular conditions, 66% for metabolic diseases, 56% for genetic syndromes, 45% for musculoskeletal abnormalities, and 60% for nephrological conditions. Re-analysis of unresolved cases was undertaken, and the program is expanding to incorporate long-read sequencing and RNA sequencing in a multi-omic framework. A distinctive component of the program is its integration of Uruguay's unique population history. The Indigenous group known as the Charrúas inhabited Uruguay at European contact and, despite genocide, their heritage persists culturally and genetically. Mitochondrial DNA studies have revealed Indigenous ancestry within modern Uruguayans in the past, and our own pilot WGS study of ten Uruguayans with self-declared Charrúa ancestry identified chromosomal segments of Indigenous origin. Specific haplotypes were enriched among these individuals but were rare in other Indigenous groups examined, underscoring the distinctiveness of Charrúa genomic contributions. Uruguay's medical genomics initiative thus not only improves diagnostic rates for rare diseases but also generates valuable insights into the country's complex population history. By integrating NGS technologies, rigorous bioinformatics, and local ancestry considerations, this program demonstrates how regional genomic efforts can enhance precision medicine while preserving and acknowledging Indigenous heritage.

76 - Comprehensive Diagnostic Approach in a Pediatric Patient with Multiple Digestive, Urinary, and Neurological Symptoms

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This abstract presents the diagnostic approach for a 7-year and 7-month-old male patient, who was referred for clinical and genetic re-evaluation due to a complex phenotype including global neurodevelopmental delay with language regression,

currently non-verbal, persistent digestive symptoms and crystalluria with urinary sediment, in the context of previously identified variants of uncertain significance (VUS). The objective is to illustrate the diagnostic challenge in multisystemic cases without a clear genetic cause. A comprehensive clinical evaluation was performed, including a detailed physical examination that revealed minor dysmorphic features. A complete clinical history was obtained, covering perinatal history (premature birth at 34 weeks due to maternal HELLP Syndrome and suspected fetal hypoxia), feeding difficulties and weight gain, and atypical neurological development with global hypotonia. Genetic studies performed included Karyotype, Array-CGH, Exome (initial analysis and re-analysis), and mitochondrial DNA sequencing in two laboratories. The patient was evaluated by multiple specialists, and provided evaluations and paraclinical tests. A family history was collected, noting only a history of renal lithiasis on the maternal side. The patient's phenotype is characterized by significant developmental delay, including loss of language skills. Systemically, there is marked gastrointestinal dysfunction (sucking difficulties, chronic constipation with scybalous stools, SIBO) and genitourinary dysfunction (persistent crystalluria, episodes of urinary retention, dysfunctional voiding with pseudodyssynergia, hypercalciuria). Laboratory analyses show persistent elevations of CPK, AST, and LDH, in addition to elevated fecal calprotectin. Genetic studies identified variants of uncertain significance (VUS) in the CNTNAP2, LYST, and MT-ND2 genes, but no pathogenic or likely pathogenic variants were detected that justified the clinical picture. Despite extensive evaluation, a definitive etiological diagnosis has not been reached. The absence of a definitive genetic diagnosis to date, despite extensive studies, highlights the need for advanced diagnostic approaches in rare diseases to shorten the diagnostic odyssey. A precise diagnosis is essential for targeted medical management and to provide an appropriate prognosis and genetic counseling to the family.

77 - DECIPHERD: Approaching Undiagnosed Rare Diseases in Chile

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Introduction: People living with an undiagnosed rare disease (URD) often face a prolonged and complex diagnostic journey. The unavailability of genetic diagnostic technics as Exome Sequencing (ES) enhances this diagnostic odyssey. The DECIPHERD project aims to address this problematic in Chile by developing local strategies for exome analysis of undiagnosed rare diseases. Methods: Patients from Chile with URD of probable genetic origin manifesting as (1) neurodevelopmental disorder (NDD), (2) multiple congenital anomalies (MCA) or (3) immune system dysfunction (ISD) were included in the study. Clinical Exome Sequencing (CES) and ES was performed using a solo, duo or trio strategy when available. Cases were analyzed locally using SOPHiA DDM or GeneSystems plataforms, and results returned to participants. Findings were classified as "categorical genetic diagnosis" if a Pathogenic or Likely Pathogenic variant in a gene explaining the phenotype was identified, or as "candidate genetic diagnosis" if Variants of Uncertain Significance in genes known to be related to the patient's phenotype were found. Results: 167 patients with URD participated in the study (age range= 0 to 52, mean= 8 years). Among them 74,8% had an NDD, 82,6% MCA, and 23,9% ISD. The most prevalent were the presence of both MCA and NDD (55,7%), followed by MCA alone (12,6%). Affected systems ranged between 2 to 12, with "neurological" (80.8%) and "head and neck" (76.6%) being the most prevalent according to HPO terms classification. We identified a categorical genetic diagnosis in 31.7% (n= 53), and a candidate diagnosis in 15.6% (n= 26). Thus, 47.3% of the cohort (n= 79) received a diagnosis, either categorical or candidate. The CES strategy, achieved a diagnostic rate of 25% (4/16). For CES-negative cases analyzed by ES analysis (solo or trio), diagnostic rate increased to 63,6% (7/11). The presence of a NDD was associated with a higher probability of obtaining a genetic diagnosis (OR= 3.02, p= 0.009). Neither age nor number of affected systems predicted diagnosis likelihood. Conclusions: The DECIPHERD project has demonstrated the utility of ES in ending the diagnostic odyssey for patients with URD and the feasibility of implementation in Chile. The findings indicate a better diagnostic yield for patients with NDD and of ES compared to CES. Follow-up studies of impact of diagnosis are being carried out. Funding: ANID-Chile Fondecyt #1211411, Child Health Foundation, Birmingham, AL, USA.

78 - Dysmorphic Patient with Intellectual Disability and Disorder of Sex Development with 46,XY Karyotype and Normal Exome

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This case presents an adolescent patient with a complex and multisystemic phenotype, with the aim of detailing his diagnostic and therapeutic evolution. The importance of establishing an etiological diagnosis for his management and family counseling is highlighted. A 14-year and 7-month-old male patient with multidisciplinary follow-up since birth. Clinical, dysmorphological, genetic (46,XY karyotype, AR gene sequencing, Array-CGH, ANKRD11 gene sequencing, Exome), audiological (cochlear implant), neurological (CT scan, EEG), cardiological (ECG and Echocardiogram), urological (surgical corrections for ambiguous genitalia and hypospadias), and neuropsychological (IQ and executive function evaluations) assessments were performed. At birth, a disorder of sex development (DSD) with a 46,XY karyotype and incompletely masculinized genitalia was diagnosed, requiring multiple surgeries. The patient exhibits multiple dysmorphic features, including hypertelorism, stellate iris, triangular face, pectus excavatum, and proximally implanted thumb. Anacusis (profound deafness) was documented from 8 months, treated with a cochlear implant in the right ear. At 3 years and 5 months, cognitive inflexibility was noted, progressing to mild to moderate intellectual disability (IQ 68, 2nd percentile) with language and executive function impairments. Other findings include right solitary kidney and hypothyroidism. Despite genetic studies (negative AR and ANKRD11 gene sequencing, Array-CGH with a VUS deletion in 11p14.1-14.2, and Exome), the etiological diagnosis remains unestablished. The patient presents a clinical picture involving a disorder of sex development,

anacusis, solitary kidney, and intellectual disability, along with multiple dysmorphic features. The absence of a definitive etiological diagnosis limits genetic counseling and prognosis. Whole Exome Sequencing (WES) was performed but yielded no clarifying results. A precise etiological diagnosis is crucial to confirm the clinical picture, assess its evolution, establish a prognosis, offer correct family genetic counseling, and evaluate possible specific treatments or follow-ups. Additionally, there is a psychological benefit for the patient's parents who have gone through a distressing journey in search of answers and guidance to optimize their child's care and allow him to develop his full potential.

79 - Early Recognition of PTEN Hamartoma Tumor Syndrome in Childhood: A Case Report

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PTEN is a tumor suppressor gene involved in the PI3K/AKT/mTOR signaling pathway. Pathogenic PTEN variants are associated with a broad clinical spectrum, including cancer predisposition and neurodevelopmental disorders such as autism. Diagnosing PTEN hamartoma tumor syndrome (PHTS) in children is challenging, as characteristic features often emerge later in life. The objective is to emphasize the importance of early diagnosis of PHTS in pediatric patients. A female pediatric patient was evaluated at the Genetics Service, Instituto Nacional de Salud del Niño San Borja, Lima, Peru. Clinical whole genome sequencing (cWGS) was facilitated by Genetic Alliance's iHope program, with testing performed by the New York Genome Center's Clinical laboratory. Neonatal period was notable for jaundice and generalized hypotonia. Developmental delay became evident in the first year of life. Family history suggested possible consanguinity, as paternal grandmother and maternal grandfather shared the same second surname. At the age of 7, the patient presented with marked macrocephaly (+3.83 DS). Dysmorphic features included triangular facies, broad prominent forehead, high anterior hairline, small palpebral fissures with epicanthus, midface hypoplasia, long and shallow philtrum, thin upper lip, dental diastema, and low-set small ears, generalized joint hyperlaxity and hyperpigmented lesions along Blaschko lines on the abdomen and thorax. Brain MRI, metabolic screening abdominal ultrasound, auditory evoked potentials, and EEG were normal. Genetic testing began with karyotyping at age 3 (46,XX) and chromosomal microarray at age 5, neither of which identified any potentially disease-causing pathogenic variants. Microarray analysis revealed 1.19% regions of homozygosity, consistent with a low level of consanguinity (inbreeding coefficient ~1/64). At age 7, trio-based cWGS identified a heterozygous pathogenic PTEN variant: c.200T>C (p.Ile67Thr). Both parents tested negative for this variant, confirming a de novo origin. This case demonstrates that early clinical recognition with concordant broad spectrum testing could have substantially shortened the time to diagnosis. Rapid diagnosis of PHTS in children is essential for improving our understanding of the natural history of the disease in pediatric populations and also enables implementation of surveillance strategies for high-risk cancers and facilitates appropriate interventions for neurodevelopmental manifestations.

80 - Nursing can facilitate management of families with rare genetic diseases

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Purpose: To recognize how nursing professionals participate in the care and management of families with rare genetic diseases. Methods: Systematic scoping review of literature on genomic literacy in nursing remains low with notable heterogeneity across countries. Personal experience with the Undiagnosed Disease Program is notable with nursing professionals in management, clinical, research, and educational roles which leads to the assumption that the same can be done on a larger scale. Key Findings: There is a workforce shortage in medical geneticists that increases the caseload and wait times for patients and their families to be evaluated. Most medical geneticists are white males over age 50 years old practicing in academic medical centers. This lack of diversity among clinical geneticists, and the associated challenges of cultural competence, introduces potential barriers to care that exacerbate existing racial and ethnic health-care disparities. Nurses make up a large percentage of the healthcare team. They need to be ready to assist their patients with finding the appropriate care to manage their conditions. Nurses can become experts for the routine collection of family history risk assessments that is the most accessible and cost-effective way to guide precision health. Nurses are well positioned to lead the implementation of precision health through interprofessional collaboration, community outreach efforts, and coordination of care. Conclusions: There are roles for nursing in genomic research, clinical care, and education that can serve their communities.

81 - Piloting a clinically-integrated undiagnosed disease program: evidence for clinical utility and clinician acceptability

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Despite contemporary genomic testing <50% of patients with suspected monogenic rare disease receive a diagnosis, creating a need for undiagnosed disease programs (UDPs). Integration of UDPs into routine clinical practice remains underexplored. We aimed to pilot an ethics-approved UDP, GeneAdd, at the Sydney Children's Hospitals Network (SCHN), Australia, and assess its clinical utility and clinician acceptability. Patients and families were consented and enrolled into the GeneAdd program, which facilitated recruitment into a range of research projects such as genomic reanalysis, frontier genomic studies (e.g. long read sequencing), functional studies with collaborators (Australia, Asia, Europe and US), and lab-based targeted treatment studies. Following communication of research results, clinicians completed a quantitative measure of utility (C-guide; Hayeems et al. 2020) with results compared to a local non-research clinical genetics cohort. Two SCHN clinician focus groups on the UDP underwent thematic analysis.151 probands from 141 families have been enrolled into GeneAdd. 38% (30/78 probands; 29/74 families) with completed analysis received a diagnosis including 6 structural variants (4 complex) and 6 from non-coding gene variants. Candidate genes were identified in 22% (17/78; 14/74 families). The clinical utility of the GeneAdd cohort was comparable to the clinical cohort (CC) in all domains (overall C-guide score 10.53 vs. 12.19, p >0.05). Utility was highest in diagnosed probands, scoring an average of 18.57 (CC 18.2) compared to 7 in those possibly diagnosed (CC 5.93) and 0.86 in undiagnosed individuals (CC 2.58). Thematic analysis revealed that clinicians considered a UDP "core business" and GeneAdd was deemed highly acceptable as it provided a secure, trusted framework which facilitated broad research pathways. Concerns for sustainability included lack of ongoing dedicated funding for core administration team and limited capacity of clinicians to discuss research with all patients, especially those with low health literacy or where English wasn't their first language, linked to clinical overwhelm. Conclusion: UDPs have high clinical utility when a diagnosis is made. Clinicians value such pathways, viewing them as core business; however, lack of dedicated time and core team funding were key challenges, linked to inequitable access. Future research will examine views of enrolled patients and health services, and how to overcome inequitable access.

82 - Precision Genetic Diagnosis in Children With Congenital Heart Disease at the Instituto Nacional de Salud del Niño San Bo

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Congenital heart disease (CHD) affects between 6-8/1000 live births and is associated with fetal loss during pregnancy. It is the most common cause of death due to structural abnormalities. A large number of genes that encode transcription factors or structural proteins have been described associated with congenital heart diseases linked to syndromic and non-syndromic forms. Our objective was to assess the clinical utility of the commercial Cardio-GeneSGKit panel in routine diagnostic of cardiovascular diseases. The commercial panel consists of 235 genes associated with various heterogeneous cardiovascular diseases, both syndromic and non-syndromic. A total of 327 patients ranging from one month to 17 years old, diagnosed with syndromic and/or isolated congenital heart disease were included in the study. DNA samples were analyzed with the NGS Panel and after data analysis, variant interpretation was performed using population databases, OMIM, ClinVar and LOVD, and classified based on the recommendations of the American College of Medical Genetics and Genomics (ACMG). Pathogenic and likely pathogenic variants accounted for 26.6% (22% and 4.6%, respectively) and variants of uncertain significance for 6.8%. 14.4% of pathogenic or likely pathogenic variants were associated with the rasopathy group. The most frequent variants were those in the NF1 and PTPN11 genes (4.3% each), followed by SOS1 (1.8%), and CBL (1.2%). Other variants such as: FBN1 (1.2%), TGFBR2 (1.2%), JAG1 (0.9%), and TGFBR1, KMT2D, EVC2, DNAH11, and CHD7 (each with 0.6%) were identified. The commercial NGS Cardio-GeneSGKit panel for congenital heart disease applied at the INSN-SB Genetics Service provides timely results with a detection rate similar to that described in the literature, i.e., 1 in every 4 patients. The most frequent detected variants belong to the rasopathy group.

83 - Precision Genetic Diagnosis in Children With Epileptic Syndromes at the Instituto Nacional de Salud del Niño San Borja

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Epilepsy is classified as symptomatic, cryptogenic, or idiopathic. Idiopathic epilepsy is an epilepsy with unknown lesion substrate, probably related to some genetic cause. Mutations have been identified in many genes associated with early childhood epileptic encephalopathy. Here, we present results of an Epilepsy Gene Panel applied in 36 patients with idiopathic epilepsy referred to Genetics from the Neuropediatrics Service. The objective of the study was to determine genetic etiology of pediatric epilepsy conditions in the INSNSB. The panel consisted on 200 genes, and was built based on those genes with sufficient scientific evidence to be associated with genetic epilepsy syndrome. Samples from patients aged between 21 days and 17 years were included in the assay. Sequencing was performed using Sequence-by-Synthesis technology in a Illumina MiSeq sequencer. Clinical interpretation of the variants was performed using the population databases OMIM, ClinVar, LOVD, and VarSome. The recommendations of the American College of Medical Genetics and Genomics (ACMG) were taken into account for variant classification. Pathogenic (P) or Probably Pathogenic (PP) variants were found in 12 cases (34%), variants of uncertain significance (VUS) in 10 cases (28%), and inconclusive in 14 cases (38%). The genetic conditions identified included: epileptic and developmental encephalopathy 42 CACNA1A (6 cases), Bartter syndrome SLC12A1 (3 cases), epileptic and developmental encephalopathy 6B SCN1A (2 cases) and Rett syndrome MECP2 (1 case). Precise genetic diagnosis of epileptic syndromes in pediatric patients allows early treatment, implementation of strategies to monitor neurological development, and provide accurate genetic counseling.

84 - Precision Genetic Diagnosis of Bone Marrow Failure in a Peruvian Pediatric Cohort

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Introduction: Inborn bone marrow failure syndromes (IBMFS) are genetic diseases characterized by deficient production of one or more hematopoietic cell lines. These conditions, caused by pathogenic or likely pathogenic variants, can also affect extramedullary tissues, causing congenital defects and increasing the risk of myelodysplastic syndromes, acute leukemias, and solid tumors. Objectives: To describe the clinical utility of a genetic panel designed for the diagnosis of IBMFS in

pediatric patients. Methodology: The genetics team at the National Institute of Child Health San Borja designed a customized panel that includes 76 genes with sufficient scientific evidence of association with IBMFS. Pediatric patients referred to genetics from the Hematopoietic Progenitor Transplantation Department were included. Clinical characterization included family history and laboratory findings. Genetic analysis comprised DNA extraction from peripheral blood, genomic library preparation, automated sequencing (MiSeq), and bioinformatic analysis. Variant interpretation was performed by medical geneticists, following the guidelines of the American College of Medical Genetics and Genomics (ACMG), with support from databases such as OMIM, ClinVar, LOVD, and Franklin by Genoox. In some cases, family studies allowed for the reclassification of variants. Results: Between 2019 and 2025, 390 samples from patients between 21 days and 17 years of age were analyzed. Pathogenic or likely pathogenic variants were identified in 73 cases (18.72%), variants of uncertain significance (VUS) in 102 (26.15%), and benign or likely benign variants in 215 (55.13%). The most common genetic conditions were: Fanconi anemia (46%), Diamond-Blackfan anemia (24%), Wiskott-Aldrich syndrome (10%), Ataxia Telangiectasia (6%), Dyskeratosis Congenita (6%), Shwachman-Diamond Syndrome (4%), and Li-Fraumeni Syndrome (4%). Conclusions: The genetic panel enabled accurate diagnoses to be made, family genetic counseling to be provided, personalized treatment to be defined, including hematopoietic progenitor transplantation, and cancer prevention follow-up to be carried out in selected cases.

085 - Romanian UDP: Building a National Framework for Rare and Undiagnosed Diseases

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This abstract presents the diagnostic approach for a 7-year and 7-month-old male patient, who was referr

086 - UDN Sweden: Integrating Short- and Long-Read WGS and RNA-seq to diagnose Undiagnosed Children with Rare Syndromes

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Rare diseases, defined in Europe as affecting fewer than 1 in 2000 individuals, affect 350 million people worldwide, including 30 million in Europe and 0.5 million in Sweden. Of over 7000 rare diseases, 70% present in childhood and at least 70% have a genetic basis. Despite advances in massively parallel sequencing, patients face long diagnostic odysseys; up to 60% remain undiagnosed even after whole-genome sequencing (WGS). Barriers include unstructured or incomplete phenotypes, limited functional validation, and difficulty capturing the full spectrum of pathogenic variants. Genomic Medicine Sweden advances nationwide precision medicine by expanding WGS access in healthcare. Within GMS, the Undiagnosed Diseases Network Sweden (UDN Sweden) unites clinicians, nurses, genetic counselors, laboratory scientists, and bioinformaticians to improve diagnoses, develop diagnostic tools, and uncover novel disease mechanisms. This study builds healthcare readiness for emerging genomic technologies and ensures equitable precision diagnostics for children with rare syndromes involving malformations and/or intellectual disability. Since 2023 we enrolled 171 undiagnosed children via the Wilhelm Foundation and Clinical Genetics units at seven Swedish university hospitals. All had prior extensive clinical/genetic testing with no diagnosis. We analysed short-read WGS (singleton/trio/quartet) for SNVs/indels, structural variants, and mobile-element

insertions; performed blood RNA-seq in 138 to detect splicing and expression outliers; and generated PacBio HiFi long-read WGS in 130. To date, analysis of short-read WGS data from Phase 1 has delivered definitive diagnoses for eleven individuals, uncovering pathogenic variants in CKLD5, TUBB4A, SCN2A, TCF4, RNU4-2, TBCE, NF1, U2AF2, and CUX2, as well as duplication of MYT1L and a 16p12.2 microdeletion. Candidate variants have been identified in three additional cases. Data analysis for the full cohort is still ongoing. A national UDN Sweden hackathon has investigated 12 selected cases in a collaborative effort. These preliminary results highlight the promise of an integrated phenotype-genome-transcriptome strategy for resolving complex rare syndromes. By combining short- and long-read WGS with RNA-seq and a coordinated clinical-research network, UDN Sweden aims to increase diagnostic yields, better streamline workflows, and ultimately improve outcomes for children with malformations and/or intellectual disability.

87 - UDPs in South Caucasus Countries: Dream or Reality?

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Background: Based on experience of the countries already implemented National Undiagnosed Diseases Program (NDP) as well as some other countries who have made successful initiatives in this field the importance of such programs today is beyond doubt. UDPs shorten the diagnostic odyssey, improve patient care, accelerate research, and contribute to precision medicine on a global scale. Objective: The aim of our study was to assess the possibility of implementing UDP in South Caucasus countries (Georgia, Armenia, Azerbaijan), at least at the level of some national initiatives. Materials and Methods: As a part of our proposal in the frame of the European Rare Diseases Research Alliance/ERDERA Project (HORIZON-HLTH-2023-DISEASE-07-01), WP24, we elaborated the survey, which was distributed among all stakeholders directly involved in rare diseases (RD) and undiagnosed diseases (UD) related problems (medical professionals, researchers, people living with RD (PLWRD) and their caregivers, healthcare decision makers and others) in the countries mentioned above: 34 respondents in Georgia, 28 in Armenia and 26 in Azerbaijan. The survey covers such areas as health policy; regulation and financing issues; scientific and clinical activities; modern treatment and diagnostics; human resources; PLWRD organizations; education and trainings; international partnership related with RD and UD. Results: Despite significant national differences in healthcare policy issues and respondents assessment of unmet needs in the field of RD and UD, in all three countries the ground for the implementation of UDP has been created, if not at the state level, then at least in the format of individual initiatives, in particular, on the basis of academic institutions or large genetic laboratories. It is worth noting that the level of availability of genetic services is higher in Georgia and Armenia than in Azerbaijan, as well as the degree of involvement of these countries in international scientific and clinical initiatives. At the same time, in Georgia and Azerbaijan, the trend of increasing state support and the formation of adequate policies in the field of RD and UD is more pronounced than in Armenia. Conclusion: The obtained results can help us to develop a unified strategy for the South Caucasus countries on the creation and implementation of the UDP and other initiatives in the field of UD, as well as help in advocacy on UD problem solving among healthcare decision makers.

88 - Unravelling Rare Disorders in a Developing Nation: Insights from the Indian Undiagnosed Diseases Program

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Introduction: Rare diseases often cause prolonged diagnostic odysseys, particularly in resource-limited countries. To address this gap, the Indian Undiagnosed Diseases Program (I-UDP), supported by the Indian Council of Medical Research, was launched as a nationwide initiative to evaluate patients with unexplained genetic conditions using integrated genomic and clinical approaches. Methods: Between February 2021-September 2024, patients fulfilling defined criteria were enrolled across three clinical sites. Clinical phenotyping was performed using a structured proforma. Where available, previously generated genomic data was reanalyzed; otherwise, exome sequencing (ES) or genome sequencing (GS) was undertaken. The bioinformatics pipeline assessed SNVs, indels, CNVs, SVs, repeat expansions, and mobile element insertions.For recurrent variants across families, mutation age estimation was used to explore founder effects.Diagnoses were based on identification of pathogenic/likely pathogenic variants. Results: Of 326 individuals studied(168 males, 152 females, 6 fetuses; age range: prenatal-45 years), family history suggestive of genetic disease was reported in 37/326 families(11%) with consanguinity, in 29(9%) without consanguinity, and in 30(9%) where consanguinity occurred without family history. ES was performed in 226 patients and GS in 100. Overall, 134/326(41%) received a molecular diagnosis.Systematic reanalysis contributed 27% of diagnoses,underscoring its cost-effectiveness. In total, 146 variants were identified across 107 genes, including 120 pathogenic/likely pathogenic and 26 VUS.GS uniquely identified SVs(TUBGCP6, SUMF1), promoter variants(GJC2, TNFRSF1A), triplet repeats(ATXN2), and deep intronic SNVs(SERPINF1). Mobile element insertions were detected in RECQL4 and GNPTAB. A recurrent homozygous 28 bp insertion in LGI4 was found in four unrelated families, with mutation age analysis suggesting a founder effect. GS also enabled diagnosis in non-specific phenotypes(SEPSECS, NOP56), while optical genome mapping confirmed an IDS inversion in a patient with MPS2. Candidate gene variants were also identified, with functional work ongoing. Discussion & Conclusion: The I-UDP marks a milestone in India's rare disease landscape, proving that structured genomic workflows can deliver equitable diagnosis and [illegible]er founder mutations even in resource-limited settings.

89 - Association between Ameridian ancestry and rare undiagnosed disease diagnostic rate in Chile

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Introduction: Investigating underrepresented populations, such as those in South America, is critical for a complete view of human genetic diversity. Most genetic research has historically centered on individuals of European ancestry, creating inequities in how well findings apply across different ethnic backgrounds. In Chile, individuals living with undiagnosed rare diseases (URD) often endure lengthy diagnostic journeys, worsened by restricted access to technologies like exome sequencing (ES). The DECIPHERD initiative was established to strengthen local capacity for exome data analysis, aiming to close this gap for underrepresented groups. This study specifically examined whether Amerindian ancestry is associated with the diagnostic yield achieved through the DECIPHERD project. Methods: We enrolled patients with URD of presumed genetic origin who presented with neurodevelopmental disorders, multiple congenital anomalies, and/or immune dysfunction. Exome sequencing was conducted primarily in duo or trio configurations, and results were interpreted using the Gene Systems platforms (Genebytes or GenebytesX). Diagnoses were categorized as "categorical" (pathogenic/likely pathogenic variants explaining the phenotype) or "candidate" (variants of uncertain significance in genes known to be linked with the clinical presentation). For ancestry estimation, patient VCF files were consolidated and merged with reference panels from the 1000 Genomes Project Phase 3, including European, African, and Admixed American samples (<90% admixture). We applied ADMIXTURE with $k = 3$ to calculate global ancestry components and subsequently compared Amerindian proportions between diagnosed and undiagnosed patients. Results: Sixty-seven patients with URD participated (age median 6 years, range 0.3-27). The average $\pm$ s.d. proportion of Amerindian ancestry in participants with a diagnosis was 0.48 ± 0.04, and without diagnosis was 0.47 ± 0.04. We found no statistically significant differences between the groups, p-value $= 0.44$. Conclusions: No statistically significant differences in Amerindian ancestry proportions were observed between patients who received a diagnosis and those who did not, suggesting that ancestry was not a determining factor in the diagnostic yield of the DECIPHERD project. Funding: ANID-Chile Fondecyt #1211411, Child Health Foundation, Birmingham, AL, USA.

90 - Atypical presentation of immune-mediated necrotizing myopathy in pediatric patients

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Introduction: Historically, pediatric inflammatory myopathies (IIMs) were classified as dermatomyositis or polymyositis. More recently, the classification has evolved into antibody-specific subtypes, reflecting distinct clinical and pathological features. Juvenile dermatomyositis remains the most common entity, whereas immune-mediated necrotizing myopathies (IMNM), including anti-SRP, anti-HMGCR, and seronegative subtypes, are exceedingly rare in children. Diagnostic and treatment guidelines remain limited due to rarity and insufficient evidence. Method: We describe a case series of three pediatric patients with IMNM at Seoul National University Children's Hospital. Clinical data, laboratory studies including CK, aldolase, myositis-specific antibodies, muscle MRI, and biopsy findings were reviewed when available. Treatment approaches and outcomes were also collected. Result: Two patients were positive for anti-SRP antibodies and one for anti-HMGCR antibodies. Initial clinical impressions included Duchenne muscular dystrophy (due to subacute regression of gross motor function), limb-girdle muscular dystrophy (due to slowly progressive chronic course), and metabolic myopathy (due to subtle weakness following rhabdomyolysis). Genetic panels for dystrophy and metabolic myopathies were negative in all cases. Skeletal MRI of lower extremities demonstrated variable muscle edema, fatty replacement, and muscle atrophy. Muscle biopsy revealed fiber size variation with degenerating and regenerating fibers, but minimal lymphocytic infiltration, consistent with IMNM pathology. Conclusion: Pediatric IMNM is rare and often mimics genetic myopathies, leading to diagnostic delay. Clinicians should consider IMNM in cases with unexplained myopathy and negative genetic results, as early recognition is crucial-immunotherapy can provide effective, potentially disease-modifying treatment.

91 - Beyond Diagnosis: Standard of Care for Adult Duchenne Muscular Dystrophy (DMD) Patients in Wales, the United Kingdom(UK)

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Duchenne Muscular Dystrophy (DMD) is a rare progressive, debilitating and fatal neuromuscular disorder caused by variants in the DMD gene. With increase in life expectancy, there are growing numbers of adults with DMD living well into their fourth decade, whose complex medical needs have not been addressed in previous international standards of care to date. Our project evaluated adult DMD care in Wales, the UK, by benchmarking against the 2021 Adult North Star Network guidelines, with the aim to improve their care holistically. We want to share our good practice (and areas needing improvement) to wider international audience as most of the recommended medications and strategies can easily be implemented, even in resources limited settings such as low- and middle-income countries. Data was collected retrospectively between June 2023-July 2024 from neuromuscular centres across Wales. All adult DMD patients ($\geq$14 years)

registered with 3 neuromuscular centres (South, West and North) were included (N=56). Results were scrutinised by stakeholders, neuromuscular team members, neurologists, public health and data experts and service user representatives. Findings show strengths in access to respiratory (88%) and physiotherapy care (85%), except in North Wales. Psychological support was identified as a critical unmet need across all regions, with 62% lacking access. Region specific top challenges include limited respite care in South/Southeast Wales (84% without access), insufficient cardiology follow-up in West Wales (42% require follow up), and the absence of clinical care coordination in North Wales (100%). Interestingly, most paediatric patients in South Wales get protected respite slots until they transition into adult care. In West Wales, appropriate pharmacotherapies with ACEI, beta blockers and mineralocorticoid inhibitors are initiated in most patients, but they were not followed up regularly by cardiac imaging or annual cardiologist follow up. The neuromuscular care co-ordinator in North Wales does not have medical background and has no medical team directly attached to them. These findings highlight critical regional disparities in adult Welsh DMD care and emphasize the need for targeted improvements in psychological, cardiac, and coordinated clinical services. Strengthening the care pathways in these areas is vital for achieving equity for DMD patients in Wales.

92 - Education in Rares Undiagnosed Diseases

Rosa Andrea Pardo Vargas *(Universidad de Chile)*

The plight of people living with a rare disease is a critical unmet need of patients in healthcare. Patients living with a rare disease wait four to ten years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection. Almost 70% of undiagnosed diseases (UNDI) have a genetic cause. The vast amount of genomic information obtained over the last decade has provided crucial insights into various health issues, which have significantly improved diagnosis and treatment for many diseases. Thus, Knowledge and skills about genomics, and the methodology and implementation of valuable tools to increase the student interest and engagement and educating undergraduate and graduate students in genomics topics. Some successful didactic techniques reported to teaching genomics are introductory courses which taught genomic principles through hands-on experience, hands-on research experience, and personal genomics kits to analysis personal genomics or microbiome data Genomics is becoming an integral part of medicine and health workers must be prepared to understand and communicate complex genomic information to patients and the public in a simple and accurate manner. Until today there are many challenges of genomic education, these include gap in knowledge among healthcare professionals, cost, time commitment, competing priorities, complexity of subject material, misconceptions from media, genomic science still developing, making implementation challenging, lack of infrastructure or resources for professional development. We are called to work together to improve globally the level of knowledge on genomics to reduce the number of undiagnosed diseases and make better the prognosis of people with them.

93 - From "Negative" to Diagnostic: The Value of Manual NGS Data Inspection

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Recessive dystrophic epidermolysis bullosa (RDEB) is a rare inherited skin disorder characterized by skin fragility, blistering, and variable extracutaneous manifestations. Molecular confirmation is essential for accurate diagnosis, prognosis, and genetic counseling, but it can be particularly challenging in cases with atypical or incomplete findings. At our center, we have diagnosed numerous patients with RDEB through Sanger sequencing and next-generation sequencing (NGS), and we have built a database including phenotype and ancestry information to help trace variant origins and support diagnosis. Here, we report two complex cases that illustrate the limitations of automated analyses and highlight the importance of in-depth data review. The first case is a newborn girl in whom NGS revealed an intronic splice-site variant, (COL7A1 NM_000094.3; c.1507+2T>C), also present in her mother. No additional pathogenic variants or variants of uncertain significance (VUS) were detected, and CNV analysis did not reveal any relevant copy number changes. The second case is a 40-year-old man presenting with clear clinical features of RDEB but without a confirmatory molecular diagnosis. NGS identified a frequent variant in central Argentina, detected in his mother as well. As in the first case, no second pathogenic or uncertain variant was detected by standard automated analysis. Given the strong clinical suspicion, we performed a detailed manual inspection of the BAM files, which revealed a set of discordant reads suggestive of a structural alteration. This led to the identification of a novel 884 bp duplication of exons 43 to 46 of COL7A1 (DUP:Chr3:48582285-48583169 (GRCh38)), subsequently confirmed by Sanger sequencing. This duplication has not been previously reported in the literature, but based on its predicted effect and low population frequency, it can be classified as likely pathogenic. After this finding, we re-analyzed other patients carrying only one identified variant and confirmed that the same duplication was present in the second case as well. These cases underscore that in patients with strong clinical suspicion, a "negative" automated NGS report may mask underlying complex variants. Manual inspection of raw sequencing data can uncover clinically relevant alterations that standard pipelines may miss, ultimately improving diagnostic yield in rare diseases such as DEB.

94 - Impact of Exome Reanalysis on the Diagnosis and Counseling of Kenny-Caffey Syndrome Type II: A Case Report

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Objective: Our aim is to describe the clinical, genetic, and diagnostic approach of a child with syndromic short stature, ultimately diagnosed with Kenny-Caffey Syndrome type II.

Methods and Results: We present the case of a 3-year-old boy with prenatal follow-up due to longitudinal shortening of limbs (35 gestacional weeks measure), with initial suspicion of achondroplasia. There was no relevant family history. He was born by cesarean section at term, weight and head circumference appropiatte for gestational age and length of 46.5 cm. Also small atrial septal defect, and laryngomalacia. Apgar scores: 9/10. Physical examination revealed severe global shortening of upper and lower limbs with rhizo-mesomelic pattern, midface hypoplasia, and prominent forehead. At 15 days of life, he had two tonic movement episodes on left hemibody, assumed as seizures, and started phenobarbital treatment. Laboratory tests showed hypocalcemia, leading to a diagnosis of hypoparathyroidism. Subsequently, hepatic, ophthalmological, dental, and ENT involvement were documented. Velocardiofacial syndrome was ruled out (22q11.2 FISH negative), clinical exome sequencing was performed (Nov 2023), with negative results. Given the patient's clinical progression, exome reanalysis was requested (May 2024) based on new HPO terms, revealing a heterozygous VUS in the FAM111A gene. Based on clinical, biochemical, radiological and molecular evidence, a diagnosis of autosomal dominant Kenny-Caffey Syndrome type II was

established. Conclusion: This case highlights the importance of longitudinal clinical follow-up, early suspicion of syndromic short stature, and the value of exome reanalysis in establishing a definitive diagnosis in rare genetic disorders. Performing reanalysis guided by clinical progression has a major impact, as a confirmed diagnosis not only influences on the counseling, regarding the patient's prognosis and clinical course, but also significantly affects reproductive counseling for the couple.

95 - Rare disease research in Africa: an opportunity to uncover novel disease-causing genes

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Although rare diseases affect individually a small number of people, taken together they afflict millions of people worldwide. They are estimated to be about 8,000 and every year, several rare diseases are discovered, due to the advances in genetic technology. Yet, more than 3,000 clinically characterized mendelian phenotypes are with no molecular diagnosis and less than a third of human genes are linked to disease. While populations with European and Asian origin were widely studied, less than <2% of all genetic studies done worldwide are performed in populations with African origin. Yet, the few genetic studies done in populations with African origin have found a lots of diversity when compared to Eurasian populations. This is reflected in our results shown below. We investigated 850 families from Mali and some neighboring countries with presumably rare diseases involving different organ systems. After giving consent, participants were clinically evaluated carefully and DNA was extracted from peripheral blood for genetic analyses including WES, WGS and long-read WGS sequencing. In silico tools, ACMG criteria, CRISPRcas9 in Xenopus model and cell studies were used to confirm pathogenicity. A molecular diagnosis was reached in about 200 families. Of these, 80 variants in disease- causing genes were not previously reported and 20 were in genes not previously linked to any disease or the phenotypes studied. While five of the putative novel genes were confirmed in cell and/or animal models, in silico analyses have shown variant deleteriousness in all the remaining candidate genes. Our study confirmed the genetic diversity of the African population and further highlights the need to extend research on rare diseases to diverse populations to delineate the underlying causes in many of them. The discovery of disease-causing novel variants and genes may further our understanding of the disease mechanism and trigger the development of new therapeutic perspectives for rare diseases.

96 - The role of ancestry-aware filtering in rare disease variant interpretation

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Next-generation sequencing (NGS) has become an essential tool in the diagnosis of rare diseases. Despite major advances in sequencing technology and bioinformatics approaches, the interpretation of variants remains a major challenge. An important factor is the reliance on allele frequency information from public reference databases such as 1000 Genomes, ExAC, and even the most recent gnomAD release. These databases contain valuable data, however, their sample composition is strongly biased toward individuals of European ancestry. Our objective is to highlight how this affects diagnostics and to suggest ancestry-aware filtering as a practical adjustment. We compared two approaches for variant filtering in rare disease diagnostics. In the first, allele frequency thresholds were applied globally across all populations, as in standard workflows. In the second, we applied ancestry-aware filtering by evaluating allele frequencies within population subgroups. The impact of these approaches was then assessed by examining how variants would be classified under each method. Standard practice can lead to misclassification. Variants may appear rare in European cohorts but can be common in other groups, resulting in false pathogenic or false benign calls. Furthermore, variants missing from reference datasets may be labeled as novel even when frequent in underrepresented populations. Ancestry-aware filtering, where allele frequencies are evaluated within population subgroups, could help address this problem. Although the concept is well known mostly in population genetics, it has received little attention in rare disease diagnostics so far. We think that modest changes to existing workflows, such as using subpopulation frequencies instead of only global cutoffs, can improve diagnostic accuracy and equity. Making better use of available data is a realistic step toward more inclusive and reliable rare disease diagnostics.

97 - Therapeutic Matching

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The Undiagnosed Diseases Network (UDN) in the United States enrolls study participants with complex medical problems that elude diagnosis despite extensive medical evaluation. Participants who receive a rare disease diagnosis are often frustrated by the lack of available therapeutic options. The UDN Therapeutic Matching Committee (TMC) was formed to explore the challenges associated with identifying and connecting participants with therapeutic research opportunities. The TMC met with study participants, novel therapy researchers and other experts to expand its understanding of therapeutic options. Selected cases from the UDN were explored during multidisciplinary teleconferences that included afffected families, subject matter experts, clinicians and therapy researchers. This presentation will outline lessons learned and explore some of the principal challenges facing patients and providers faced with this challenge.

98 - Three Cases of Common Variable Immunodeficiency Type 2 in a Colombian Family With Different Clinical Presentation

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Aim. To describe the cases of a 50-year-old mother (ARA) and her two daughters (ALHA, 29 years old and LMHA, 24 years old), with different clinical presentations and a common diagnosis of common variable immunodeficiency type 2. Methods. Clinical assessments were carried out by different medical specialties. Routine laboratory assessments and immunoglobulin levels were determined. Acylcarnitines were measured in blood by tandem mass spectrometry, amino acids by HPLC, and organic acids in urine by GC-MS. Whole exome sequencing was performed (CentoXome GOLD®). Results. ARA presents axial pain, oppressive pain in the chest, fatigue, lichen planus in the neck, groin and armpits, paresthesias in the upper and lower limbs, esclerosis of the aortic arch, dorsal spondylosis and multilevel degenerative disc disease, lumbar spondylosis with facet osteoarthritis from L5 to S1. Bilateral apical basal emphysematous bullae, bilateral basal fibroscar tracts with isolated cylindrical bronchiectasis, left posterior basal granuloma, osteoarthritis, and tenosynovitis of the right knee. LAHA presents bilateral vesicoureteral reflux, asthenia, adynamia, generalized myalgias and arthralgias, and repeated pneumonia, bilateral suprapatellar bursistis. LMHA presents hypotension, syncope, myoclonic epilepsy, constant dizziness, stabbing chest pain unrelated to physical activity, severe hypotension with concomitant vomiting. All laboratory paraclinics were normal in the 3 cases. In the 3 patients, two heterozygous variants were identified in the TNFRSF-13B gene: c.121G>C p.(Asp41His) and c.298dup p.(Cys100Leufs*6), confirmed by the Sanger sequencing method, compatible with a dominant form of common variable immunodeficiency type 2. Conclusions. Common variable immunodeficiency encompasses a heterogeneous group of diseases characterized by hypogammaglobulinemia of unknown cause, inability to produce specific antibodies after immunization, and susceptibility to bacterial infections (Orphanet-ORPHA:15-72). The variants in question have been reported by Salzer 2009. (PMID: 18981294), who detected them in a family where one of the members had common variable immunodeficiency. The 2 variants were located on the same allele (that is, in cis), thus forming a haplotype. Two heterozygous relatives showed no symptoms of disease, indicating that the variant is associated with an autosomal dominant phenotype with low penetrance.

99 - Toward LC-FAOD genetic diagnoses: Insights from a rhabdomyolysis gene panel

Tatiele Nalin, Omar Riemersma, Andrea Schenone, Carla Judice, Heraclio Gutierrez, Daniela Visconti, Omid K. Japalaghi, Vanessa Rangel Miller
(Ultragenyx Pharmaceutical)

Introduction: Long-chain Fatty Acid Oxidation Disorders (LC-FAOD) commonly present with muscular symptoms such as muscle weakness and recurrent rhabdomyolysis. Newborn screening is not universally available, and therefore, these disorders are often misdiagnosed as metabolic, inflammatory, or mitochondrial myopathies, making biochemical and genetic testing essential for accurate diagnosis. Methods: Patients with suspected muscular symptoms of LC-FAOD and a history of rhabdomyolysis are eligible for this no-charge genetic testing program. Comprehensive gene sequencing panels were used that include either six LC-FAOD genes plus 127 additional genes or four LC-FAOD genes plus 47 rhabdomyolysis-related genes. Diagnosis is classified as positive (≥2 pathogenic/likely pathogenic variants) or potential positive (including Variants of Uncertain Significance). Results: As of January 31, 2025, 166 patients were tested. Six patients had a positive or potential positive genetic diagnosis for LC-FAOD (all CPT2 variants), while 28 had a positive or potential positive diagnosis for other genes (16 genes in total, being the most prevalent 6 RYR1, 3 DMD and 3 PYGM). Seven patients had genetic findings not consistent with a molecular diagnosis. Of the 6 patients with CPTII deficiency, five are from Argentina and one from Guatemala. All are compound heterozygotes genotypes, and the most frequent variant was p.Ser113Leu present in five alleles (five patients). The age at LC-FAOD diagnoses were observed as 1 age 1-12 years, 4 age 13-20 years, and 1 age 21-40 years. The rate of molecular diagnoses to all genes varied with age: 2/2 (<1 year), 6/29 (1-12 years), 8/40 (13-20 years), 14/57 (21-40 years), and 4/38 (≥40 years). Conclusions: This study highlights the importance of genetic testing with a comprehensive gene panel for diagnosing LC-FAOD in patients with muscular symptoms and/or rhabdomyolysis. It reveals a diverse genetic landscape of myopathies diagnosed across ages, emphasizing the importance of a timely and accurate diagnosis, especially given the lack of universal newborn screening for LC-FAOD.

100 - Case Without Diagnosis

Waldo Espinosa Caballero *(Jose D Obaldia Children's Hospital, Panama City, Panama)*

A 6-year-old patient, daughter #2 of a 32-year-old mother, G2P1C1, was born vaginally at 36 weeks of gestation, weighing 2.5 kg, height 52 cm, head circumference 35 cm, APGAR 9:9. She presented with cardiorespiratory arrest at 24 hours , a small VSD with dilated right atrium and ventricle, pulmonary hypertension, and elevated lactate. Neonatal screening showed elevated immunoreactive trypsin levels, and a negative Wescor sweat test. At 1 year of age, she was hospitalized with respiratory syncytial virus pneumonia, and positive Wescor sweat test. At 2 years of age, she was hospitalized with chronic cough, seizures, and Mycoplasma pneumoniae pneumonia, Bronchial secretion culture was positive for Pseudomonas. Genetic panel by Sanger sequencing and duplication deletion for cystic fibrosis was reported negative. At 3 years she was hospitalized with due to generalized seizures, normal brain CAT, positive stool fat, normal pancreatic tests. At 4 years had viral pneumonia, negative stool fat, chest CT scan reports fibrosis in both lung bases, and hepatobiliary ultrasound reports small gallbladder stones. The exome report indicated the probably pathogenic variant p.(Asn167Thrfs*25) in the MFRP gene, unrelated to the patient's clinical presentation.

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Promoters

Genetics for All Institute

UDNI Undiagnosed Diseases Network INTERNATIONAL

Wilhelm Foundation 25 Years of Impact

Partners

ACMGen Asociación Colombiana de Médicos Genetistas y Medicina Genómica

AINP Academia Iberoamericana de Neurología Pediátrica

ECLAMC Estudio Colaborativo Latinoamericano de Malformaciones Congénitas

European Reference Network for rare or low prevalence complex diseases
Network Hereditary Metabolic Disorders (MetabERN)

RELAGH

Sociedad Argentina de Genética S. A. G.

SBGM Sociedade Brasileira de Genética Médica e Genômica

SBTEIM Sociedade Brasileira Triagem Neonatal Erros Inatos do Metabolismo

SOCHIGEN

Sociedad Chilena de Pediatría 1922

115 Anos sociedade brasileira de pediatria

Conference Organizers

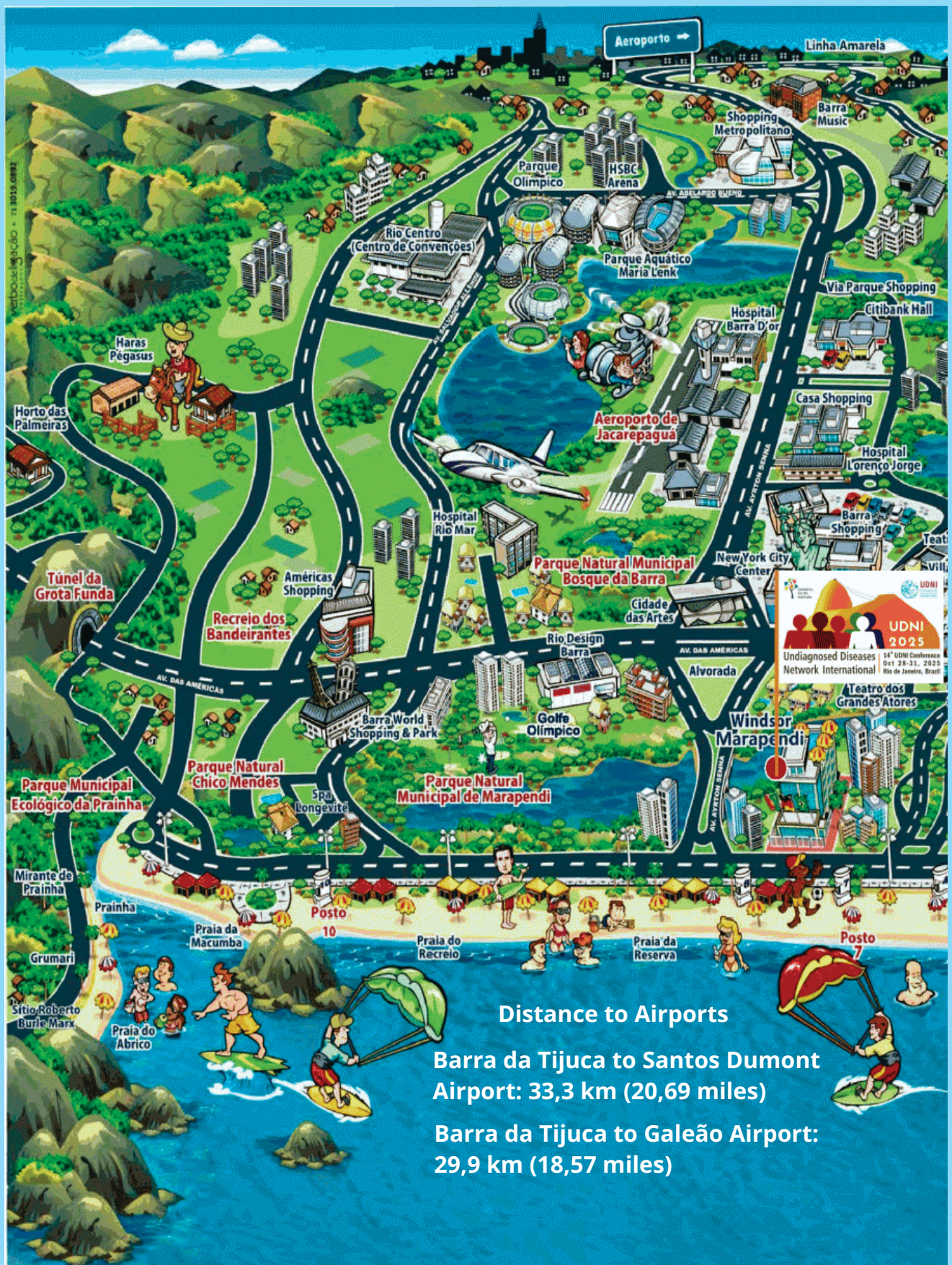
Goya eventos

Consulting and Events Vicky Simon Consultoria e Eventos

Local Support

visit RIO

Barra da Tijuca Map



Distance to Airports

Barra da Tijuca to Santos Dumont Airport: 33,3 km (20,69 miles)

Barra da Tijuca to Galeão Airport: 29,9 km (18,57 miles)


RIO DE JANEIRO - BRASIL
Alto da Boa Vista
Floresta da Tijuca
Itanhanga Golf
Pedra da Gávea
Levitate
Shopping Downtown
Città America
Ilha da Gigóia
Barrapoint
Metrô
Igreja São Francisco
Centro de Convenções
Windsor Tower
Windsor Oceanico
Windsor Barra
AV. ARMANDO LOMBARDI
RUA ERICO VERISSIMO
RUA OSCAR MACIEL
AV. LÚCIO COSTA
Posto 3
Praia do Pepê
Posto 1
Quebra Mar

Program at a glance

October 28, Tuesday

19:00	Welcome Session (specific registration needed)

October 29, Wednesday

8:00-9:00	Session 1: Welcome, Origins of UDNI, from UDPs to Hackathons
9:00-10:00	Session 2: Online Tools to Diagnose the Undiagnosed
10:00-10:30	Coffee-break / Poster Viewing
10:30-12:00	Session 3: Highlights of UDPs and Hackathons Worldwide
12:15-13:15	Lunchtime Sponsored Symposium - ULTRAGENYX and CENTOGENE
13:30-14:30	Session 4: Presentation of Selected Abstracts (Emerging Research 1)
14:30-16:00	Session 5: Policy Innovations - Strategies to Tackle the Undiagnosed
16:00-16:30	Coffee-break / Poster Viewing
16:30-18:00	Session 6: Innovative Approaches for Undiagnosed Diseases
18:00-19:00	Session 7: Case Reports - Solved and Unsolved Cases

October 30, Thursday

8:30-10:00	Session 8: Networks, Training and Education on Undiagnosed Diseases
10:00-10:30	Coffee-break / Poster Viewing
10:00-12:00	Proficiency Test (Specific Application Needed) - Barás Room on the Ground Floor
10:30-12:00	Session 9: Genomic Standards and Population Genomics
12:15-13:15	Lunchtime Sponsored Symposium - ASTRAZENECA
13:30-14:30	Session 10: Presentation of Selected Abstracts (Emerging Research 2)
14:30-16:00	Session 11: How to create, structure and fund a UDP program
16:00-16:30	Coffee-break / Poster Viewing
16:30-18:00	Session 12: From Diagnosis to Therapies
18:00-19:00	Session 13: Closing Session: Abstract Prize, Next Conference, Closure
19:30	Buses depart to Networking Activity (specific registration needed)

October 31, Friday

9:00-13:00	UDNI Board & Committee Meetings (open to UDNI members and non-members)