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ORAL PRESENTATION

WEDNESDAY 13/09

Session 1- Adult syndromology & syndrome delineation

15:15 DEEP PHENOTYPING OF ADULT PATIENTS WITH GENETIC SYNDROMES

Presenting author: Ana Isabel Sánchez Barbero

Ana Isabel Sánchez[1], Fiona Blanco Kelly[1,2,] Fermina Lopez Grondona[1,2], Maria Isabel Lorda Sánchez[1,2], Berta Almoguera[1,2], Carmen Ayuso[1,2].

1.Department of Genetics, Health Research Institute-Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain.
2.Center for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain.

Email for correspondence: ana.sbarbero@quironsalud.es

Next-generation sequencing (NGS) technology has led to identify the etiology of many monogenic genetic syndromes in individuals with dysmorphic features plus neurological conditions such as developmental delay, intellectual disability, epilepsy, movement disorder, hypotonia, autism spectrum disorder and other behavioral problems.

There is little information regarding detailed clinical phenotype of patients with genetic syndromes reaching adulthood. Therefore, age-specific clinical manifestations are less known than those described for the same genetic conditions in the pediatric population.

In this cohort, we assess the clinical data of 10 adult patients with genetic syndromes with a confirmed molecular diagnosis of Cohen Syndrome, Kabuki Syndrome, Okur-Chung Syndrome, Pitt Hopkins Syndrome, Rett Syndrome, Say-Barber-Biesecker-Young-Simpson Syndrome, Schuurs-Hoeijmakers Syndrome and White-Sutton Syndrome.

Through deep phenotyping of these syndromes in adulthood, we expect to contribute to their rapid recognition, optimize their clinical management and provide correct genetic counseling for families.

15:30 THE PHENOTYPE OF COFFIN-SIRIS SYNDROME IN ADULTHOOD

Presenting author: Ariane Schmetz

Ariane SCHMETZ[1], Nuria BRÄMSWIG[1], Herman-Josef LÜDECKE[1], Harald SUROWY[1], Roseline CAUMES[2], Cindy COLSON[2], Patrick EDERY[3], Laurence FAIVRE[4], Andrew GREEN[5], Lotte KLEINENDORST[6], Amaia LASA-ARANZASTI[7], Vanesa LÓPEZ-GONZÁLEZ[8], Julien MARAVAL[4], Barbara OEL-JASCHKOWITZ[9], Florence PETIT[2], Renata POSMYK[10], Audrey POUTOUX[3], André REIS[11,12], María José SÁNCHEZ-SOLER[8], Tinatin TKEMALADZE[13], André TRAVESSA[14], Laura TRUJILLANO LIDÓN[7], Irene VALENZUELA PALAFOLL[7], Georgia VASILEIOU[11,12], Mona WALTHER[11], Krystyna H CHRZANOWSKA[15], Arndt BORKHARDT[16], Dagmar WIECZOREK[1,17]

1: Institute of Human Genetics, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany, 2: Service de Génétique Clinique, Hôpital Jeanne de Flandre, CHRU de Lille, Lille, France, 3: Service de Génétique, Hôpitaux de Lyon et Centre de Recherche en Neurosciences, Université Lyon 1, France, 4: Centre de référence Anomalies du Développement et Syndromes Malformatifs, Fédération Hospitalo-Universitaire TRANSLAD, CHU Dijon, Dijon, France., 5: Dept of Clinical Genetics, Children's Health Ireland at Crumlin, Dublin, Ireland., 6: Department of Clinical Genetics, Amsterdam UMC, Amsterdam, the

Netherlands, 7: Area of Clinical and Molecular Genetics, Vall d'Hebron University Hospital, Barcelona 08035, Spain., 8: Sección Genética Médica, Servicio de Pediatría, Hospital Clínico Universitario Virgen de la Arrixaca (HCUVA), IMIB-Arrixaca, El Palmar, Murcia, Spain, 9: Gemeinschaftspraxis für Humangenetik Homburg/Saar, Homburg, Germany., 10: Department of Clinical Genetics, Podlaskie Medical Center, Bialystok, Poland., 11: Institute of Human Genetics, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany, 12: Centre for Rare Diseases Erlangen (ZSEER), Erlangen, Germany, 13: Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia, 14: Medical Genetics Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal, 15: Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland, 16: Department of Pediatric Oncology, Hematology & Clinical Immunology, University Children's Hospital, Heinrich Heine University, Düsseldorf, Germany, 17: Center for Rare Diseases, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany

Email for correspondence: ariane.schmetz@hhu.de

Introduction: In the past decades, the widespread use of next generation sequencing technologies has enabled the identification of the genetic basis for many rare disorders. Pathogenic variants in genes encoding subunits of the SWI-SNF complex were found to be causal in Coffin-Siris syndrome (*ARID1B, ARID1A, SMARCB1, SMARCA4, SMARCE1, ARID2, DPF2, SMARCC2, SOX11, SOX4, SMARCD1, BICRA*). However, there is very little information on the clinical phenotype in adulthood. In particular, the long-term outcomes and associated risks are not well known which leads to great uncertainty.

Methods: Through an ERN-ITHACA call for collaboration, social media, collaboration with syndrome-specific foundations and collaborating colleagues, we have recruited adult patients with Coffin-Siris syndrome. Participants' phenotype was assessed using a comprehensive questionnaire.
Results: Recruitment was not completed at the time of abstract submission. However, we already had phenotypic data of 31 patients with Coffin-Siris syndrome. Preliminary analysis of the phenotype of selected patients indicate interesting new features of the syndrome in adulthood. Especially, weight problems that need further investigation.

Conclusion: In order to fill the knowledge gap on the adult phenotype of this syndrome, we initiated our study as a collaborative project. We will present the phenotypic data from our adult-only cohort of patients. The collected data will delineate the evolving features of the syndrome, allow a more accurate prediction of the relative risks and will be of great value to affected patients and their caregivers in making preventive and therapeutic decisions.

15:45 A COHORT OF SEVEN INDIVIDUALS EXPANDING THE PHENOTYPE OF XIA-GIBBS SYNDROME

Presenting author: Elisa D'Acunto

D'Acunto Elisa [1,2]; Sanges Remo [3,4]; Brunetti-Pierri Nicola [5,6]

[1]*Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II, Naples, Italy*
[2]*U.O.C. Genetica Medica A.O.U. Federico II, Naples, Italy*
[3]*Functional and Structural Genomics, Scuola Internazionale Superiore di Studi Avanzati (SISSA), Via Bonomea 265, 34136, Trieste, Italy*
[4]*Central RNA Laboratory, Istituto Italiano di Tecnologia (IIT), Via Enrico Melen 83, 16152, Genova, Italy*
[5]*Telethon Institute of Genetics and Medicine, Pozzuoli*
[6]*Department of Translational Medicine, Federico II University of Naples, Naples, Italy*

Email for correspondence: elysa93@hotmail.com

Background: Xia Gibbs syndrome (XGS) is due to pathogenic variants in *AHDC1* gene, that encodes a multi-function protein involved in transcription, epigenetic regulation, axonogenesis and DNA repair. The spectrum of XGS manifestations includes hypotonia, neurodevelopmental delay with a particular

impairment of expressive language, recognizable dysmorphic facial features, epilepsy, failure to thrive, short stature, laryngomalacia and obstructive sleep apnoea.

Cases: We describe seven Italian individuals with XGS, all carrying novel heterozygous *de novo* truncating variants in *AHDC1* gene: p.Glu730*, p.Ser823*, p.Ser172Lysfs*8, p.Arg587Thrfs*56, p.Val483Tyrfs*16, p.Glu863Valfs*26 and p.Arg587* (NM_001371928.1). A young boy with aortic root dilatation was also found to carry a pathogenic variant in *FBN1* gene (p.Asn1504Ser) inherited from his affected mother. All patients had developmental delay and intellectual disability. The mean age for independent walking was 2.3 years (range: 18 months to 3.5 years) but at least 5 individuals had walking difficulties and motor clumsiness. The mean age for the first words was 2 years and most individuals could spoke by the age of 4 years, although verbal expressive language was limited and one child was nonverbal at 4.7 years. Recurrent dysmorphic features in our series were high and prominent forehead, synophrys, broad and horizontal eyebrows, bulging or deeply set eyes, ectropion, malar hypoplasia, large and uplifted ear lobes, short nose with wide nasal bridge, long smooth philtrum, micrognathia and thin upper lip. However, the combination of these features resulted in a recognizable facial phenotype in 3/7 male individuals but not in the remaining 4 cases. Although with variable severity and response to anti-seizure medications, epilepsy was present in 4/7 individuals. On brain MRI all subjects showed nonspecific abnormalities, such as thin corpus callosum. Vision abnormalities were reported in 6/7 children with strabismus present in 4/7. Although head circumference was normal in aging individuals, absolute or relative macrocephaly was frequently present at birth (4/7 individuals). Short stature was found in 3/7 individuals, a child reached normal stature after GH therapy, and another subject had normal height that fell below her genetic target. None of them showed laryngomalacia or obstructive sleep apnoea.

Conclusions: We present 7 individuals with XGS supporting variability in clinical heterogeneity of the condition, especially for the severity of the language involvement and epilepsy. We also report the novel finding of absolute/relative macrocephaly at birth.The degree of neurocognitive impairment ranged from moderate to severe. Consistent with literature data, all cases carried heterozygous *de novo* frameshift or nonsense variants in *AHDC1* gene, predicted to result in the premature stop of protein synthesis. No clear genotype-phenotype correlation was identified.

16:00 A GERMLINE MUTATION IN MYELIN REGULATORY FACTOR (MYRF) CAUSING A PHENOTYPE WITH REDUCED PENETRANCE AND VARIABLE EXPRESSION WIHTIN A MULTIGENERATION FAMILY

Presenting author: Sietse Aukema

Sietse M. Aukema[1,2], Alexander P A Stegmann[1], Christine E M de Die-Smulders[1]

[1]Department of Clinical Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands. [2]Department of Human Genetics, Radboudumc, Nijmegen, The Netherlands.

Email for correspondence: smaukema@gmail.com

Introduction: Germline mutations in the myelin regulatory factor (*MYRF*) gene have been recently described as cause for cardiac-urogenital syndrome (MIM #618280) (Pinz, 2018). Abnormalities include congenital heart disease including hypoplastic left heart syndrome, genitourinary anomalies, diaphragm anomalies and pulmonary hypoplasia (Rossetti, 2019). The majority of mutations represent loss-of-function variants with haploinsufficiency as the proposed pathogenic mechanism. The majority of reported patients represent simplex cases with a *de novo* variant and few familial cases have been described (Gupta, 2022). Here we present a three-generation family with an inherited *MYRF* splice site variant.

Methods: In the prenatal outpatient clinic we saw a pregnant women for genetic counselling as fetal cardiac abnormalities were detected on the 20-s ultrasound anomaly scan (hypoplastic left heart syndrome). Prenatal exome sequencing on DNA of the fetus and parents was performed with the gene panels for congenital heart abnormalities (WES-HEART PANEL/CHD, 303 genes) and Mendelian Inheritance/OMIM (3839 genes).

Results: The OMIM-panel identified a maternally inherited heterozygous splice-site variant in the *MYRF* gene: c.2664+2del; r.(spl?) which was classified as likely pathogenic according to ACMG-guidelines. Before the results of fetal exome sequencing were available the pregnancy was terminated because of severity of the clinical manifestations. No fetal autopsy was performed. The mother was born small for gestational age and had a clinical history of short stature, delayed motor development and dextrocardia without associated structural heart defects. Further co-segregation in the family showed that the mutation in the mother was paternally inherited. Phenotyping in the mothers father (the proband's grandfather) was normal (cardiac ultrasound and ECG).

Conclusion: We present the clinical history of a multi-generation family with a likely pathogenic splice variant in *MYRF* initially identified with prenatal exome sequencing in a fetus with hypoplastic left heart syndrome. Co-segregation revealed variable phenotypes with dextrocardia in the mother and even no cardiac abnormalities in the father of the mother also carrying the variant. Our findings point to variable expression and possibly even reduced penetrance for this inherited variant in *MYRF* and contribute to further syndrome delineation.

16:15 A NEDD4 HOMOZYGOUS FRAMESHIFT VARIANT IN A BOY WITH MULTIPLE CONGENITAL ANOMALIES OVERLAPPING THE NEDD4 KNOCK-OUT MURINE MODEL

Presenting author: Giulia Severi

Severi GIULIA[1], Isidori FEDERICA[2], Vancini ALESSANDRA[3], Baroni MARIA CHIARA[1], Scarano EMANUELA[4], Seri MARCO[5] and Pippucci TOMMASO[2].

1 *U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
2 *S.S. Genomica Computazionale, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
3 *U.O.C. Neonatologia e Terapia Intensiva Neonatale, Ospedale Maggiore di Bologna, Italy*
4 *S.S.U.O. Malattie Rare Congenito-Malformative, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
5 *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*

Email for correspondence: giulia_severi@aosp.bo.it

We performed whole exome sequencing (WES) in a patient with a possible clinical diagnosis of CHARGE syndrome, where *CHD7* analysis and array CGH did not identify any pathogenic variant. An alternative clinical hypothesis was Baraitser-Winter syndrome, but *ACTB* and *ACTG1* resulted wild-type.
The boy was the first child of consanguineous parents from Pakistan and presented prenatally with left cleft lip and palate and right clubfoot. Karyotype from amniotic fluid resulted 46,XY. He was born at 36+3 weeks from C-section. Weight was 2530 g, Apgar score 6 at 1' and 8 at 5'.

At birth, cleft lip and palate and clubfoot were confirmed, but he also showed post-axial right polydactyly, bilateral iris coloboma and some dysmorphic features: low set posteriorly rotated ears, micro-retrognathia, left supernumerary nipple, bilateral single palmar crease. Cardiac ultrasound revealed patent foramen ovale and ductus arteriosus. Brain MRI confirmed bilateral iris and optic nerve coloboma.
He showed developmental delay: at 4 years (last evaluation), he could walk only if assisted and he was still non-verbal. He had short stature (-3.3 SD) and microbrachycephaply (-4.1 SD; -3.3 SD related to his stature).

Exome sequencing revealed a homozygous c.1369_1375delATTTCATinsCG (p.Ile457AlafsTer15) mutation in *NEDD4*; his parents were both heterozygous.

To date, *NEDD4* is not associated to disease in humans. In the murine model, functional studies demonstrate that *Nedd4* regulates the craniofacial development, promoting neural crest cells survival and maintaining their staminality. When Nedd4 expression is abolished in a mouse model (*Nedd4*$^{-/-}$), neural crest cells migrating from the posterior forebrain, midbrain and rostral hindbrain may undergo aberrant apoptosis, resulting in an insufficient population of these cells for proper brain functioning. *Nedd4*$^{-/-}$ mice have severe cranio-facial defects with a prevalent maxillar and mandibular involvement, clef lip and palate, and deficiency of the trigeminal ganglia. They are also significantly smaller than the wild type littermates.
The patient's parents underwent a second pregnancy: the baby had no morphological abnormalities and he did not carry the *NEDD4* variant.

In conclusion, the phenotype of this patient shows consistency with in phenotypic features in mice, but more patients with putative homozygous loss of function mutations are needed to prove that *NEDD4* is implicated in human disease.

Session 2- phenotyping and technology

17:00 DEEPLASIA: PEDIATRIC BONE AGE ASSESSMENT AI FOR SKELETAL DYSPLASIAS

Presenting author: Behnam Javanmardi

Sebastian RASSMANN[1], Alexandra KELLER[2], Alexander HUSTINX[1], Klaus MOHNIKE[3], Peter KRAWITZ[1], Behnam JAVANMARDI[1]

1: Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Germany
2: Kinderzentrum am Johannisplatz, Leipzig, Germany
3: Medical Faculty, Otto-von-Guericke-University Magdeburg, Germany

Email for correspondence: bjav@uni-bonn.de

Skeletal dysplasias (SDs) collectively impact a significant number of patients worldwide. Since the majority of SDs cause growth anomalies, assessing the maturity of the skeletal system by determining bone age (BA) is an essential diagnostic tool for these disorders. Also, regular BA assessments play a crucial role in monitoring the growth of SD patients, particularly for timing hormone treatments or orthopedic interventions. However, manual BA assessment is time-consuming and prone to high variability among different raters and even within the same rater. This challenge is exacerbated by SDs that result in severely dysmorphic bones. While various methods for automating BA assessment have been proposed, only a few have been validated for children with abnormal development. In this contribution, we present *Deeplasia*, an open-source prior-free deep-learning ensemble approach. By training *Deeplasia* on the publicly available RSNA BA dataset, we achieve state-of-the-art performance, with a mean absolute error (MAE) of 3.87 months based on the average of six different reference ratings. Additionally, we demonstrate the generalization capability of *Deeplasia* by evaluating it on an unseen dataset comprising 568 X-ray images from 189 patients with confirmed diagnoses of seven different genetic bone disorders, including Achondroplasia and Hypochondroplasia. In this evaluation, *Deeplasia* achieves an MAE of 5.84 months compared to the average of two references. Furthermore, using longitudinal data from a subset of the patient cohort (149 images), we assess the test-retest precision of our model ensemble and find it to be at least comparable to that of human experts, with a difference of 2.74 months. Based on these results, we conclude that *Deeplasia* is a suitable tool for assessing and monitoring bone age in patients with skeletal dysplasias.

Link to the interactive figure of the results: http://deeplasia.de
medRxiv: https://doi.org/10.1101/2023.03.07.23286906

17:15 SMARCA2 – ONE GENE, HOW MANY PHENOTYPES?

Presenting auhor: Daniela Oliveira

Daniela Oliveira[1,2,3], Joana Rosmaninho Salgado[1], Carla Marques[4], Inês Nunes Vicente[4], Sérgio B. Sousa[1,2,3]

1- Medical Genetics Unit, Paediatric Hospital, Coimbra Hospital and University Centre, Portugal
2- University Clinic of Genetics, Faculty of Medicine, University of Coimbra, Portugal
3- Clinical Academic Centre of Coimbra, Portugal
4- Child Development Centre, Paediatric Hospital, Coimbra Hospital and University Centre, Portugal

Email for correspondence: danielaoliveira@chuc.min-saude.pt

BACKGROUND: *SMARCA2* gene encodes one of the two helicase-related catalytic subunits of BAF chromatin remodeling complex. It was firstly associated with Nicolaides-Baraitser syndrome (NCBRS) due to non-truncating variants within the helicase domains (exons 15-25). More recently, specific *SMARCA2* missense variants (exons 8, 9 and 19) were shown to cause a new recognizable syndrome – Blepharophimosis-intellectual disability syndrome (BIS). Moreover, several other patients with non-specific (NS) intellectual disability (ID) phenotypes were identified as carrying *SMARCA2* variants.

CASE REPORT: We report three patients followed-up in our centre, all carriers of a different *SMARCA2* variant and presenting remarkably distinct phenotypes.

Case 1: We report an 11-year-old girl with ID, important behavioural problems, febrile seizure, umbilical hernia, scoliosis, bilateral metatarsus varus and dysmorphisms. Typical NCBRS phenotype was recognized and this diagnosis was confirmed by targeted testing which identified the *de novo* heterozygous likely pathogenic variant p.(Met751Thr), novel but located at the *SMARCA2* helicase ATP-binding domain.

Case 2: We report a 16-year-old boy with severe ID, absent speech, severe hypotonia with very limited walking, cryptorchidism and balanic hypospadias, postnatal short stature and microcephaly, recurrent upper respiratory tract infections, important neonatal feeding difficulties, gastro-oesophageal reflux refractory to surgical intervention, reduced visual acuity, dysplastic corpus callosum, blepharophimosis and other distinct dysmorphic features. WES identified a *de novo* variant p.(Arg937His), in heterozygosity, in exon 19 of *SMARCA2.* This was one of the first cases identified as having BIS and p.Arg937 turned out to be one of residues recurrently affected in this syndrome.

Case 3: We report an 8-year-old boy with ID, myopia, umbilical hernia, unilateral retractile testis, atopic eczema, recurrent diarrhoea and mild dysmorphisms. Mild/atypical NCBRS diagnosis was proposed. BAFopathies multigene NGS panel revealed a *de novo* heterozygous *SMARCA2* variant p.(Lys493del), novel and located outside the helicases domains, being the first variant identified at the conserved HSA domain (exon 8). The closest pathogenic variants were identified in BIS cases. DNA methylation studies showed an NCBRS episignature.

DISCUSSION: Here we discuss the different *SMARCA2*-related phenotypes and respective genotype correlations, well-illustrated by the cases described. It has been a growing challenge and we will also address the experience with opinion requests that reach us regarding this issue. Transcriptomic and methylation studies have clearly showed overlapping but also specific profiles of gene expression and DNA methylation, respectively, in NCBRS and BIS patients, but this has not been as useful for other NS ID phenotype patients.

Further investigations are needed to clarify the disease mechanisms of the different groups of *SMARCA2* variants.

17:30 THE EVOLVING COMPLEX GENOTYPE-PHENOTYPE CORRELATION OF RBM10

Presenting author: Christina Ringmann Fagerberg

Jeanne Mari Vejen Bang[1], Christina Ringmann Fagerberg[2], Thomas Koed Doktor[1], Mark Burton[2], Brage Storstein Andresen[1] - And a large group of clinicians and other collaborators to be mentioned in the talk.

1 *Department of Biochemistry and Molecular Biology, University of Southern Denmark, Denmark*
2 *Department of Clinical Genetics, Odense University Hospital, Odense, Denmark*

Email for correspondence: christina.fagerberg@rsyd.dk

RNA binding motif 10 gene (*RBM10*), located at Xp11.23, encodes the RNA binding protein RBM10 known to be involved in regulation of alternative splicing. Germline loss of function variants in *RBM10* are known to cause TARP syndrome (acronym for Talipes equinovarus, Atrial septal defect, Robin Sequence, and Persistent left superior vena cava). While the phenotype of TARP syndrome initially was described as very severe and with death in infancy, cases with long term survival and milder phenotypes have been published, thus broadening the phenotypic spectrum.

We describe a cohort of almost 30 male individuals with different types of *RBM10* variants.
We define three main phenotypes:

- TARP
- TARP like (TARPL)
- RBM10 associated intellectual disability (RAID)

The phenotypes of TARP and TARPL have many similarities as preterm birth, hypotonia, severe developmental delay, and optic nerve hypoplasia. I TARP syndrome however, severe respiratory problems are seen, and death in infancy is frequent. Individuals with TARPL develop to have severe ID, severe speech delay, severe motor delay, growth delay, and some have hearing loss. The number of phenotypes as defined by the acronym of TARP is higher in TARP syndrome than in TARPL. The dysmorphic features are quite similar for TARP and TARPL.
Individuals with RAID have rather variable but milder phenotypes. Frequent features for some are moderate ID, behavioral anomalies (mostly ADHD), short stature, macrocephaly, and speech delay. Other individuals had mild to moderate ID and tall stature. The dysmorphic features are different from what is seen in TARP and TARPL.

RBM10 variants are scattered throughout the gene, but three clusters of variants are seen: frameshift or nonsense variants in exon 4; missense variants affecting the RRM2 domain, and missense variants affecting the ZF2 domain.

We describe the evolving complex genotype–phenotype correlation of the RBM10-gene.

17:45 THREE CASES OF FATCO SYNDROME

Presenting author: Ozge Beyza Gundogdu Oğutlu

Ozge Beyza Gundogdu Oğutlu[1], Ezgi Urtekin[1], Gulsum Kayhan[1], E. Ferda Percin[1]

[1] Gazi University, Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey

Email for correspondence: ozgebeyzag@gmail.com

Introduction: FATCO Syndrome (#246570) is a rare syndrome with a prevalence <1:1000000 characterized by fibular aplasia, tibial campomelia and oligosyndactyly. The genetic etiology and inheritance pattern of this syndrome are not yet known. Although mostly isolated cases have been reported, there are reports in the literature suggesting autosomal dominant, autosomal recessive or X-linked inheritance with variable expressivity, decreased penetrance or gonadal mosaicism.

Patient findings and methods: A 3-day-old female patient (P1) whose parents were consanguineous to the 3rd degree, a 1-day-old male patient (P2) whose parents were not consanguineous, and an 8-month-old female patient (P3) whose parents were not consanguineous were evaluated because of limb anomalies. Dimples and campomelia were present in the tibia in all three patients. Unilateral oligosyndactyly of the hands was observed in P1 and P2, while fibular aplasia and oligosyndactyly of the feet were observed bilaterally in P1 and unilaterally in P2 and P3. Microarray analysis and whole exome sequencing (WES) were performed to exclude other diseases in the differential diagnosis (P1, P3 and P1, P2, P3 respectively).

Results: WES analysis in all three patients did not reveal any pathogenic/potential pathogenic variants explaining the skeletal findings and were clinically compatible with FATCO syndrome when evaluated together with other patients in the literature. The sequenced regions of *WNT7A, TP63*, and *WNT10B* genes which are found in the differential diagnosis of FATCO syndrome were found normal. Array analysis resulted as normal. Common genes among rare variants in patients were analyzed and evaluated.

Discussion: To date approximately 32 patients have been reported in the literature. Lower extremity findings are more common than upper extremity findings among the reported patients. The most common findings are fibular aplasia-hypoplasia and tibial campomelia. Two of our patients had both upper and lower extremity findings, while P3 only has lower extremity findings. Such clinical variability in FATCO syndrome may be considered as variable expression. In our patients, clinical variations such as bilateral fibular aplasia and oligosyndactyly of the feet in P1, unilateral in P2 and P3 are noteworthy. *WNT7A, TP63* and *WNT10B* genes were analyzed in patients in the literature but no mutation was found. Our patients also did not have mutations in these genes. Although FATCO syndrome can be diagnosed clinically, its etiology is still unclear. Identification of candidate genes and further analysis of these genes may contribute to the elucidation of the etiology.

Key words: FATCO syndrome, fibular aplasia, tibial campomelia, oligosyndactyly

18:00 VERY MILD PHENOTYPE IN INDIVIDUALS OF A THREE-GENERATION FAMILY WITH A NOVEL HRAS VARIANT AFFECTING ALA59: EMERGENCE OF A NEW RASOPATHY DISTINCT FROM COSTELLO SYNDROME

Presenting author: Katharina STEINDL

Katharina STEINDL,[1] Tanja FREY,[1] Ivan IVANOVSKI,[1] Angela BAHR,[1] Markus ZWEIER,[1] Julia LAUBE,[1] Isabelle LUCHSINGER,[2] Anita RAUCH,[1]

1 Institute of Medical Genetics, University of Zurich, Schlieren-Zurich, Switzerland,
2 Pediatric Skin Center, Department of Dermatology, University Children's Hospital Zurich, Zurich, Switzerland

Email for correspondence: Katharina.Steindl@medgen.uzh.ch

Costello syndrome is a severe, clinically recognizable neurodevelopmental disorder caused by activating variants in HRAS. Most affected patients share recurrent variants affecting codons 12 and 13 and show a relatively uniform phenotype. We now observed an attenuated phenotype of 6 individuals in an extended family carrying the HRAS variant Ala59Gly, which, to our knowledge, has never been reported as a germline variant in patients so far. HRAS Alanine 59 has been previously functionally investigated as an oncogenic hotspot and this substitution was shown to impair intrinsic GTP hydrolysis. All six individuals of this family share ectodermal anomalies and mild features suggestive of a RASopathy, reminiscent of patients with Noonan syndrome-like disorder with loose anagen hair. Intelligence is normal in all six individuals and none has a history of failure to thrive or malignancy, and they are neither known to have cardiac nor neurologic problems. Our observation adds to the previous reports of patients with rare variants affecting amino acids located in the SWITCH II/G3 region of HRAS and suggests a consistent, attenuated phenotype distinct from classical Costello syndrome associated with codons 58, 59, and 60.

THURSDAY 14/09

Session 3 – Prenatal diagnosis

9:00 INVITED TALK: LORE LANNOO, IMPLEMENTATION OF GENOME-WIDE CELL-FREE DNA SEQUENCING (GIPSEQ) FOR THE EARLY IDENTIFICATION AND EFFICIENT MANAGEMENT OF HIGH-RISK PREGNANCIES

09:45 INHERITED VARIANTS IN PRENATAL WES. IMPORTANCE OF CORRECT CLINICAL INFORMATION

Presenting author: Ivan Ivanovski

Ivanovski Ivan[1], Bahr Angela[1], Steindl Katharina[1], Rauch Anita[1]

1: Institute of Medical Genetics, University of Zurich

Email for correspondence: ivan.ivanovski@medgen.uzh.ch

Whole Exome Sequencing (WES) has become an essential part of diagnosing various disorders in both children and adults. In recent years its use has been greatly expanded into prenatal testing, in addition to microarray techniques, but there are still challenges to overcome. These include ensuring the adequacy and quality of input samples, reducing turnaround times, and maintaining consistent interpretation and reporting of identified variants. The accuracy and reliability of the input information play a crucial role in variant classification and can significantly impact the analysis results. Finally, many known disorders do not have a known prenatal phenotype or have phenotype that is different from one seen postnatally. In these situations, accurate variant classification is possible only with combining ultrasound findings and findings in the parents.

Hereby we present three prenatal analyses from our Institute, where disease causing variants were inherited from seemingly healthy parents. We explore the findings and examine the complexities and potential challenges encountered during the prenatal WES analyses.

10:00 DETECTION OF RARE GENETICS CONDITIONS IN ROUTINE PRENATAL DIAGNOSTICS – ANALYSIS OF GENETIC OUTCOME IN MORE THAN 350 PREGNANCIES AFTER INVASIVE PRENATAL PROCEDURES

Presenting author: Diana Mitter

Diana Mitter, Fachbereich Humangenetik, Zotz/Klimas Düsseldorf, Germany, mitter@zotzklimas.de
Claudia Behrend, Fachbereich Humangenetik, Zotz/Klimas Düsseldorf, Germany, behrend@zotzklimas.de
Julia Klein, Fachbereich Humangenetik, Zotz/Klimas Düsseldorf, Germany, klein@zotzklimas.de
Karl-Ludwig Marquet, Pränatale Praxis Aachen, Germany, marquet@praenatale-praxis.de
Markus Schmidt, Pränatalmedizin, Sana Kliniken Duisburg, Germany, markus.schmidt@sana.de
Bernd Berschick, Praxis für Pränatale Diagnostik, Willich, Germany, praxis@praenatale-diagnostik.de
Yasmina Neuhaus, Praxis für Pränatale Medizin, Krefeld, Germany, info@praenatal-krefeld.de
Christian Enzensberger, Klinik für Gynäkologie und Geburtsmedizin, Uniklinik Aachen, praenatalmedizin@ukaachen.de
Johan Mertens, Pränataldiagnostik, Frauenarztpraxis Düsseldorf, Germany, info@frauenarzt-mertens.de
Alf Beckmann, MVZ Eberhard & Partner Dortmund, Germany, abeckmann@labmed.de
Moneef Shoukier, Pränatal-Medizin München, Frauenärzte und Humangenetiker MVZ, Germany, shoukier@praenatal-medizin.de

Prenatal genetic testing after invasive procedures is a powerful tool to identify genetic diseases and rare genetic syndromes in a fetus. Prenatal genetic analysis can reveal genetic diseases that will influence the course of pregnancy but also provide important information for medical care and possible treatments during pregnancy or after birth.
We carried out a retrospective review of our prenatal laboratory database for the period from April 2019 to April 2023. Prenatal samples from chorionic villus sampling, amniocentesis or cordocentesis were sent in from cooperating prenatal centers. Genetic analyses includes karyotyping, chromosomal microarray, targeted gene panels or exome/ trio exome sequencing, as well as specific genetic testing for familial diseases.

More than 350 samples were processed during the study period. Besides common chromosomal anomalies, such as trisomy 21, trisomy 18, trisomy 13 and triploidy, we detected various Deletions and Duplications using karyotyping and array analysis. Next generation sequencing revealed a number of rare genetic conditions with severe phenotypes in fetuses with CHARGE syndrome, CAKUTHED syndrome, Opitz-B/GGG syndrome, osteogenesis imperfect, tuberous sclerosis, distal arthrogryposis type 5D and fetal akinesia deformation sequence, as well as milder phenotypes in fetuses with orofacial cleft 15, familial bilateral cleft lip and palate and microduplication syndrome 22q11.2. We will report on the genetic findings and present further details on the prenatal phenotypes of these rare genetic syndromes.

Using the whole range of diagnostic genetic testing, including Next generation sequencing (NGS), prenatal analysis has become more effective in early detection of rare genetic diseases to better care for pregnant women. In view of the rapid development of genetic technologies and fast growing genetic knowledge, care providers must constantly educate themselves to make well-reasoned medical decisions in pregnancy. There is a great need for genetic counselling of patients with abnormal genetic test results.

Session 4 – Syndrome delineation

11:00 INVITED TALK: JOHANNES ZSCHOCKE, DOMINANT OR RECESSIVE? FUNCTIONAL VARIANT INTERPRETATION IN GENETIC DIAGNOSTICS

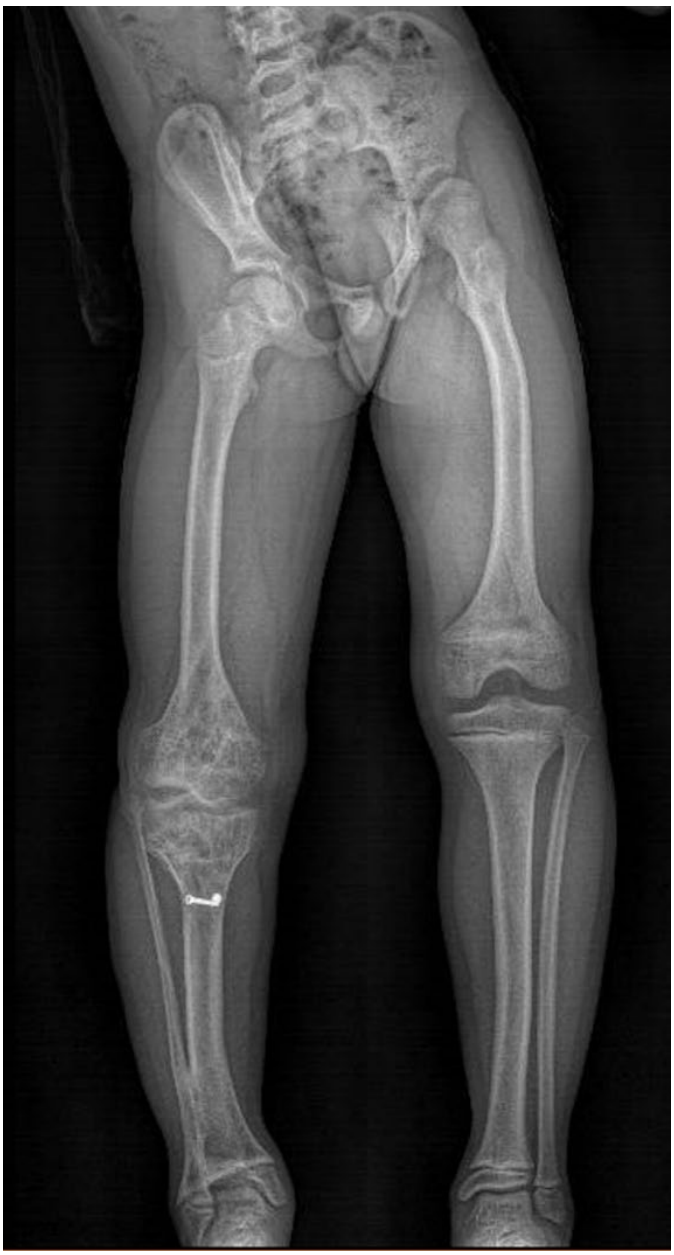
11:45 UNILATERAL SKELETAL LESION IN TWO BROTHERS WITH BIALLELIC VARIANTS IN NTRK1 GENE RELATED TO CONGENITAL INSENSITIVITY TO PAIN

Presenting author : Cristina Peduto

Cristina Peduto[1-2], Lucille Boutaud de la Combe [1,3,] Valerie Cormier-Daire[1,3]

[1]Reference center for skeletal dysplasia, AP-HP, Hôpital Universitaire Necker-Enfants Malades, Paris, France
[2]Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy.
[3]15 Université Paris Cité, Molecular and Physiopathological Bases of Osteochondrodysplasia, INSERM UMR1163, Institut IMAGINE, Paris, France.

Email for correspondence: drcristinapeduto@gmail.com; valerie.cormier-daire@inserm.fr



Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN-IV), is a rare and severe autosomal recessive disorder caused by mutations in the neurotrophic tyrosine receptor kinase 1 gene (*NTRK1*). This gene is believed to have a crucial role in the development of nociceptive sensory and sympathetic autonomic neurons in the dorsal root sensory ganglia. Characteristically, patients with this disorder exhibit a complete diminution of pain and temperature sensations over the body, disrupted sweat gland functioning, and variable degrees of cognitive impairments. Patients are commonly characterized by profound bone loss, diffuse synovitis, and instability in the knee joint. We report the case of two Algerian siblings that show first signs at 8 years-old for the older boy and 3 years-old for the younger. Both presented with recurrent left knee joint swelling episodes and instability with an extreme unilateral deformation of the lower right limb, incurvation and progressive leg length discrepancy. The asymmetrical deformation of the left knee was characterized by progressive epiphyseal deformation with intra-articular foreign bodies and areas of lysis. The radiography shows complete absence of epiphyseal plate of the left distal femur and proximal tibia. The severe leg length discrepancy (~9 cm) of the left knee was treated several times by surgery that caused repeated infections. They present absence of pain, dry and fair hairs, xerosis cutis and mild language delay as well. *Whole Genome Sequencing (WGS)* show compound heterozygous variants in ***NTRK1*** (c.1488C>A;p.Tyr496Ter and c.2127C>A;p.Asp709Glu) never reported so far and both classified likely pathogenic according to the ACMG criteria. The literature review shows a casually distribution of the lesion mainly associated with the fracture side that does not allow to explain the interesting correlation of the lesion to the same side in the two patients. Otherwise, the genetic findings of our study expand the gene mutation spectrum of CIPA. Moreover, our cases illustrate that leg length discrepancy should raise the clinical suspicion of NTRK1-related disorder.

11:48 LMBR1 DUPLICATION IN A GIRL WITH UNILATERAL UPPER LIMB REDUCTION DEFECT

Presenting author: Dorota Wicher

Dorota WICHER[1], Kamila ZDUŃCZYK[1], Klaudia MARKOWSKA-KRAWCZYK[1], Marlena MŁYNEK[1]

[1]*Depratment of Medical Genetics, Children's Memorial Health Institute, Warsaw, Poland*
Email for correspondence: d.wicher@ipczd.pl

Duplications in *LMBR1* gene (*Limb Development Membrane Protein 1*) involving the ZPA (Zone of Polarizing Activity) regulatory sequence (ZRS) are correlated with triphalangeal thumb-polysyndacytyly syndrome (TPTPS, OMIM#190605), syndactyly type IV (SD4, OMIM#186200), as well as with Laurin-Sandrow syndrome (OMIM#135750).

To date, the only *LMBR1*-related limb reduction defects were described in 5 unrelated Brazilian families with acheiropody (autosomal recessive disorder characterized by bilateral congenital amputations of the upper and lower extremities and aplasia of the hands and feet) due to homozygous 4- to 6-kb deletion in the *LMBR1* gene (Ianakiev et al., 2001).

Our patient was born at term from a pregnancy complicated by polyhydramnios, birth weight 4550g, 8-9-10 AS. Limb defect was described in radiology investigation as an amputation of the left forearm bones below the biceps attachment site. No other skeletal abnormalities or congenital defects were found. Motor and speech development are within normal limits.

A family history revealed that the mother has two sons from her first relationship, one of them was born with hydrocephalus and actually required antiepileptic drugs; *L1CAM* defects were excluded. Additionally, mother has two cousins with postaxial polydactyly due to Bardet-Biedl syndrome.
Array CGH (Agilent Technologies SurePrint G3 ISCA V2 CGH 8x60K) revealed gain within *LMBR1* gene containing at least exons 2-17 arr[GRCh37] 7q36.3(156407387x2,156475621_156661877x3,156676105x2). ZRS is located within *LMBR1* intron 5, it regulates the expression of SHH protein, which is a major determinant of cell fate and identity during early limb development. Duplications and other mutations involving this region lead to autosomal dominant limb malformation phenotypes. Further investigations, including array CGH analysis in parents, are planned.

The cases reported so far, clearly indicate the connection of *LMBR1* duplications with limb malformations. However, in the vast majority of cases, these are cases with bilateral hand and/or foot syndactyly. The limb defect in our patient is quite different than in patients with duplications previously described in the literature. We wonder, whether *LMBR1* duplication containing ZRS is responsible for the unilateral limb defect in our patient. In accordance with previous results that ZRS duplications affect the spatial expression pattern as well as dosage of SHH during limb bud development. As a consequence stochastic effects and misregulation of other down-stream targets and signaling pathways most probably contribute to phenotypic variability in limb malformation syndromes.

11:51 SPLIT HAND-FOOT AND DEAFNESS IN A PATIENT WITH 7Q21.13-Q21.3 DELETION NOT INCLUDING THE DLX5/6 GENES

Presenting author: Irene Ambrosetti

Irene AMBROSETTI[1,2], Laura BERNARDINI[3], Marzia POLLAZZON[2], Maria Grazia GIUFFRIDA [4], Valentina GUIDA[3], Francesca PELUSO[2], Valeria POLIZZI[5], Manuela NAPOLI[6], Simonetta ROSATO[2], Gabriele TRIMARCHI[2], Chiara GELMINI[2], Stefano Giuseppe CARAFFI[2], Anita WISCHMEIJER[2,7], Daniele FRATTINI[8], Antonio NOVELLI[9], Livia GARAVELLI[2]

1: U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
2: Clinical Genetics Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
3: Division of Medical Genetics, Fondazione IRCCS-Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy
4. Cytogenetics Unit, IRCCS Casa Sollievo della Sofferenza Foundation, Viale Cappuccini, San Giovanni Rotondo, Italy.
5. Department of Audiology,Centre for Clinical and Basic Research, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
6. Neuroradiology Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy.
7. Clinical Genetics Service and South Tyrol Coordination Center for Rare Diseases, Department of Pediatrics, Regional Hospital of Bolzano, Bolzano, Italy.
8 Child Neurology and Psychiatry Unit Azienda AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
9. Translational Cytogenomics Research Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

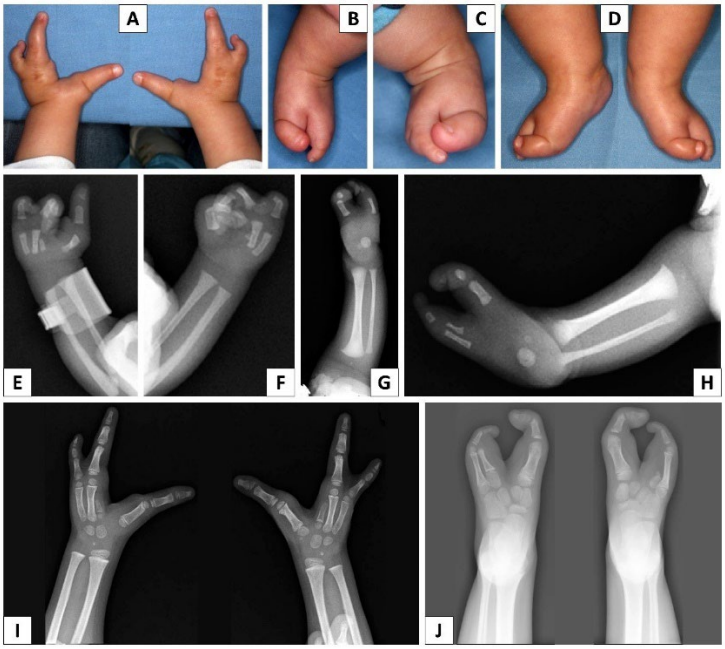
Email for correspondence: irene.ambrosetti@studio.unibo.it

Split Hand-Foot Malformation (SHFM) is a congenital limb defect characterized by median cleft of the hands and/or feet due to absence/hypoplasia of the central rays. It may occur within a syndromic condition or as an isolated malformation. Six different loci have been linked to the phenotype, the most common of which is correlated to SHFM1 and maps in the 7q21q22 region. SHFM1 is characterized by autosomal dominant transmission, incomplete penetrance and variable expressivity. Associated features often include hearing loss, intellectual disability/developmental delay and craniofacial abnormalities. Monoallelic deletion of the *DLX5/DLX6* genes, mapping within the SHFM1 locus, is now known to be responsible for the phenotype. Point mutations in the *DLX5* gene (with both autosomal dominant and recessive patterns of inheritance) and disruption of regulatory elements acting on *DLX5/6* expression have also been identified as a cause of SFHM1.

We present the case of a boy affected with bilateral split hands and feet, mild developmental delay, bilateral severe-profound hearing loss (worse on the left side, for which he underwent surgery for left cochlear implant at the age of 9 years and 9 months) and a bilateral malformation of the inner ear known as Mondini dysplasia, which has been previously described in patients with SHFM1. The patient also showed growth delay (height, weight, and head circumference were all <3° centile on our last evaluation) and some mild dysmorphic features (slight brachycephaly, mild synophrys, a small nose with anteverted nostrils, slightly arched upper lip, raised palate, normal ears and sinus pilonidalis). Karyotype and FISH analysis, performed using SHFM1 locus-specific probes, were negative. Through SNP-array, we identified a de novo deletion in 7q21, not involving the *DLX5/6* genes, but including exons 15 and 17 of the *DYNC1I1* gene, which are known to act as exonic enhancers (eExons) of the *DLX5/6* genes. The deletion spanned for 6300 kb and included many other genes, which may be partly responsible for the phenotype.

We further demonstrated the role of *DYNC1I1* eExons in regulating *DLX5/6* expression, by showing a reduced expression of the *DLX5*/6 genes through RT-PCR on the patient's RNA extracted from the lymphoblastoid line. We performed a review of published cases of deletion of the *DYNCH1I1* eExons without *DLX5/6* involvement and cases of balanced chromosomal rearrangements separating the enhancers from their target genes. We then considered if our data could explain whether *DLX5/6* are imprinted in humans, as the topic is still being debated in the literature; this could affect the recurrence risk of this condition by causing parent-of-origin effects in SHFM1 transmission. Our data and the review of published cases do not support the imprinting hypothesis.

This case is an example of how disruption of regulatory elements can be responsible for congenital malformations by altering patterns of gene expression, and of how cases of chromosomal rearrangements can help shed light on the complex mechanisms regulating embryogenesis and fetal development.



11:54 PHENOTIPIC DESCRIPTION OF A PATIENT WITH ODLURO SYNDROME AND FUNCTIONAL CHARACTERIZATION OF SYNONYMOUS VARIANT c.186G>A

Presenting author: Sofia CESARINI

Sofia CESARINI[1], Emanuele PANZA[2,3], Enrico AMBROSINI[1], Marco SERI[3], Pietro PALUMBO[4] Massimo CARELLA[4] and Giulia SEVERI[1]

1 *U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
2 *Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy*
3 *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
4 Unità di Genetica medica, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Email for correspondence: sofia.cesarini@studio.unibo.it

O'Donnell-Luria-Rodan (ODLURO) syndrome is an autosomal dominant disorder, described for the first time in 2019 by O'Donnell-Luria et al. It is caused by mutations in the *KMT2E* gene and it is characterised by global developmental delay, autism, epilepsy, hypotonia, macrocephaly and mild dysmorphisms.
The proband is a 6-year-old boy; he started walking at 18 months and he still has difficulties with motor coordination. He spoke his first words at the age of 3, and he is undergoing speech therapy; he has relational and emotional difficulties. The EEG test was unremarkable, the brain MRI showed non-specific alterations of the white matter near the trigones and the posterior part of the lateral ventricles.
His height is 122 cm (+0,7 SD), his weight is 27,5 kg (+0.3 SD for statural age) and his head circumference is 55,5 cm (+2 SD for statural age) with dolichocephaly. His phenotypic traits include horizontal palpebral fissures with bilateral inverted epichantal folds, wide nasal root, long philtrum, fleshy ears, mild small joints hyperlaxity, bilateral clinodactyly of the IV and V digits of the foot, inverted nipples, small thoracic hypochromic patch.
NGS analysis of a panel of genes related to neurodevelopmental disorders on DNA extracted from blood samples identified a *de novo* heterozygous synonymous variant, c.186G>A (p.Ala62=) in *KMT2E*. The variant had already been described in a 5-year-old patient with similar clinical characteristics, and it was predicted to alter splicing, but no functional characterization was performed.
Our patient's and his mother's RNA samples were obtained from buccal swabs and were reverse transcribed into cDNA. PCR was used to amplify the target region, with primers designed on exon 1 and exon 3, and the products were run on agarose gel. In the mother's cDNA only a 315 bp band was visualised (expected size, previously visualized in a healthy control), while in the patient's cDNA there were 2 bands: one was the same 315 bp band, the other was a 200 bp band, absent in the mother. The PCR products were sequenced; in the mother's sample the mutation was absent, and the sequence showed the regular presence of exon 2. In the patient's sample, the mutation was present and the sequence confirmed the presence of two spliced transcripts: one wild type and one with the skipping of exon 2. These results confirm that the c.186G>A variant alters splicing, and must therefore be considered causative of ODLURO syndrome in the proband.

11:57 TWO UNRELATED PATIENTS WITH NAIL-PATELLA SYNDROME AND UNUSUAL ADDITIONAL FEATURES

Presenting author: Nathalie Vanden Eynde

Nathalie Vanden Eynde[1], Thomy de Ravel[1], Laura Pölsler[1], Alexander Gheldof[1], Sara Seneca[1], Peter Janssens[2], Veronique Bissay [3], Kathelijn Keymolen[1], Frederik Hes[1], Boyan Dimitrov[1]

1. *Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Clinical Sciences, research group Reproduction and Genetics, Centre for Medical Genetics, Brussels, Belgium*
2. *Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Department of Nephrology, Brussels, Belgium*
3. *Vrije Universiteit Brussel (VUB), , Universitair Ziekenhuis Brussel (UZ Brussel), Department of Neurology, Brussels, Belgium*

Email for correspondence: nathalie.vandeneynde@uzbrussel.be

Introduction: Nail-patella syndrome (NPS) is an autosomal dominant disorder characterized by nail, patella and elbow changes, and the presence of iliac horns. It is caused by haplo-insufficiency of the *LMX1B* gene. While classic renal changes leading to nephropathy and kidney failure are well known in NPS, this report presents two unrelated patients with NPS who exhibit additional atypical features.

Patient 1: A male of 26 years presented with nail abnormalities, as had his father. He was lean and could not extend his elbows fully. X-ray showed iliac horns and dysplastic patellae. Additionally he had a left hypoplastic kidney resulting in a nephrectomy. Renal function presently remains normal. Genetic testing revealed a deletion of exon 3 in the *LMX1B* gene.

Patient 2: A 25-year-old male was born dysmature to consanguineous parents. He presented with the classical features of neonatal hypotonia and feeding problems, high frontal hairline, dysplastic nails and seizures. Additional features are persisting hypotonia, muscle weakness, high arched eyebrows, downslanted palpebral fissures, ptosis, partial syn-/campto-/clino-dactyly bilateral fifth finger, right-sided hemihypertrophy, developmental delay and intellectual disability. There was growth retardation, progressive scoliosis, unilateral cryptorchidism with micropenis, lower bone mineral density and pelvic kidney. He developed obesity and hyperphagia with insulin resistance. Triploidy, neuromuscular disorders, Prader-Willi syndrome, Silver-Russel syndrome and metabolic disorders were excluded. Functional and histological studies of muscle were normal. Clinical exome testing revealed a *de novo* pathogenic nonsense variant p.(Tyr169*) in the *LMX1B* gene.

Conclusion: Both patients presented features unusual for NPS. Classic NPS features do not include congenital anomalies of kidney and urinary tract (CAKUT), developmental delay, obesity, cryptorchidism and severe scoliosis. This resulted in diagnostic delay. Genetic results lead to reverse phenotyping in the second patient. The hypothesis of an extended phenotype in NPS including CAKUT is one possibility, but is not suggested by animal model studies. The presence of a second genetic disorder is another possibility.

Session 5 – Syndrome delineation

14:00 INVITED TALK: FRÉDÉRIC BRIOUDE, NEW INSIGHTS IN IMPRINTING DISORDERS: THE EXAMPLE OF SILVER-RUSSELL AND BECKWITH SYNDROMES

14:45 TWO SIBLINGS HARBOURING TWO NONSENSE VARIANTS: KAUFMAN OCULOCEREBROFACIAL SYNDROME WITH VARIABLE INTRAFAMILIAL EXPRESSION

Presenting author: Elif SARAÇ

Elif SARAÇ[1], Kürşat Bora ÇARMAN[2], Beyhan DURAK ARAS[1], Sevilhan ARTAN[1]

1.Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Genetics, TURKEY
2.Eskisehir Osmangazi University, Faculty of Medicine, Department of Pediatric Neurology, TURKEY

E-mail for correspondence: elif.sarac@ogu.edu.tr

Kaufman oculocerebrofacial syndrome (KOS) (OMIM #244450) is an extremely rare autosomal recessive disorder caused by biallelic loss-of-function variants in *UBE3B. UBE3B* gene encodes an E3 ubiquitin-protein

ligase that is highly expressed during development and in various adult tissues. KOS is characterized by moderate to severe intellectual disability,growth deficiency,microcephaly and a distinctive facial gestalt. Common craniofacial features include short upslanting palpebral fissures, blepharophimosis, ear anomalies, hearing loss and laryngomalacia. Feeding difficulties,low cholesterol,axial hypotonia,neurological,cardiac and renal anomalies were also reported.
A 40-day-old female patient was referred to our clinic with dysmorphism. Polyhydramnios and single umbilical artery were observed on prenatal follow-ups, and amniocentesis was performed. Conventional cytogenetic studies demonstrated a normal karyotype and microarray analysis revealed no genomic imbalances. She was born after a full-term pregnancy by caesarean section. At birth, she was hospitalized in the neonatal intensive care unit for 10 days due to meconium aspiration. At initial admission, her weight was 2,920 gr (-2,6 SD),length was 47cm (-3 SD),occipitofrontal circumference was 34 cm (-3,2 SD). On examination prominent forehead, bilateral epicanthus,flat and wide nasal root,thick alae nasi,wide columella,anteverted nostrils, smooth philtrum,retrognathia,low-set ears,bilateral single transverse palmar crease and overlapping toes were observed. Midgut malrotation was suspected on esophagogastroduodenoscopy. On initial echocardiography, multiple cardiac masses were observed. Brain MRI showed no significant abnormalities. The family stated a distant consanguinity of unknown degree. Their 9-year-old son had a history of neuromotor developmental delay,autism,cryptorchidism and similar dysmorphic features. Laryngomalacia and hypocholesterolemia were observed in both patients.
We performed single gene sequencing (Illumina MiSeq/Nextera XT) for *UBE3B* and found heterozygous c.142C>T (p.Arg48Ter) and c.1261C>T (p.Gln421Ter) mutations (NM_183415.3). Sanger sequencing was performed in order to validate the variants and analyze the segregation. The parents were found to be heterozygous carriers and probands brother was heterozygous for both mutations.
Although Blepharophimosis-Intellectual Disability syndromes represent a clinically and genetically heterogeneous group of disorders, distinct morphological findings in specific disorders such as KOS, allow us to opt for targeted diagnostic testing. Intrafamilial clinical variability has been observed between affected sibs in the literature as well as our patients. Our report expands the phenotypic and mutational spectrum associated with this rare disorder.

14:48 TWO NOVEL CASES OS SNIJDERS BLOK-CAMPEAU SYNDROME IN POLISH POPULATION (SNIBCPS; #618205)

Presenting author : Ewelina PREIZNER-RZUCIDŁO

Magdalena JANECZKO[1], Ewelina PREIZNER-RZUCIDŁO[1]

1: University Children Hospital Cracow (UCH)

Email for correspondence: magdalena.janeczko78@gmail.com; e.preizner@gmail.com

Introduction: Characteristic features of Snijders Blok-Campeau syndrome include intellectual development ranges from mild to severe, seizures, muscular hypotonia, brain defects, speech problems, autistic behaviors and distinctive facial features. Pathogenic variants in CHD3 gene are proven to cause the disease. So far, about 150 cases of this syndrome have been described, including 2 de novo cases in Poland.
Case presentation:
Two children (8-year-old girl and 5-year-old boy) came to our genetic clinic independently, who from the beginning presented with delayed achievement of milestones, delayed speech development and similar dysmorphic features. The psychological examination in children revealed features of mild to moderate degree of intellectual disability, respectively. Common dysmorphic features in patients included: macrocephaly, flat face, midface hypoplasia , wide-set eyes, high-set eyes, proximal palpebral fissures, thinning eyebrows. Apart from hypospadias in the boy, no other birth defects were found. MRI of brain

showed no abnormalities. Initially cytogenetic microarray test was performed (Agilent Technologies, Santa Clara USA), which was normal in both cases. Then whole-exome sequencing was carried out (WES; Ilumina HiSeq 1500; Core Exome + Twist mtDNA Panel + Twist RefSeq Panel + ClinVar Custom Panel). In girl case the WES examination showed the presence of the heterozygous variant c.3535G>C (p.Asp1179His) in the CHD3 gene. The detected variant has not yet been described in the ClinVar, gnomAD and dbSNP databases. Bioinformatics analysis in the Varsome and Franklin programs indicates the likely pathogenic nature of the variant.
Boy's results showed heterozygous variant c.3692G>A (p.Arg1231Gln) in the CHD3 gene and heterozygous variant c.266G>A (p.Arg89His) in the EDAR gene.The c.3692G>A variant (p.Arg1231Gln) in the CHD3 gene has been described in the ClinVar database as pathogenic/likely pathogenic and correlated with SNIBCPS; #618205.The variant in the first case was inherited from the mother. Mother has as well typical facial features. The mother functions in the society in the lower range of the norm, earns her living from occasional paid work. However, in the second case we were unable to examine the boy's father, he died in an accident. Archival family photos show that father did not present dysmorphic features characteristic of the Snijders Blok-Campeau syndrome, which allows us to assume that the boy has a "de novo" variant in the CHD3 gene.

Conclusion:
Snijders Blok-Campeau'a syndrome is not only rare, but also rarely diagnosed due to ambiguous symptoms. As in our cases we need to consider positive family background.

14:51 SKELETAL DYSPLASIA WITH AMELOGENESIS IMPERFECTA IN TWO SIBLINGS HARBORING BIALLELIC PATHOGENIC MISSENSE VARIANT IN SLC10A7 GENE

Presenting author: Akçahan Akalın

Akçahan Akalın[1], Ercan Ayaz[2]

[1] *Department of Pediatric Genetics, Diyarbakir Children's Hospital, Diyarbakır, Turkey*
[2] *Department of Pediatric Radiology, Diyarbakir Children's Hospital, Diyarbakır, Turkey*

Email for correspondence: akcahanbalci@gmail.com

Homozygous or compound heterozygous mutations in the Solute Carrier Family 10 (Sodium/Bile Acid Cotransporter Family), Member 7 (*SLC10A7*, MIM#611459) gene cause Short Stature, Amelogenesis Imperfecta, and Skeletal Dysplasia with Scoliosis (SSASKS, MIM#618363). According to Nosology and Classification of Genetic Disorders of the Skeleton 2023 revision, it is grouped under "Group 5-Dysplasias with multiple joint dislocations". To our knowledge, 9 individuals with pathogenic biallelic variants in *SLC10A7* gene have been reported so far. Affected individuals display dysmorphic features, such as dental abnormalities, severe pre- and postnatal disproportionate short stature, multiple dislocations with monkey wrench appearance of the proximal femora, shortened long bones with metaphyseal widening, and advanced carpal and tarsal bone age. Herein, we describe two siblings with disproportionate short stature and amelogenesis imperfecta due to a pathogenic biallelic missense variant in *SLC10A7* gene. The first case was a 4-year and 9-month-old boy who referred to our department for short stature, kyphoscoliosis, joint laxity, and distinctive facial findings. The patient was the third live-born child of first cousin parents following a 36th gestational week pregnancy with a birth weight of 2,600 gr (-0,23 SDS). Birth length and occipitofrontal circumference (OFC) were not noted. At the 20th gestational week, prenatal ultrasonography revealed shortening of the long bones and macrocephaly. The patient had respiratory distress requiring neonatal intensive care unit support. He was discharged without respiratory assistance on the postnatal 15th day. Before admission to our center, he had been evaluated for growth retardation and characteristic facial features. Karyotype analysis was consistent with 46, XY, and FGFR3 sequence analysis was normal. Physical

examination at his admission revealed a body length of 81 cm (−6.32 SDS), weight of 10.2 kg (-5.09 SDS), and OFC of 40 cm (-3.03 SDS). He had a round flat face, a high forehead with prominent metopic suture, epicanthus on the left eye, bilateral proptosis, a short nose, a long philtrum with a thin upper lip, microstomia, and retromicrognathia. A short neck, a single palmar crease on the left hand, joint laxity without dislocations, and kyphoscoliosis were also noted. In addition, hypo-mineralized amelogenesis imperfecta and bilateral fundus atrophy were detected on eye and dental examination. Abdomen ultrasound was normal yet echocardiography showed tricuspid insufficiency. Plain radiograms revealed shortened long bones with metaphyseal widening, genu valgus, advanced carpal ossification, and thoracolumbar levoscoliosis. Epiphyseal anomalies were not observed. The iliac bones were broad and round and the acetabula were shallow as well. The Denver Developmental Screening Test II (DDSTII) was compatible with retardation except for the language. His sibling,19 years old, underwent several operations for kyphoscoliosis, had similar facial gestalt and radiological findings. Based on these a clinical diagnosis of SSASKS was made on clinical and radiological grounds. Next-generation sequence analysis identified a *SLC10A7* pathogenic biallelic variant (NM_032128.4): c.221T>C, p.Leu74Pro) in exon 3. This change was previously reported in the Turkish population. Notably, dental abnormalities have not been described so far for this dysplasia group; hence, amelogenesis imperfecta can be suggested as a new clinical feature indicative of *SLC10A7* mutations. We believe that as more patients are reported in the literature, the phenotypic features of the disease and the genotype-phenotype correlation can be more accurately defined.

Figure Legends:

Fig.1 AP spine radiograph reveals thoracolumbar levoscoliosis, rounded iliac wings with flattened acetabular roofs.

Fig. 2 PA chest radiograph shows bilateral shortened humerus with widened distal metaphysis and mild diaphyseal irregularity.

Fig. 3 Lateral skull radiograph showing flattened face with mild retromicrognathia.

Fig. 4 Bilateral femur radiographs of the present case (a) and a healthy boy at the same age. Please note that widened metaphyses were more prominent in the present case than in the control.

Fig. 5 Hand radiograph of the present case (a) and healthy control (b) at the age of 4-year and 9-month-old. Advanced bone age was a striking feature compared to the healthy control.

Fig. 1

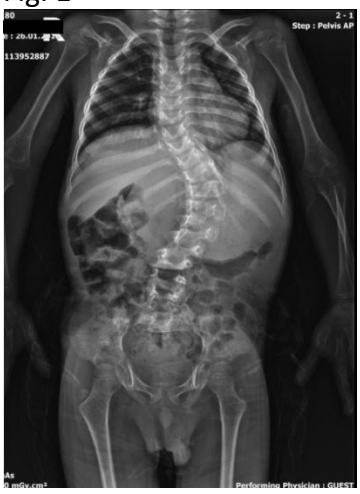


Fig. 2

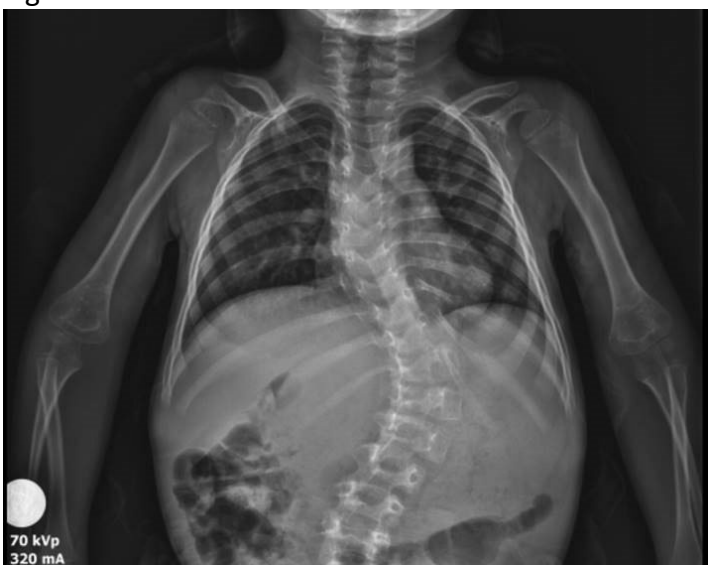


Fig. 3

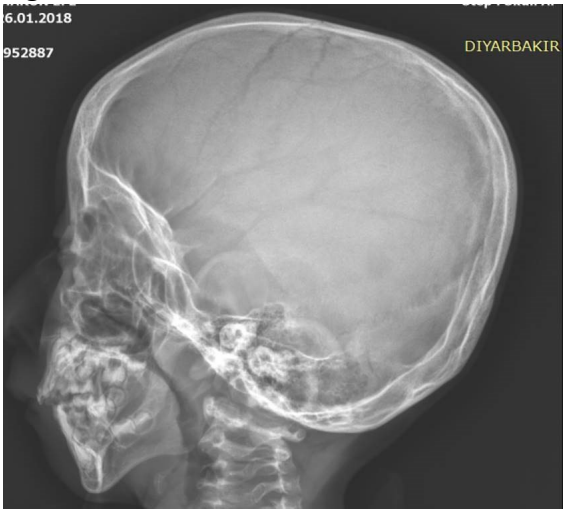


Fig. 4

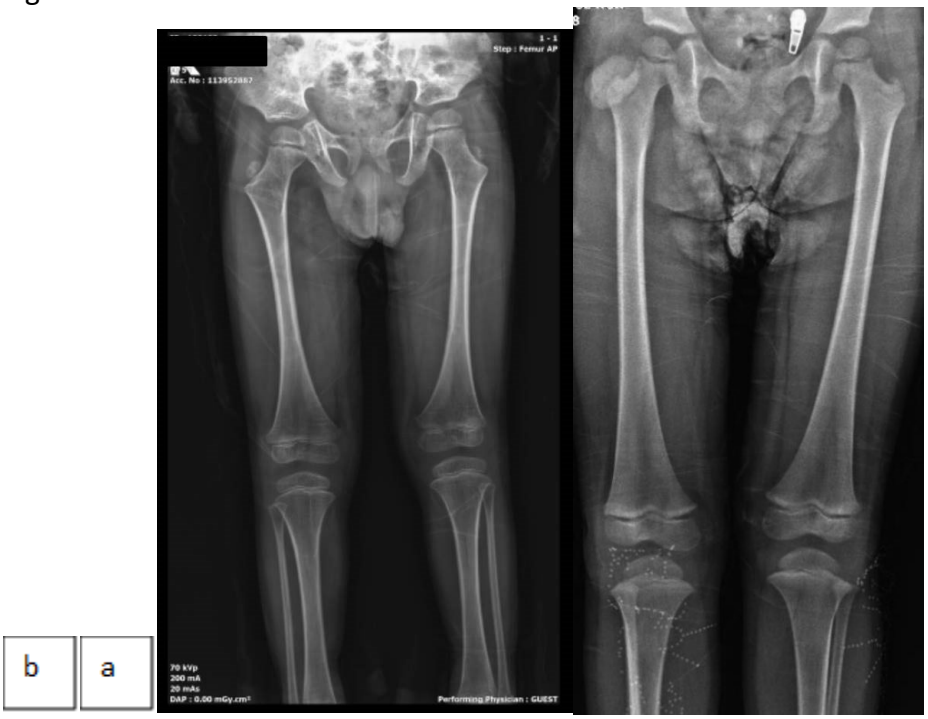
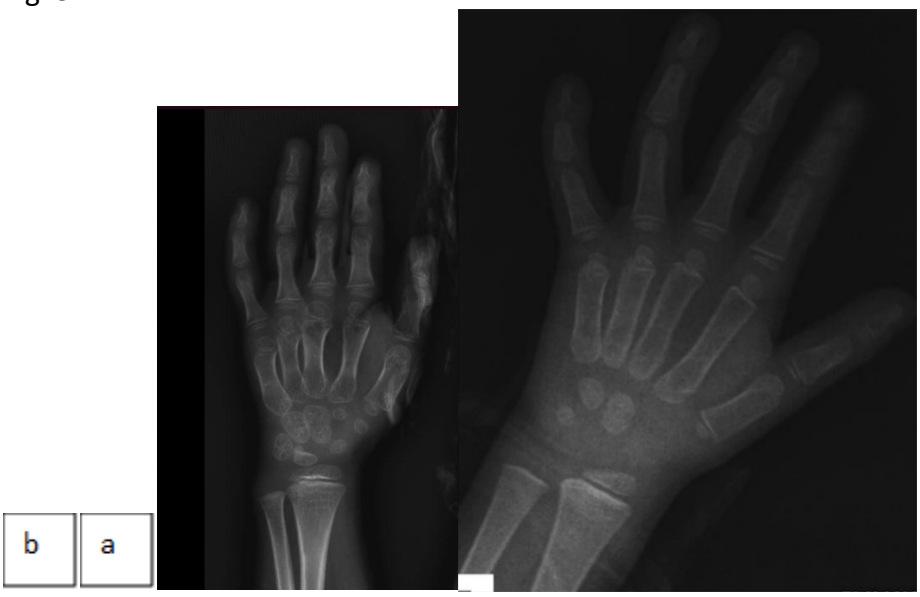


Fig. 5



15:07 REPORT OF THE FIRST ENDOCRINE-CEREBRO-OSTEODYSPLASIA PATIENT TO REACH CHILDHOOD AGE

Presenting author: Derya Hazal ÖZBAKIR

Derya Hazal ÖZBAKIR[1], Sinem KOCAGİL[1], Ebru ERZURUMLUOĞLU GÖKALP[1], Oğuz ÇİLİNGİR[1]

1: Department of Medical Genetics, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Turkey

E-mail for correspondence: hazalozbakirogu@gmail.com

Endocrine-cerebro-osteodysplasia (OMIM #612651, ECO) is an extremely rare, neonatal lethal, autosomal recessive disorder with multiple anomalies involving the endocrine, cerebral, and skeletal system. To date, seven cases diagnosed with ECO, that all died in utero or in neonatal period, have been described in the literature.

Here we report a 18 month-old female patient who was born at 37+6 weeks to consanguineous parents. Physical examination revealed hydrocephalic appearance, short nose, depressed nasal bridge, broad nasal ridge, long philtrum, thin lips, low-set ears, brachydactyly, bilateral postaxial polydactyly of the hands, sandal gap and short micromelia. In her cranial MRI, hypoplasia of the brainstem and intensity changes in peripheral white matter in both cerebral hemispheres that may be due to delayed myelination, and external hydrocephaly due to cortical atrophy were detected. In her abdominal ultrasonography dilated pelvicalyceal structures of the left kidney and increased echogenicity in both kidneys were noted.

Whole exome sequencing analysis revealed a homozygous likely pathogenic *CILK1* (NM_014920.5):c.1664_1665del (p.Tyr555CysfsTer48) variant in the patient, and segregation analysis showed the healthy parents as carriers. In addition to that the patient had a pathogenic *LMNA* (NM_170707.4):c.808A>C (p.Lys270Gln) variant that was inherited from her healthy mother.

This is the first report of ECO diagnosed in childhood. There might be several underlying mechanisms that lead to prolonged survival for our patient; such as *CILK1* variant being a null variant located at the 13th exon which is the penultimate exon, therefore leading to a partial decrease of protein expression and/or it may be caused by the presence of a secondary pathogenic *LMNA* variant.

15:10 REANALYSIS OF EXOME DATA IS USEFUL: EFEMP1 ASSOCIATED CONNECTIVE TISSUE DISORDER IS DIAGNOSED

Presenting author: Natalja BANNINK

Natalja BANNINK Genetic and developmental pediatrician[1] , Serwet DEMIRDAS Clinical geneticist[2]

1. *Franciscus Gasthuis & Vlietland Rotterdam & Schiedam, The Netherlands*
2. *Erasmus Medical Center Rotterdam, The Netherlands*

Email for correspondence: n.bannink@franciscus.nl

We present a boy of now 16 years old with Marfanoid habitus. He had on early age an inguinal hernia on both sides and an umbilical hernia combined with hypermobility of the joints. The hernias are corrected. Molecular genetic testing at ages 7 and 12 years didn't show an explanation for this clinical picture of a suspected hereditary connective tissue disorder.
Six years after first presentation, he visited the hospital because of abdominal pain attacks, weight loss and vomiting 2-6 times a day. Examination showed a normal belly, an inguinal hernia on both sides and a severe scoliosis, not known before. He was referred to the surgeon and the orthopedic surgeon in an academic hospital.
Four months later, he presented an acute abdomen with free air. The X-ray of the chest showed a high aperture. We transferred him to the intensive care of the academic hospital. He had a perforation of the stomach after para-esophageal herniation of the stomach into the thorax. During the surgical correction the surgeon saw multiple diverticula of the bowels and the bladder. He needed extracorporeal membrane oxygenation after resuscitation.
The exome data were reanalyzed and two variants of unknown significance were found in the EFEMP1 gene:
- NM_001039348.2(EFEMP1):c.698G>A, p.(Gly233Asp)
- NM_001039348.2(EFEMP1):c.1320+2T>A, p.?.
Both parents proved to be carrier of one variant. His brother known with inguinal hernias and milder Marfanoid habitus was tested en affected also. The results of the RNA sequencing on fibroblasts of our patient will follow.
EFEMP1 is described as being expressed primarily in the vasculature, retina, and skin fibroblasts. In 2020, a new EFEMP1 gene associated connective tissue disorder is described. It inherited autosomal recessively with a pronounced visceral, as distinct from cutaneous, presentation. Facial features are downslanting of the eyes, high narrow palate and long narrow face. Inguinal, femoral and Bochdalek herniae are common combined with visceral diverticula of colon and bladder, myopia, hypotonia and arachnodactyly. The phenotype of our patient was comparable with the described cases in the literature.
Do you know patients with variants in the EFEMP1 gene? Let's include them for research, as we are collecting a cohort of known patients for clinical description.

15:13 PRENATAL DIAGNOSIS OF SIFRIM-HITZ-WEISS SYNDROME: POSTNATAL FOLLOW UP IN A 2-YEAR-OLD PATIENT AND LITERATURE REVIEW

Presenting author: Yvan Herenger

Yvan HERENGER [1], Katja LUDIN[1], Benno ROETHLISBERGER[1]

1: Genetica AG, 8001 Zürich, Suisse

Email for correspondence: y.herenger@genetica.ch

Introduction: Sifrim-Hitz-Weiss syndrome is an autosomal dominant condition with neurodevelopmental disorder (NDD) and multiple congenital anomalies (MCA), first described in 2016. The condition is believed to be associated with a highly variable phenotype and nonspecific facial features.
Methods: We performed whole exome sequencing and trio analysis in a fetus with MCA and identified a de novo missense variant in CHD4 gene. We describe the molecular and clinical data, including detailed postnatal course until the age of 2 years. We review actual knowledge from the literature.
Results: In a fetus with prenatal finding of a bilateral postaxial polydactyly of the hands and feet in the 17th week of gestation we identified a de novo heterozygous and previously undescribed missense variant in CHD4 gene (p.(Arg1095Cys)). The fetus was carried to term and born with birth measurement in the low normal range (P3-10). The polydactyly was corrected surgically, and no other congenital abnormalities were identified in the comprehensive postnatal checkup. The neuropediatric assessment at 4 and 12 months fand a mild muscular hypotonia. At the age of 2 years the patient had a development in the normal range and showed suggestive facial features of Sifrim-Hitz-Weiss syndrome. We review the literature and compare with already published patients. We try to identify a recognizable facial gestalt.
Conclusion: our case report attests the broad spectrum of in Sifrim-Hitz-Weiss syndrome and confirms the possibility of a good developmental prognosis.

Session 6 – WES and WGS

16:00 WHOLE-GENOME SEQUENCING OF RARE DISEASES IN A NATIONAL HEALTHCARE SYSTEM: CLINICAL AND DIAGNOSTIC IMPLICATIONS

Presenting author: Silvia Kalantari

Silvia Kalantari[1], Francesco Bassanese[2,3], John W. Belmont[4], Ryan J. Taft[4], Julia Ortega[4], Alicia Scocchia[4], Diana Carli[5], Alessandro Mussa[5], Giovanni Battista Ferrero[5], Elisa Giorgio[6,7], Enza Maria Valente[6,7], Fabio Sirchia[6,8]

[1] *Department of Medical sciences, University of Turin, Turin, Italy.*
[2] *University of Pavia, Pavia, Italy.*
[3] *Department of Pediatrics, IRCCS San Matteo Foundation, Pavia, Italy.*
[4] *Illumina Inc., San Diego, CA, USA.*
[5] *Pediatric Genetics Unit, Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy.*
[6] *Department of Molecular Medicine, University of Pavia, Pavia, Italy.*
[7] *Medical Genetics Unit, IRCCS Mondino Foundation, Pavia, Italy.*
[8] *Medical Genetics Unit, IRCCS San Matteo Foundation, Pavia, Italy.*

Email for correspondence: silvia.kalantari@unito.it

Patients with hereditary rare diseases often do not receive a molecular diagnosis for many years. The main cause of this “diagnostic odyssey” is the fragmentary approach to genetic testing, often restricted to chromosomal microarray and candidate genes.
Thanks to improving technologies and sinking costs, whole exome (WES) and whole genome sequencing (WGS) recently made their appearance in clinical settings. WGS has shown numerous advantages over the former, as it detects variants in non-coding regions and in mitochondrial DNA, copy number variants, balanced chromosomal rearrangements and uniparental disomies. The adoption of WGS in clinical settings faces challenges including costs and a huge number of variants found for each genome. The analytic burden can however be lightened when the analysis is limited to the clinical genome (cWGS), i.e. *in silico* bioinformatic analysis of coding regions of known disease genes.
Our Medical Genetics Units in Torino, Trieste and Pavia started a collaboration with Illumina Company offering family-based cWGS to patients with undiagnosed rare diseases within the context of the Italian

National Healthcare System, where such testing is normally not available. Inclusion criteria were normal first-tier genetic testing (either chromosomal microarray analysis and/or gene-panel analysis) and clinical suspicion of an ultra-rare monogenic disease. A definitive molecular diagnosis was reached in 65.6% of the 64 paediatric patients enrolled, including a mosaic trisomy 9, a case of disease due to a variant in a small nuclear DNA gene, and two cases in which small indels could not be detected with previous methods nor with WES.
Our study demonstrates that the use of cWGS in a rare disease setting increases our ability to make diagnoses even in complex unsolved cases. We therefore speculate that its introduction within the Italian health system as a first-tier test might have diagnostic and economic advantages.

16:15 THE CHALLENGE OF NEW GENES IN CLINICAL EXOME AND MOLECULAR KARYOTYPING

Presenting author: Damien Lederer

Damien Lederer, Olivier Monestier, Lucie Evenepoel, Marianne Crespin, Florence Arts 1

1 Institut de Pathologie et de Génétique, Centre for Human Genetics, Gosselies, Belgium

Email for correspondence: damien.lederer@ipg.be

Exome sequencing, in many countries, has now become a routine diagnotic test in children and adults with intellectual deficiency or developmental disorders. Even though it is a powerful tool that helps the clinicians in the diagnostic process, it is limited by available datas on gene-disease association. Such associations require powerful and up-to-date databases. Therefore, it creates a gap when a new gene-disease association is described in the literature and is not yet present in databases used for exome analysis.
Here, we describe 3 patients with inherited deletion or de novo missense variants in genes that were reported without gene-disease association.
The first patient is a 3 years old boy seen in 2015 with developmental and speech delay, growth retardation and behaviour trouble. Molecular karyotyping revealed a 132 kb deletion at 10p15.3 including ZMYND11 and a 132 kb deletion in the DDX53 gene located on Xp22.11. Both deletions were maternally inherited. Since the mother reported to have no difficulties at school and poor datas were available for ZMYND11, only the Xp22.11 deletion was considered. A research collaboration was done to better study the impact of Xp22.11 and after few years of research, it was concluded that the Xp22.11 deletion has probably no impact on the phenotype. Updated literature review revealed that ZMYND11 deletion is related to intellectual deficiency. Maternal grand parent anamnesis and analysis revealed that the ZMYND11 deletion occured de novo in the mother and that the mother had serious difficulties at school overcame by hard work from maternal grand-parents.
Two other patients had de novo variants in KCNH3, and ADGRL1/TAF4. No gene-disease association was available for those genes but they were highlighted by the biologists based on prediction softwares. Clinical work up and literature review then confirmed the suspected gene-disease association. Classification of those variants will be debated.

16:30 CHD4, KANSL1, HFE – WHICH DIAGNOSIS FOR A 3 YR. OLD BOY WITH GLOBAL DEVELOPMENTAL DELAY AND "TRIPLE TROUBLE" IN EXOME SEQUENCING?

Presenting author: Cord-Christian Becker

C.-C. Becker[1,#], K. Alt[1], E. Grauer[1], M. Seidl[2], G. Miltenberger-Miltenyi[1]

[1] *MVZ genetikum, Munich/Neu-Ulm/Stuttgart, Germany.*
[2] *Social Pediatric Center, Memmingen Hospital, Germany.*

Corresponding author: Becker@genetikum.de

Next generation sequencing (NGS) methods have improved considerably over the last few years enabling an increase in the diagnostic yield for exome sequencing technologies up to 30-40% (Srivastava et al., 2019; Alvarez-Mora et al., 2022). Multiple potentially relevant genetic findings (MPRF) have been reported in 4,9% to 8,5% of patients with genetic diagnoses (Posey et al., 2017 ; Smith et al., 2019 ; Beetz and Bauer, 2020). Around 3-7% percent of patients with MPRF even receive triple diagnoses (Posey et al, 2017 ; Smith et al., 2019). Therefore, there have been claims to be cautious with "broadening" the phenotype for a single-gene disorder on a single case level (Beetz and Bauer, 2020).

Here we describe a 3-year-old boy with global developmental delay, atrial septal defect, turricephaly, ear dysplasia, obesity and ametropia. Trio whole exome sequencing detected two novel heterozygous de novo missense variants in the genes CHD4 (Sifrim-Hitz-Weiss syndrome) and KANSL1 (Koolen-De Vries syndrome). Both variants were evaluated as likely pathogenic (Class 4) and therefore as likely clinically causative for the patient's symptoms. Furthermore, as an incidental finding we detected two pathogenic compound heterozygous HFE gene variants and, hence, a potential future diagnosis of hereditary hemochromatosis. Chromosome analysis, array-CGH and diagnostics on fragile X or Prader Willi syndrome did not reveal any disease-causing alterations.

CHD4 is involved in the epigenetic regulation of gene transcription, DNA repair, and cell cycle progression by chromatin remodeling. Malfunction of CHD4 leads to impaired synaptic connectivity. KANSL1 also acts as chromatin remodeler and is also associated with synaptic regulation. Malfunction of CHD4 leads to memory deficits.

Syndromes associated with both genes show marked overlap of phenotypes: developmental delay, intellectual disability, muscular hypotonia and congenital heart defect. On the other hand, some features occur more likely in connection with Sifrim-Hitz-Weiss syndrome such as impaired vision, infantile strokes, moyamoya disease, short stature, and hypogonadotropic hypogonadism. On the contrary, some features are associated more often with Koolen-De Vries syndrome such as musculoskeletal anomalies (joint hypermobility, short stature, pectus excavatum, scoliosis), urogenital malformations, tracheo-/laryngomalacia, structural brain malformation and skin abnormalities.

The reported findings in our patient emphasize that multiple potentially relevant genetic findings are rare but should be taken into account with exome interpretation. Discontinuing exome analysis after obtaining one relevant genetic finding might lead to missing a potential second or even third relevant finding.

16:45 APPLICATION OF GENOME SEQUENCING TO DIAGNOSE AN ATYPICAL CASE OF RETT SYNDROME

Presenting author: Sarah SCHUHMANN

Sarah SCHUHMANN[1], Georgia VASILEIOU[1], Christian THIEL[1], Bavarian Genomes Network for Rare Diseases, André REIS[1]

[1]Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg FAU, Erlangen, Germany

Email for correspondence: Sarah.Schuhmann@uk-erlangen.de

Exome sequencing (ES) has become the first-tier diagnostic approach in diagnosing Mendelian disorders, especially those with high genetic heterogeneity, e.g. neurodevelopmental disorders. Despite huge improvements in recent years, still some 50% remain without a diagnosis. To identify this "missing heritability" genome sequencing (GS) is proposed as a second-tier approach in unsolved cases. The ongoing project Bavarian Genomes addresses this problem and aims at identifying causative genetic variants in unsolved individuals with rare disorders using GS in combination with various other genomic techniques and an interdisciplinary data interpretation approach.

We included in this project a six-year-old male individual from healthy non-consanguineous parents with severe developmental delay, inability to speak, unsteady gait, muscular hypotonia, microcephaly, short stature, cryptorchidism and cardiac arrhythmia. Chromosomal analysis showed a 47,XXY karyotype as an incidental finding. Trio ES and copy number variant (CNV) analysis of exome data did not reveal any pathogenic alteration. Performing GS we now identified a *de novo* 1.92 kb deletion spanning a part of exon 4 and the 3' untranslated region of the *MECP2* gene, leading to a predicted loss of 235 coding basepairs (78 amino acids). This CNV was not identifiable in ES because of the partial nature of the deletion of this exon and the absence of untranslated sequences from the target. Intragenic deletions of *MECP2* often localized in exon 3 or 4 are encountered in 5-10% of Rett syndrome individuals. Because of the Klinefelter syndrome chromosomal constellation, the clinical manifestations of this male individual resembled that of the female Rett syndrome cases. Occurrence of atypical Rett syndrome in Klinefelter individuals is well described in the literature.

Our case highlights the benefits of GS in sequencing of regions not included in the exome target and in detection of small CNVs, missed by either chromosomal microarray analysis or ES. GS is thus superior to re-analysis of ES data, as evidenced by recent studies, which reported up to three times higher yield. A systematic evaluation of GS for diagnosing unsolved cases of rare disorders within the Bavarian Genomes Network is ongoing.

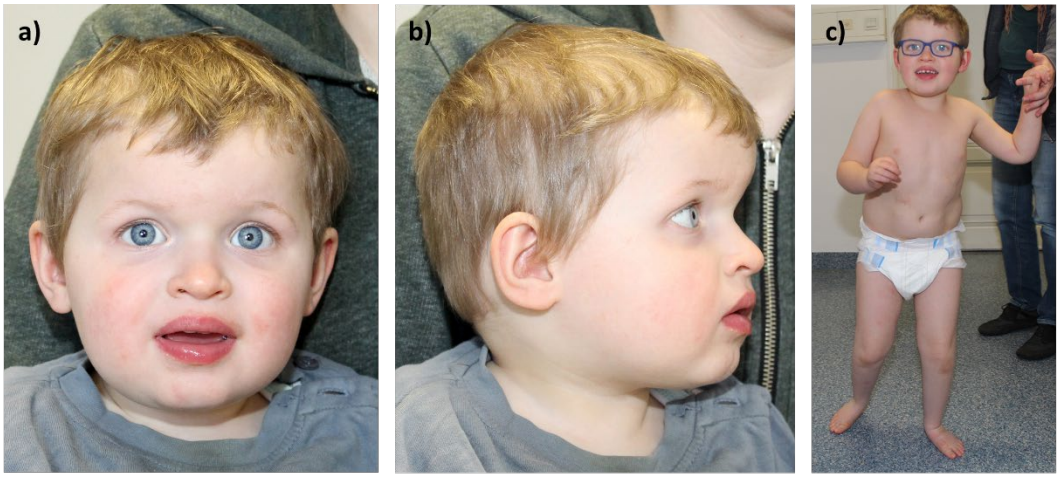


Figure 1: Individual with XXY Karyotype and MECP2 partial deletion. a) and b) Individual at age 2.5 years presenting with prominent forehead, sparse eyebrows, deeply set eyes, short philtrum, thick upper and lower lip vermilion and small teeth. c) Individual at age 6.25 years showing muscular hypotonia, unsteady gait, flexion contractures of hips and knees, pes planus (right) and drop-foot (left)

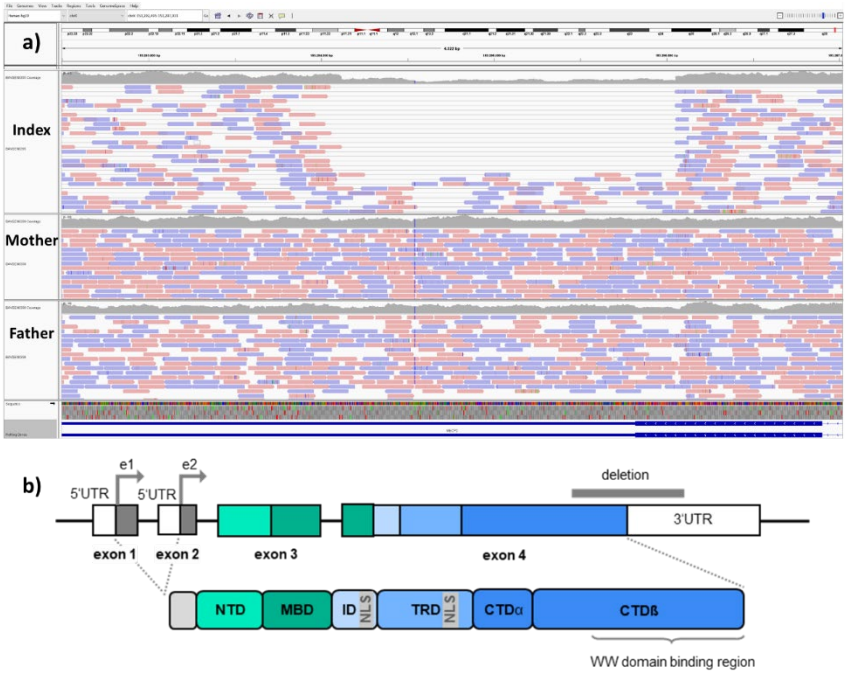


Figure 2: De novo partial deletion of exon 4 and 3'UTR of *MECP2*. a) IGV views of the individual (top panel) and the parents (lower panels) showing a de novo deletion spanning the last 235 coding basepairs of exon 4 and a part of the 3'UTR of *MECP2*. b) Schematic presentation of *MECP2* gene structure and functional domains. Two different isoforms (e1, e2) result from alternative translation start sites. NTD, N-terminal domain; MBD, methylated DNA-binding domain; ID, interdomain; TRD, transcription repression domain; CTD, C-terminal domain containing a WW domain binding region; NLS; nuclear localization signals. The deletion identified in the individual is displayed as a gray line.

16:48 PHELAN MCDERMID SYNDROME - IS IT THE BEGINNING OR THE END OF THE DIAGNOSTICS?

Presenting author: Karolina ŚLEDZIŃSKA

Karolina ŚLEDZIŃSKA1, Monika CICHOŃ-KOTEK1, Anna KŁOSOWSKA1, Jolanta WIERZBA2

1: Department of Pediatrics, Hematology and Oncology, MUG, Gdansk, Poland
2 : *Institute of Nursing and Midwifery, Division of Internal and Pediatric Nursing, MUG, Gdansk, Poland*

Email for correspondence: ksledzinska@gumed.edu.pl

We would like to present 2 atypical cases of Phelan McDermid syndrome.
First is 18 months old girl, born in 39hbd, Apgar 7, with post-partum complications of respiratory distress, hypoglycemia, congenital infection treated with antibiotics, suffered from feeding difficulties with suspicion of malrotation. On further diagnostics, abnormalities of the CNS, eyes, heart, urogenital system, hearing impairment, together with dysmorphic features and hypotonia were described. Moreover, on physical examination increased amount of fat tissue/oedema of the limbs, especially hands and feet, with atypical creases were found.
Genetic diagnostic was performed: karyotype with aCGH showed the presence of 22 ring chromosome with 4.6 Mbp duplication of the region 22q11.21q12.1 and 9.1 Mbp deletion of region 22q13.2q13.33, containing gene *SHANK3*. Due to marked delay in psychomotor development and the presence of multiple congenital defects, WES was perfomed, which didn't reveal any further abnormalities.

The second child, is a 4-months old male infant, born in a poor condition, with respiratory distress, congenital infection, treated with antibiotics. On the following days suffered from feeding difficulties, and was diagnosed with bilateral hydronephrosis complicated with urinary tract infection. Further radiological tests

of the brain showed thin corpus callosum and bilateral subdural hygromas. On examination presented with atypical ?oedema ?skin folds on upper and lower limbs and facial dysmorphic features.
Genetic testing (karyotype and aCGH) were performed showing 6.69 Mbp deletion of the region 22q13.31q13.3 containing gene *SHANK3*. Due to phenotypical similiarity to Symmetric circumferential skin creases, congenital, 1 syndrome related to gene TUBB, WES was performed – the result is pending. To conclude, on example of Phelan McDermid patients, the diagnosis of chromosomal rearrangements may sometimes not fully explain the phenotype, with a need of further analysis.

16:51 NOVEL HOMOZYGOUS NONSENSE VARIANT IN THE INPP4A GENE IN A PATIENT WITH NEURODEVELOPMENTAL DELAY, STRABISMUS AND CEREBELLAR ANOMALIES

Presenting author: Enrico AMBROSINI

Enrico AMBROSINI[1], Vera ULIANA[2], Francesca FOTI[3], Alessandra TERRACCIANO[4], Giulia VITETTA[2], Valeria BARILI[1], Emanuela Claudia TURCO[5], Benedetta PICCOLO[5], Antonio NOVELLI[4], Antonio PERCESEPE[1,2]

1 Medical Genetics, Department of Medicine and Surgery, University of Parma, Italy
2 Medical Genetics Unit, University Hospital of Parma, Italy
3 Unit of Neuropsychiatry of Children and Adolescents, AUSL of Parma, Italy
4 Medical Genetics Laboratory, IRCCS Pediatric Hospital "Bambino Gesù", Rome, Italy
5 Child Neuropsychiatric Unit, Mother and Child Department, University Hospital of Parma, Italy

Email for correspondence: enrico.ambrosini@unipr.it

Type I inositol polyphosphate-4-phosphatase (INPP4A) is a phosphoinositide phosphatase highly expressed in the brain, heart, and skeletal muscle. Its physiological role has been studied in two mouse models, showing a neuroprotective function during postnatal development. The INPP4 gene has not been associated to known diseases in OMIM yet, but homozygous truncating mutations have been found in at least 5 independent families in association with a spectrum of neurodevelopmental disorders ranging from moderate intellectual disability to developmental and epileptic encephalopathy, with pontocerebellar hypoplasia, microcephaly and strabismus.
Here we describe a 6-year-old girl with a novel homozygous truncating variant in *INPP4A*,referred to medical attention for a delay in psychomotor development. Neuropsychiatric evaluation at 1 year attested mild distal tremors of the upper limbs, alternating exotropia, horizontal nystagmus with consequent tendency to recline the head, mild hyperreflexia, poor head control and mild axial hypotonia. Brain MRI showed cerebellar hypoplasiawith enlarged subarachnoid spaces and thinning of the medio-posterior portion of corpus callosum. Blood tests and abdominal ultrasound were normal. In the following years, there was a severe delay in language and motor development: currently, the girl pronounces only a few words but shows sufficient comprehension, she can't walk autonomously and maintains a wide-based standing position.
On a new pregnancy of the mother, a genetic evaluation was performed: parents are second cousins and had a previous pregnancy hesitated in neonatal death. The proband has two healthy brothers and shows no relevant cranio-facial dysmorphisms.
CGH-array was negative but identified several regions of homozygosity located on chromosomes 2 and 5. The proband and the parents were then analyzed with clinical exome (ClinEX pro kit – 4bases) and the homozygous variant c.2816G>A (p.Trp939*) was found in the INPP4A gene, on chromosome 2. The variant was found in heterozygosis in both parents, it's absent in general population databases and it's located on the last exon (26th) of the gene: other two truncating variants affecting the last exon were already described, predicted and demonstrated as deleterious by functional studies, escaping nonsense-mediated mRNA decay and altering the intracellular distribution. We then considered this variant as likely pathogenic. The

variant was found in heterozygosis in the DNA extracted from cordonal blood of the female newborn of the couple, who showed no relevant symptoms.
Unlike the other reported patients, our proband had no relevant dysmorphisms like microcephaly, large and low-set ears or micrognathia, no contracture of the hands and no seizures, suggesting a variable expressivity of the syndrome. More clinical reports and functional studies are needed to improve the clinical and molecular characterization of INPP4A-related syndrome.

16:54 NOVEL HETEROZYGOUS ZFHX4FRAMESHIFT VARIANT IN A FETUS WITH ISOLATED OROFACIAL CLEFT

Presenting author : Maria Luisa Garau

Maria Luisa Garau[1]*, Marny Fedrigo[2], Paola Veronese[3], Leonardo Salviati[1], Ugo Sorrentino[1]

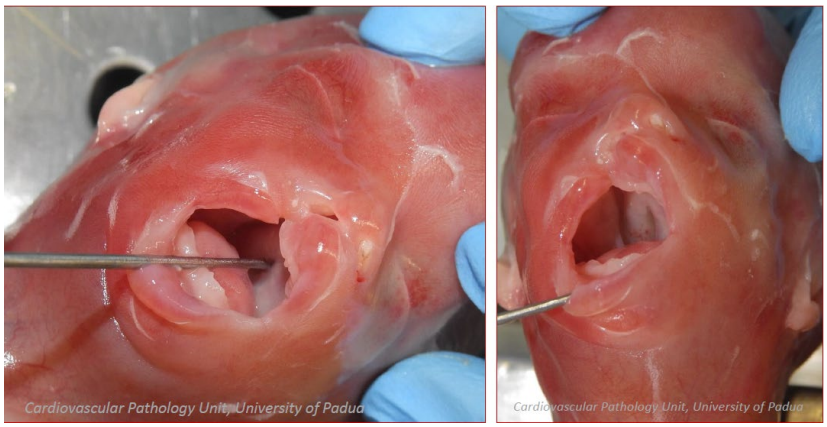
[1]: *Clinical Genetics Unit, Department of Women's and Children's Health, University of Padova, Padova, Italy*

[2]: *Cardiovascular Pathology and Pathological Anatomy Unit, Department of Cardiac, Thoracic,Vascular Sciences and Public Health, University of Padova, Padova, Italy*

[3]:*Maternal-Fetal Medicine Unit, Department of Women's and Children's Health, Padova, Italy*

Corresponding author: marialuisa.garau@studenti.unipd.it

Recent literature, based both on gene set enrichment studies and single case reports, has provided evidence that the *ZFHX4* gene on chromosome 8 should be considered as a candidate gene for isolated orofacial cleft. However, the data provided so far are biased by some confounding factors, which have not yet allowed the unequivocal recognition of the specific role of ZFHX4 in determining the orofacial phenotype. We would like to help define the effect of *ZFHX4* loss-of-function mutations by reporting an additional case recently diagnosed in our University Hospital. The proband was a fetus, diagnosed at the second trimester ultrasound screening with an apparently isolated, right sided orofacial cleft, involving the hard palate and the upper lip. Whole exome sequencing analysis of the DNA extracted from an amniotic fluid sample allowed the identification of a *de novo* NM_024721.4:c.3943delG p.(Glu1315Argfs*29) frameshift variant in exon 9 of the *ZFHX4* gene. The variant is novel, being absent from the gnomAD 2.1 and 3.1 databases and from the main mutation archives (ClinVar, LOVD, HGMD), and it is predicted to cause loss of protein function. The parents decided to terminate the pregnancy regardless of the molecular diagnosis. Pathological examination confirmed the isolated, monolateral orofacial malformation, in the absence of other major abnormalities. In conclusion, the identification of a *de novo* loss of function mutation in a proband affected by isolated, unilateral cleft lip and palate reinforces the hypothesis that *ZFHX4* loss of function mutations should be considered a self-sufficient cause of orofacial abnormalities.



Unknowns

20:00 AN UNSOLVED CASE OF UNILATERAL HEMIHYPERTROPHY WITH MILD INTELLECTUAL DISABILITY AND CENTRAL PRECOCIOUS PUBERTY

Presenting author : Diogo Fernandes da Rocha

Diogo Fernandes da Rocha, MD[1]; Pedro Louro, MD[1,2]

1: Serviço de Genética Médica, Centro Hospitalar e Universitário de São João, Porto, Portugal
2: Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal

Email for correspondence: diogo.fernandes.rocha@chsj.min-saude.pt

Unilateral hypertrophy can result from genetic causes such as Proteus and Klippel-Trenaunay syndromes, which are associated to pathogenic variants in the *AKT1* and *PIK3CA* genes. These genes regulate cell growth and proliferation, leading to asymmetrical overgrowth of tissues. Here we present an 8-year-old girl who was a late preterm infant and required neonatal ventilation due to apnea and hypotonia. She has been a macrosomic girl since birth, and presently she has unilateral hypertrophy affecting the left hemiface and limbs. At the last appointment, she was over 170cm tall and weighed around 70kg. Additionally, she has been manifesting a few learning difficulties at school and some issues in social integration due to the early development of secondary sex characteristics (with central precocious puberty since age six). It is also known that she was born with an umbilical hernia, a congenital melanocytic nevus, an enlarged lobulated spleen, bilateral pelvis dilation and strabismus. Brain MRI was normal, with the exception of a pituitary gland of reduced dimensions without apparent hormonal deficit. No relevant family history or parental consanguinity are known. Previous genetic testing on blood was negative, including methylation analysis for Beckwith-Wiedemann syndrome, karyotype, microarrays, and trio whole exome sequencing. At the moment, she maintains a multidisciplinary follow-up in our hospital center, although we have not been able to clarify its etiology. Nevertheless, we recognize the importance of establishing a proper diagnosis in order to offer her an adequate clinical surveillance and to the family an individualized risk of recurrence.

20:10 AN UNSOLVED PATIENT WITH A COMPLEX PHENOTYPE INCLUDING INTELLECTUAL DISABILITY, DYSMORPHIC FEATURES AND OBESITY

Kristi Tael[1,2], Kaisa Teele Oja[1,2], Sander Pajusalu[1,2], Katrin Õunap[1,2]

1Department of Clinical Genetics, Genetic and Personalized Medicine Clinic, Tartu University Hospital
2Institute of Clinical Medicine, University of Tartu

Email cor correspondence : Krist.tael@kliinikum.ee

We report the case of a 6-year-old female referred to the clinical geneticist due to developmental delay, dysmorphic features and morbid obesity.

She was born to a non-consanguineous couple. The mother is morbidly obese (BMI 46.6), the mother's mother and sister are also morbidly obese; the father is overweight with unremarkable family history. The girl was born by an emergency caesarean section due to preeclampsia at 38 weeks of pregnancy; Apgar scores were 7/6/8; birth weight 2964 g. Motor development was appropriate for age. She has had panic attacks, anxiety since infancy. The mother noticed already in infancy that the child was constantly hungry and would breastfeed until vomited; a pacifier did not satisfy the child. She also had recurrent infections in early childhood and asthma.

Examination at 6 years 5 months showed marked obesity (weight 76 kg, +12SD, BMI 46), height 136 cm (+3 SD), macrocephaly (60 cm, +5.5 SD) motor clumsiness due to obesity, behavior problems with aggressive episodes, poor speech; coarse facial features, deep-set eyes, broad neck, bilaterally inverted nipples. Ultrasound showed hepatosplenomegaly, hepatosteatosis. Brain MRI - no pathological changes.

She is physically active (swimming and dancing lessons 5 times a week) and adheres to a strict diet assigned by the nutritional therapy team, but her BMI keeps increasing despite all efforts.
Thorough clinical and genetic investigations have found no clear molecular cause. However, a *de novo* missense variant of unknown significance in *CTR9* (NM_014633.5(CTR9):c.383A>T p.(Gln128Leu)) was reported on trio exome sequencing (ES). A recently published study described 13 patients in whom different *de novo* missense mutations of the *CTR9* gene were associated with developmental disorders and other symptoms (Meuwissen et al., 2022) thus this could explain the developmental problems.

As obesity in this family could not be explained by ES, they were offered the opportunity to participate in a research study involving reanalysis ES, RNA sequencing from fibroblasts and untargeted metabolomics from plasma samples. Reanalysis of ES did not reveal any good candidates – a variant of unknown significance in a novel disease gene *VAMP8* was considered, but did not segregate in the family. The aberrant expression analysis in RNA sequencing data using the OUTRIDER tool (Brechtmann et al., 2018) revealed low expression levels for *ERP29* and *NGLY1* genes. The metabolomics analysis is still in progress.
This is a patient with complicated clinical problems. Although we might have a solution for the developmental problems there is still a question of morbid obesity running in the family. We welcome suggestions of a clinical or genetic diagnosis.

Funding: Estonian Research Council grant PRG471

20:20 WHEN THE DIAGNOSIS DOES NOT EXPLAIN THE WHOLE PHENOTYPE - A CASE TO DISCUSS

Presenting author: Mariana Neves

Mariana NEVES[1], Patrícia DIAS [1], Ana Berta SOUSA[1]

1 Serviço de Genética Médica, Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal

Email for correspondence: neves.mariana3@gmail.com

Case presentation: We describe a 12-year-old boy with a severe syndromic intellectual disability (ID) with blepharophimosis. His mother has a moderate ID and had surgery for blepharophimosis. Several maternal relatives also presented ID.
Personal history: Gestation was uneventful. Neonatal period was complicated with respiratory insufficiency associated with meconium aspiration and feeding difficulties. He was prescribed with spectacles for moderate hypermetropia and convergent strabismus since the 1st year and at 5 years of age had surgical correction of blepharophimosis with epicanthoplasty and levator palpebrae superioris muscle advancement. He presented hypotonia that evolved with global developmental delay and severe intellectual disability, behaviour problems and intention tremor.
Dysmorphologic examination: Normal head circumference (52 cm) and height (141 cm) at 11 years. Presents a syndromic *gestalt* with a triangular face, hypertelorism, short and up slanted palpebral fissures, dystopia canthorum, broad eyebrows, synophrys, prominent cheekbones, anteverted nares, broad alae nasi, thin upper lip, wide mouth, hyperlordosis, tapered fingers, bilateral valgus ankle hallux valgus, mild limbs and lumbar hypertrichosis. Mother was also observed and presented similar craniofacial features, obesity and short stature.
Investigations: Negative array CGH (Cytoscan 750K). WES-trio (with the parents) revealed a de novo heterozygous variant c.417del, p.(Trp140Glyfs*30) in exon 4 of *ZMYND11* gene (NM_006624.5) classified as likely pathogenic.

Discussion and conclusion: The *ZMYND11* gene is associated with an autosomal dominant intellectual disability (OMIM: #61608) due to haploinsufficiency variants. Described features for this pathology are mostly consistent with our patient phenotype, however no craniofacial *gestalt* has been suggested for *ZMYND11* related pathology and blepharophimosis has not been described a prominent feature. Additional, the fact that mother presents similar craniofacial features but lacks the *ZMYND11* variant and there are maternal relative's com ID, suggests that an additional genetic condition could explain this family phenotype with a dominant inheritance.

20:30 INCONCLUSIVE DIAGNOSIS OF EXTREMELY DYSMORPHIC GIRL WITH INTELLECTUAL DISABILITY

Presenting author: Klaudia Berk

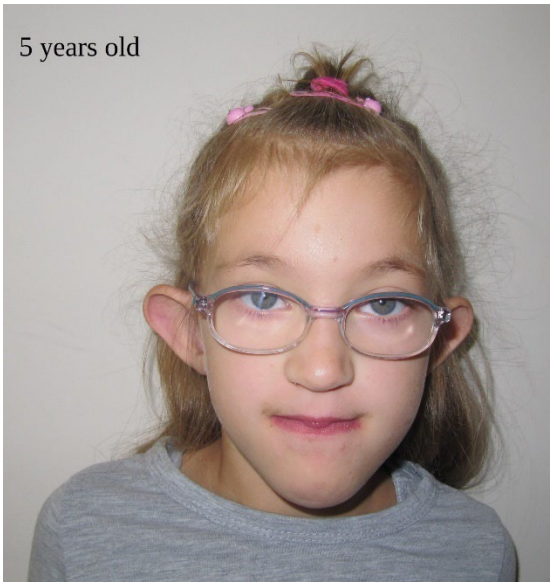
Klaudia BERK M.D. [1], Renata POSMYK M.D.,PhD[1]

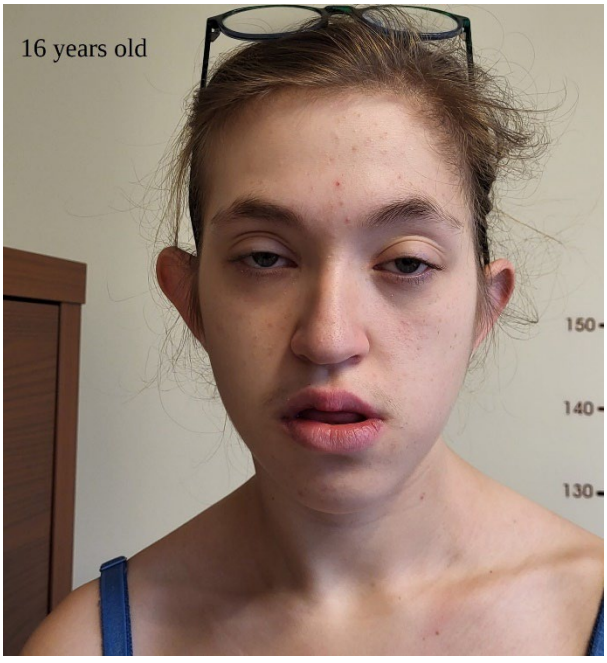
1: Department of Clinical Genetics, Medical University of Bialystok, Poland

Email for correspondence: klaudia.berk@gmail.com

I describe a dysmorphic 17-year-old girl with a moderate intellectual disability. She is the first child of unrelated parents with a family history of learning problems in the mother and mild intellectual disability in the mother's brother. Prenatal history was negative for exposure to drugs and teratogens. Birth parameters were: weight3350g, length-52 cm, OFC-33cm, Apgar score 10/10. The prenatal period was uncomplicated.

Her psychomotor, speech, and language development were delayed. Neuroimaging, EEG, and metabolic tests were normal at 5 years of age.
The girl currently suffers from mitral regurgitation, nephrocalcynosis, scoliosis, and bilateral hyperopia. She speaks single words and she has self-aggressive behavior.
Dysmorphic features evolved significantly with the patient's age. Examination at 16-yo showed a long, triangular face, highly arched eyebrows, hypertelorism with bilateral ptosis, bulbous nose, low-set, protruding ears, open mouth, thick upper and lower lips, and hoarse voice.
Throughout the years, extensive investigations were performed, with karyotype, array-CGH, FMR1 expansion analysis, MLPA subtelomers, microdeletion/microduplication, all were unremarkable. Single whole exome sequencing was performed in 12/2022, revealing the presence of the following variants: het. c.12116A>G in *BLTP1* gene -VUS,het. c.8962G>A in *HERC1* gene- VUS, het. c.916A>G in *LETM1* gene -VUS, het. c.187G>A in *PLAA* gene -VUS of maternal origin, hom. c.3293A>G in *TOP2B* gene -VUS, het. c.2337A>C in *TOP3A* gene -VUS, het. c.235G>T in *TSPAN7* gene -new of maternal origin, het. c.2702del in *WASHC4* gene- new.
She probably has an undiagnosed autosomal dominant syndromic intellectual disability with variable expressivity, inherited from the mother with milder manifestation. However, are any of these variants enough to justify the entire clinical picture?
I'll be grateful for any suggestions.





20:40 UNKNOWN: CASE-REPORT OF 8-YEAR OLD GIRL WITH SEVERE MULTIPLE DISABILITIES, SHORT STATURE AND DYSMORPHIC FEATURES

Presenting author: Joyce Geelen

J. Geelen, pediatrician developmental and genetic pediatrics, Amalia Pediatric Hospital, Radboudumc, Nijmegen, The Netherlands

Email for correspondence: joyce.geelen@radboudumc.nl

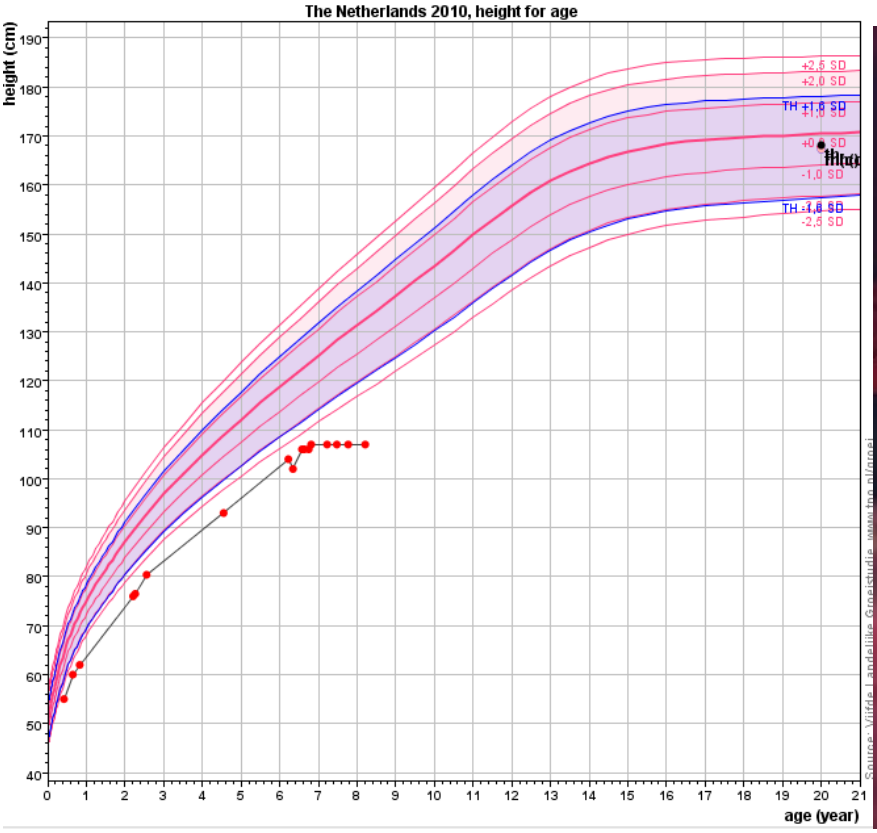
L is a 8-year old girl with a severe developmental delay, multiple medical conditions, short stature and dysmorphic features.

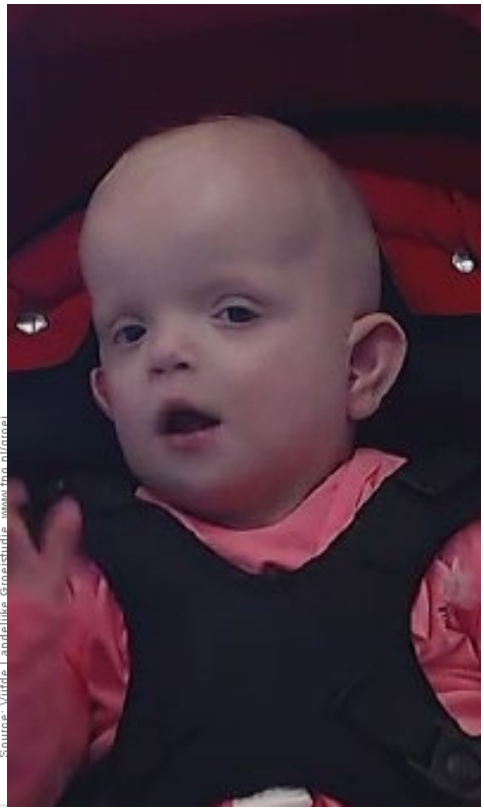
She was born after a pregnancy with growth retardation (AD 37+1) with a low birth weight of 2150 gr (<P3). She also has a short stature (<P3) and microcephaly (<P3). After birth she developed feeding problems for which she received tube-feeding. Her heel prick showed congenital hypothyroidism for which suppletion was started. Also, hearing loss and visual impairment was detected.

Several imaging studies were performed: L had a normal heart and normal kidneys. Vesico-uretral reflux was detected and she developed several urinary tract infections for which she received prophylactic antibiotics. Cerebral imaging showed focal periventricular white matter lesions and delayed myelinization. No structural defects or craniosynostosis. Repeating the scan after 2 years (2017) showed the same results. But the pituitary gland was reported to be small.

Genetic and metabolic analyses were performed at different timepoints:
* 2014 array: maternal deletion 9p24.1, GLDC-gene involved
* metabolic screening in blood en liquor: does not suit non-ketotic hyperglycinemia (NKH)
* mutation analysis of genes for Robinow (DVL1, WNT5A, ROR2) and Saethre-Chotzen (TWIST1): no variants
* 2015 whole exome sequencing (craniofacial panel, intellectual disability panel, hearing loss panel, OMIM-panel, open): 2 variants of unknown significance in GLDC-gene
*2021 whole exome sequencing (craniofacial panel, intellectual disability panel, short stature panel, visual impairment panel, OMIM-panel, open): 2 variants of unknown significance in GLDC-gene

At this moment L has a profound intellectual disability. She is wheelchair-bound, she can not speak, she is almost blind and deaf. She is fed through a jejunostomy. She has episodes of discomfort of unknown origin. She has short stature and microcephaly.





Parents gave informed consent for this case-report. Additional pictures from different ages will be added in the presentation.

20:50 UNKNOWN CLEFT PALATE & HYPOSPADIAS SYNDROME

Presenting Author: Shauna Quinn

Dr Shauna Quinn[1], Dr John Coleman[1], Prof Sally-Ann Lynch[1]

1 Children's Health Ireland, OLCHC, Dublin, Ireland

Email for Correspondence: squinn8@tcd.ie

We present the case of a 3 year old boy with multiple congenital anomalies and no identifiable unifying diagnosis despite extensive genetic investigations.

The first baby of healthy, non-consanguineous Irish parents, there was no significant family history of note. The mother did not take any teratogenic agent. It was a spontaneous conception, the 20-week anomaly scan identified concern for cardiac anomalies and skeletal shortening with estimated fetal weight <5th centile. Amniocentesis and antenatal microarray were normal and TORCH screen was negative. A fetal echocardiogram was normal. MRI performed at 25 weeks' gestation was concerning for small lungs and a pelvic left kidney. He was subsequently born by c-section due to severe intrauterine growth restriction, abnormal dopplers and breech presentation. Following delivery. he required brief resuscitation due to low APGAR scores and subsequent non-invasive respiratory ventilation for respiratory distress syndrome.

Multiple congenital anomalies were evident at birth. His clinical features include severe hypospadias, Pierre robin sequence (PRS) with bilateral soft cleft palate and left pelvic kidney. Examination demonstrated a small jaw, thick eyebrows, prominent ears and syndactyly of 2nd and 3rd toes bilaterally. His weight (1.16kg) and length (36cm) were both <0.4th centile and OFC (30.6cm) 36th centile. His length dropped to -6 SD and weight to -4SD below the mean, both of which have been slow to recover. He has significant failure to thrive, with

severe gastro-oesophageal reflux and poor oral intake necessitating PEG-feeding. His OFC has been crossing centiles. Developmentally, he has some gross motor delay, demonstrating an AIMS score of 12 (<5th centile for age) but socially is keeping up with peers.

Postnatal investigations included overnight sleep studies, skeletal survey, echocardiogram and MRI brain – all of which were normal. Endocrine investigations and urinary steroid profile were unremarkable. Genetic testing demonstrated a negative ArrayCGH. Karyotype/ FISH confirmed an SRY +ve male. Trio whole exome sequencing (WES) was performed in 2021 and did not identify any potentially causative variants.

Despite multiple genetic tests, the cause of his symptoms and clinical features remains unknown.

21:00 WHICH PHENOTYPE FITS BETTER? UNDIAGNOSED CASE – 8-YEAR-OLD BOY WITH DYSMORPHIC FEATURES, DELAYED PSYCHOMOTOR DEVELOPMENT, ABERNETHY MALFORMATION

Presenting author: Monika KOWALCZYK

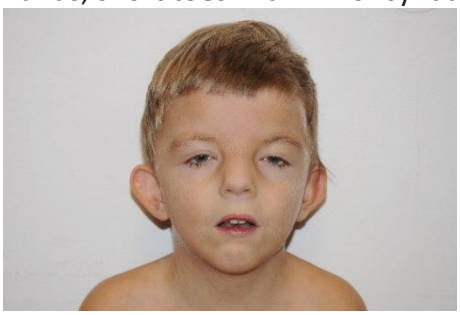
Monika KOWALCZYK[1], Dorota WICHER[1], Ewelina BIELSKA[1], Elżbieta CIARA[1]

1. Department of Medical Genetics, Children's Memorial Health Institute, Warsaw, Poland

Email for correspondence: monika.kowalczyk@ipczd.pl

This boy was born as the first child of healthy non-consanguineous parents in 38 week of pregnancy, by uncomplicated delivery, weight 2390g, 10 Apgar points. During pregnancy there was a suspicion of cardiomegaly and ductus venosus agenesis- not confirmed. After birth the Abernethy malformation was diagnosed, there was no significant heart defect (only patent ductus arteriosus). The portosystemic fistula was closed at the age of 8 months (by embolization). Psychomotor development was delayed: independent walking 24 months, poor active speech. Prior genetic diagnostics in the other center included karyotype, comparative genomic hybridization to microarray (aCGH) and next generation sequencing (NGS) including of *PTPN11* and *NIBPL* genes–with no abnormalities detected.

At first presentation in our out-patient clinic we observed microsomia (weight, height and head circumference < 3percentile) and distinct dysmorphic features: low front and back hairline, synophrys, wide nasal bridge, hypertelorism, ptosis, down-slanting palpebral fissures, low-set posteriorly rotated ears, small hands, short toes with minor syndactyly.



In next diagnostic step performed NGS–Cornelia de Lange syndrome (CdLS) customized panel. We have identified a novel heterozygous missense variant c.4405G>A (p.Asp1469Asn) in *KMT2A* gene. The variant was absent in control chromosomes in GnomAD project, but it was observed in healthy adults in gnomAD exomes with allele count = 5. In-silico tools (CADD, FATHM-MKL, LRT, Mutation Taster and Meta SVM) predict a pathogenic outcome for this variant, but computational evidence by MetaRNN support a benign effect. Variant has been reported in ClinVar as Uncertain significance (VUS). Family segregation showed that this variant was inherited from the healthy father. According to literature data, variants in

KMT2A may be related to Wiedemann-Steiner syndrome or Cornelia de Lange syndrome [Castiglioni S et al. Genes 2022 Mar 15;13(3):514].

The questions are as follows:

-Which phenotype fits better? Wiedemann-Steiner syndrome or Cornelia de Lange syndrome? Phenotypes strongly overlap. Or should we consider completely different diagnosis?

-Is it a good idea to perform in next step NGS in DNA from buccal swab, due to high rate of mosaicism in individuals with Cornelia de Lange syndrome? [Huisman SA, Redeker EJ, Maas SM, Mannens MM, Hennekam RC. High rate of mosaicism in individuals with Cornelia de Lange syndrome. J Med Genet. 2013 May;50(5):339-44]

21:10 WHEN TRIO EXOME SEQUENCING IS NOT ENOUGH: AN UNDIAGNOSED CASE OF FACIAL DYSMORPHISM AND MULTIPLE CONGENITAL ABNORMALITIES

Presenting author: Davide Calosci

Davide Calosci[1*], Rebecca Affuso[1], Licia Turolla[2], Ugo Sorrentino[1], Daniela Zuccarello[3]

[1]: *Clinical Genetics Unit, Department of Women's and Children's Health, University of Padova, 35128 Padova, Italy.* [2]*: Medical Genetics Unit, Treviso Hospital, Treviso, Italy.* [3]*: Clinical Genetics Unit, University Hospital of Padova, 35128 Padova, Italy.*

Corresponding author: davide.calosci@studenti.unipd.it

We report a 3 years old girl with a plurimalformative syndrome of unknown etiology. She is the first child of non-consanguineous Albanian parents, with unremarkable family history. Her pregnancy was complicated by IUGR and polyhydramnios in the third trimester, and ultrasound examination suspected hexadactyly of the left hand. She was born at full term by eutocic delivery. At birth, she presented with microcephaly and evident facial dysmorphisms, including frontal bossing, scalp haemangioma, bilateral epicanthus inversus, short palpebral fissures, blepharophimosis, low-set cupped ears with poorly represented helix, wide nasal bridge, underdeveloped nasal alae, long columella, bifid nasal tip, short and smooth philtrum, cleft palate, and thin vermilions. She also displayed clinodactyly of the fifth digit on both hands and feet, cutaneous syndactyly between fourth and fifth toe and duplication of the first ray of both hands. Subsequent assessments revealed cerebral atrophy with hypoplasia of the corpus callosum, moderate conductive hearing loss, ocular abnormalities (microphthalmia, bilateral iris coloboma, lenticular opacity of the right eye, retinal coloboma of the left eye) and annular pancreas with duodenal obstruction. Heart was normal. She also exhibited severe global developmental delay. First line genetic testing was uninformative: karyotype was normal (46,XX), while array-CGH identified only a 500 Kb duplication of paternal origin of chromosome region 1p36.31. Trio whole exome sequencing analysis was then performed, identifying only two compound heterozygous missense variants in the *TRIT1* gene, which were classified as VOUS and were considered not

sufficient to justify the whole phenotype anyway. A hypothesis of Kapur-Toriello syndrome was also proposed, however the lack of an etiologic definition of this nosological entity has not allowed molecular confirmation. We are open to other diagnostic suggestions.

21:20 UNDIAGNOSED CASE OF SEVERE SHORT STATURE, GLOBAL DEVELOPMENTAL DELAY AND DYSMORPHIC FEATURES

Presenting author: Adelaide Peruzzi

Peruzzi ADELAIDE[1], Isidori FEDERICA[2], Vancini ALESSANDRA[3], Tamburrino FEDERICA[4], Scarano EMANUELA[4], Seri MARCO[5], Pippucci TOMMASO[2], Severi GIULIA[1]

1 *U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
2 *S.S. Genomica Computazionale, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
3 *U.O.C. Neonatologia e Terapia Intensiva Neonatale, Ospedale Maggiore di Bologna, Italy*
4 *S.S.U.O. Malattie Rare Congenito-Malformative, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
5 *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*

Email for correspondence: adelaide.peruzzi@studio.unibo.it

Introduction. We report the case of a 6-year old male with short stature, congenital malformations, facial dysmorphisms, and global developmental delay.
Clinical case. The boy is the first child of consanguineous parents from Pakistan with negative family history of developmental delay, intellectual disability and genetic conditions. He was born at 27 weeks from urgent C-section due to severe IUGR and maternal Systemic Lupus Erythematosus flare-up. At birth, weight was 480 g (SDS -2.15), length 28 cm (SDS -3.04), HC 20.7 cm (SDS -2.71), Apgar score 5 at 1' and 9 at 5'. He was hospitalized in neonatal care unit due to respiratory distress and cardiac US revealed patent foramen ovale and mild tricuspid insufficiency. Physical examination showed bilateral inguinal hernia and cleft palate together with pre-term related complications such as bronchopulmonary dysplasia, retinopathy, anaemia, neutropenia, and intraventricular haemorrhage. Brain MRI revealed enlarged lateral ventricles with thin corpus callosum.
At our first visit (11 months of corrected age) the patient presented with severe developmental delay, short stature (L 64,5 cm, SDS -3.7), low weight (5 kg, SDS -5.1), microcephaly (CC 39 cm, -3.3 SD related to his stature) and inability to maintain sitting position. Dysmorphological evaluation showed positional plagiocephaly, triangular face, arched and thick eyebrows, low-set ears with abnormal shape of helix and antihelix, pear-shaped nose, thin lips, pointy chin, pectus excavatum, dry skin and bilateral syndactyly of II-III fingers and toes. At the last clinical evaluation (6 years of age), the boy had hyposomy [L 100 (SDS -3.5), P 12.4 kg (SDS -4.0), HD 42.5 cm (-6.9) with statural age of 3 years and 5 months], severe expressive language delay, but adequate comprehension. IGF-1 values were normal, while growth hormone stimulation test was not possible to perform.
Investigations. Array-cgh, MS-MLPA for Silver-Russel syndrome, in silico analysis of a NGS panel of 46 short stature-related genes, and clinical exome sequencing have been performed with negative results. The Whole-Exome-Sequencing (singleton) showed a homozygous variant, NM_001024660.5 c.7795A>G, p.(Thr2599Ala), of unknown significance, in the *KALRN* gene, which is still not associated to human disease. *KALRN* encodes the protein kalirin, a GTP-exchange factor protein, known to regulate dendritic spine formation in hippocampal and cortical neurons, but its role in neurodevelopmental disorders and short stature needs to be clarified. One single family with a homozygous likely pathogenic missense variant in *KALRN* gene has been reported: two affected siblings, offspring of consanguineous parents, with global developmental delay, hypotonia and short stature with growth hormone deficiency. The variant segregated with the disorder in the family, but functional studies were not performed. The specific variant identified in

our patient is rare and it has not been reported in medical literature, so further studies would be needed. Whole-genome sequencing is ongoing.
Conclusion. Our patient underwent multiple genetic tests but the cause of his condition is yet to be evaluated.

21:30 UNRAVELING A GENETIC ENIGMA: A CASE REPORT OF A DYSMORPHIC NEURODEVELOPMENTAL DISORDER IN A 11-YEAR-OLD GIRL

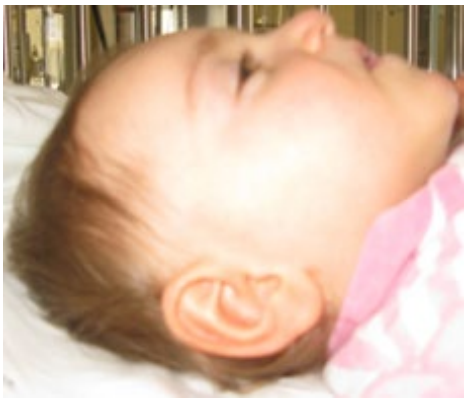
Presenting author: Joana Catanho

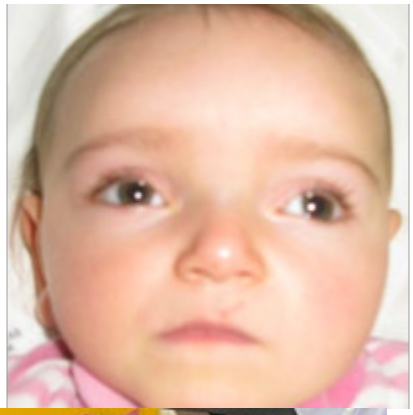
Joana CATANHO[1], Marta AMORIM[2], Inês CARVALHO[1]

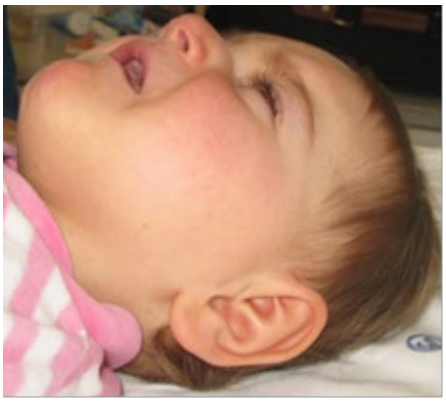
[1] Serviço de Genética Médica, Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal
[2] Consulta de Genética Médica, Hospital Lusíada, Lisbon, Portugal

Email for correspondence: joana.silva9@chlc.min-saude.pt

We report a case of a 11-year-old (yo) girl, second child of healthy, non-consanguineous parents.
Pregnancy follow-up started at 16th week of gestation (w-o-g). Second-trimester ultrasound raised suspicion of fetal microcephaly, but confirmation in subsequent evaluations was difficult due to maternal biotype. Pregnancy was also complicated with gestational diabetes and hypertension diagnosed at 33rd w-o-g.
The patient was delivered at 37th w-o-g, with an Apgar score of 9/10, a weight of 3250g (37th percentile), a length of 46,5 cm (9th percentile) but occipitofrontal circumference was not available.
She was referred to our outpatient clinic at 16 months of age, due to developmental delay, progressive microcephaly and multifocal epilepsy. Upon examination, she presented with microbrachycephaly, fine hair, with a high anterior hairline, broad forehead, long eyelashes, hypertelorism, strabismus. Additional features included asymmetric ears, left ear with prominent helix and concha extrafold, thin upper lip vermilion, with downturned corners and bilateral single palmar crease.
At 2yo, the patient was diagnosed with choreic movements, hypermetropy and gastric reflux.
Revaluation at 9 yo revealed the patient had a weight centile P<1 (-2.8 SD), intellectual disability, hypotonia, spastic paraparesis, dystonia, epilepsy and absence of language. Other dysmorphic features observed include long face, left eye ptosis, long and narrow nose, bilateral macrotia, microstomia, tongue protrusion, pointed and long chin.
At 11 yo, there were no clinical changes reported.
Cranial magnetic resonance imaging revealed delayed myelination and dysgenesis of the telencephalic commissures. Extended metabolic investigation, Angelman syndrome study and microarray were normal.
A clinical exome was performed and identified a heterozygous variant of unknown significance in *SPTAN1* (NM_001130438.2: c.5664A>C) gene classified as a variant of unknown significance. Pathogenic variants in this gene are associated with autosomal dominant Developmental and Epileptic Encephalopathy 5, (OMIN #613477). Segregation studies revealed that this variant was inherited from a healthy mother.
This case report emphasizes a complex clinical presentation and diagnostic odyssey in a patient with global developmental delay, microcephaly, epilepsy, movement disorder and dysmorphic features.







21:40 AN ONGOING DIAGNOSTIC ODYSSEY: A SYNDROMIC INTELLECTUAL DISABILITY CASE WITHOUT A CONCLUSIVE MOLECULAR DIAGNOSIS

Presenting author: Susana Lemos Ferreira

Susana Lemos FERREIRA[1], Teresa KAY[1], Marta AMORIM[2], Inês CARVALHO[1]

[1] Serviço de Genética Médica, Hospital Dona Estefânia – Centro Hospitalar Lisboa Central, Lisboa, Portugal
[2] Consulta de Genética Médica, Hospital dos Lusíadas, Lisboa, Portugal

Email for correspondence: susana.ferreira2@chlc.min-saude.pt

A 19-years-old male was first referred to our outpatient genetic department at the age of 16-month-old with global development delay, epilepsy and hypotonia. He is the only child of non-consanguineous parents with no relevant family history. Pregnancy was unremarkable.

The patient was born at 40 weeks of gestation without complications and with adequate birthweight, length and cephalic perimeter for gestational age. He had an unremarkable neonatal period. At 6-months-old, he presented with epilepsy, hypotonia and motor development delay. Brain magnetic resonance imaging identified ventriculomegaly and electroencephalography irregular activity.

Subsequently, at our observation, he showed broad forehead, strabismus, epicantus, long philtrum, joint laxity and cryptorchidism. In the first 3 years of age, he had several hospital admissions as result of decompensation of epilepsy and upper respiratory infections. From the age of 3-years-old, he remained epilepsy-free. In addition, he revealed a progressive global developmental delay with moderate cognitive impairment (global IQ of 43).

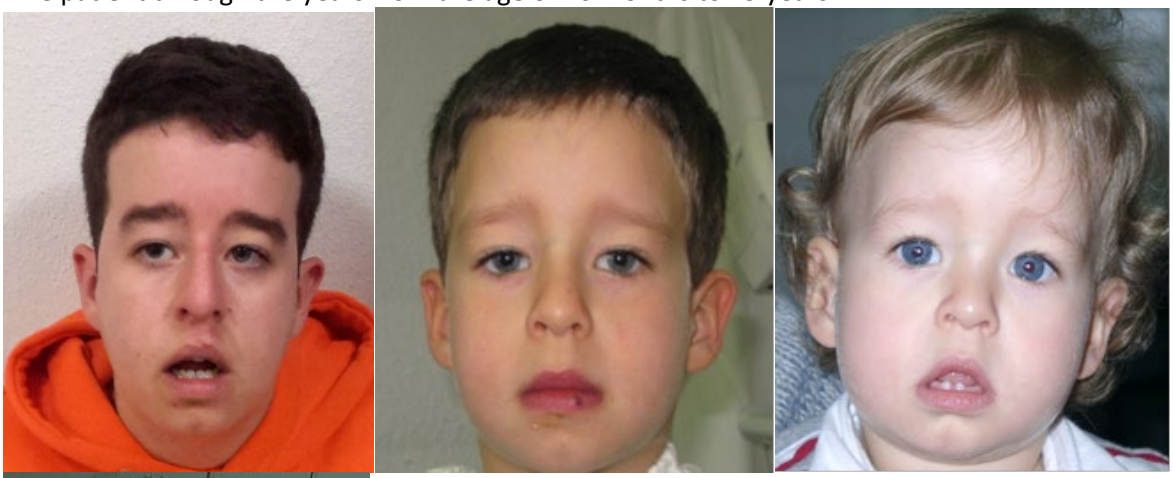
At 13-years-old, he presented with pulmonary hypertension. A patent foramen ovale was the only finding in the echocardiogram. A transcatheter closure was performed, targeted medical treatment was initiated and since then the patient remains asymptomatic.

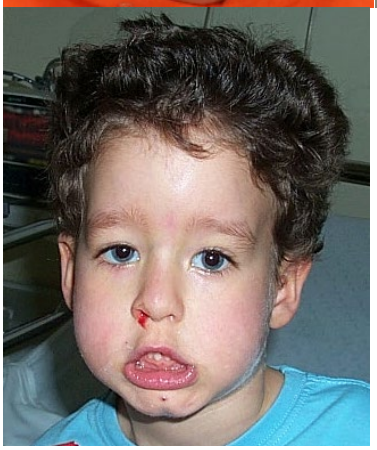
Throughout the years, he showed progressive coarse facial features. At last evaluation by the age of 19 years, facial dysmorphims became more evident such as long face, bitemporal narrowing, pear-shaped nose, open mouth, thick inferior lip, prominent incisors, small hypothenar eminence with tapering fingers, lumbar hyperlordosis, and bilateral sandal gap. The patient's neurologic condition remains stable.

Extensive metabolic investigation, karyotype, FRAXA study, and MS-MLPA assay for the 15q11-q13 region were normal. Chromosomal microarray identified a heterozygous deletion encompassing *NRXN1* classified as likely pathogenic, inherited from a healthy father. However, this finding does not seem to fully explain our patient's phenotype. Due to the patient's phenotype, we suspected of a BAFopathy but clinical exome was inconclusive, without any variant of interest in this genes.

This case remains without a conclusive molecular diagnosis that could offer an appropriated genetic counselling and a better surveillance to this patient and family. By presenting this case, we hope that this discussion can bring us one-step closer to a possible molecular diagnosis.

The patient through the years from the age of 16 months to 19 years





Session 7 – New genes & new syndromes

09:00 A HOMOZYGOUS FRAMESHİFT VARİANT İN THE CILK1 GENE CAUSES CRANİOECTODERMAL DYSPLASİA: A NEW GENE İN THE ETİOLOGY

Presenting author: Abdullah Sezer

Abdullah Sezer[a,b,c], Sukru Sadik Oner[d], Hanife Saat[b,c,e], Mehmet Ali Ergun[b], Oktay Ismail Kaplan[f]

[a] Department of Medical Genetics, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research Hospital, Ankara, Turkey
[b] Department of Medical Genetics, Faculty of Medicine, Gazi University, Ankara, Turkey
[c] Department of Medical Genetics, Etlik City Hospital, Ankara, Turkey
[d] Department of Medical Pharmacology, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey
[e] Department of Medical Genetics, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey
[f] Rare Disease Laboratory, School of Life and Natural Sciences, Abdullah Gul University, Kayseri, Turkey

Cranioectodermal dysplasia (CED), commonly known as Sensenbrenner syndrome, is a ciliopathy characterized by skeletal and ectodermal defects, along with persistent renal failure and liver fibrosis. Two-thirds of CED patients have the pathogenic variants in the genes (*IFT43, IFT122, IFT140, IFT52, WDR19* and *WDR35*) that encode components of the protein complexes controlling intraflagellar transport and one-third have remained with unknown etiology. Here, we will present the pathogenic variant detected in the ciliogenesis-associated kinase 1 (*CILK1*, also known as *ICK*) gene in a large family that includes more than one individual with the CED phenotype, and the functional data of this variant.

CED phenotype was detected in three cousins aged 10, 9, and 4 years in a large family with frequent consanguineous marriages. The patients had common dysmorphic facial features, sparse hair-eyebrows-eyelashes, retinal problems, dental abnormalities, brachydactyly, dystrophic nails, chronic renal failure, and liver dysfunction. In clinical exome analysis, a previously unreported variant in the *CILK1* gene (NM_014920, c.1664_1665delAT, p.Tyr555CysfsTer48) was homozygous in common in all three patients. In order to evaluate the effect of the detected variant on the ciliary morphology and function, patient fibroblast samples were taken and CRISPR mutants were created in the *C. elegans* model organism. Similar to the cilia lengths detected in mammalian cell models in which *CILK1* expression is downregulated via siRNA, patient-derived fibroblasts were observed to have longer cilia than control fibroblasts in serum-deprived conditions. Even though the localization of the mutant protein was not altered, some ciliary proteins showed abnormal accumulation. In addition, both anterograde and retrograde transport were affected in C. elegans.

The *CILK1* gene is expressed in primary cilia and regulates ciliogenesis. To date, some missense variants located in the catalytic domain of the *CILK1* protein have been associated with ciliopathies in the skeletal dysplasia phenotype that lead to perinatal death while in the biallelic state. Some heterozygous variants located in both the catalytic and non-catalytic domains were determined to be responsible for the etiology in epilepsy patients. The frameshift variant in the *CILK1* detected in the patients in this study and located in the non-catalytic domain in the C-terminal region of the protein is expected to cause shortening of the protein. The type and location of the *CILK1* variant detected in CED patients differ from the variants in the other phenotypes associated with this gene. In addition, the phenotype of the patients presented differs from other *CILK1*-related ciliopathies, both in terms of affected organs and systems and survival. In conclusion, the results suggest that the frameshift variant of the *CILK* gene altered ciliary morphology and function and caused CED.

09:15 DOMINANT ARF3 VARIANTS DISRUPT GOLGI INTEGRITY AND CAUSE A NEURODEVELOPMENTAL DISORDER RECAPITULATED IN ZEBRAFISH

Presenting author: Francesca Clementina Radio

Francesca Clementina Radio[1], Giulia Fasano[1], Valentina Muto[1], Martina Venditti[1], Niloufar Mosaddeghzadeh[2], Simona Coppola[3], Graziamaria Paradisi[1,4], Erika Zara[1,5], Farhad Bazgir[2], Alban Ziegler[6,7], Giovanni Chillemi[4,8], Lucia Bertuccini[9], Antonella Tinari[10], Annalisa Vetro[11], Francesca Pantaleoni[1], Simone Pizzi[1], Libenzio Adrian Conti[12], Stefania Petrini[12], Alessandro Bruselles[13], Ingrid Guarnetti Prandi[4], Cecilia Mancini[1], Balasubramanian Chandramouli[14], Magalie Barth[7], Céline Bris[6,7], Donatella Milani[15], Angelo Selicorni[16], Marina Macchiaiolo[1], Michaela V. Gonfiantini[1], Andrea Bartuli[1], Riccardo Mariani[17], Cynthia J. Curry[18], Renzo Guerrini[11], Anne Slavotinek[18], Maria Iascone[19], Bruno Dallapiccola[1], Mohammad Reza Ahmadian[2], Antonella Lauri[1], Marco Tartaglia[1].

[1]Molecular genetics and Functional Genomics, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. [2]Institute of Biochemistry and Molecular Biology II, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [3]National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy. [4]Department for Innovation in Biological Agrofood and Forest systems (DIBAF), University of Tuscia, Viterbo, Italy. [5]Department of Biology and Biotechnology "Charles Darwin", Università "Sapienza", Rome, Italy. [6]UFR Santé de l'Université d'Angers, INSERM U1083, Angers, France. [7]Département de Génétique, CHU d'Angers, Angers, France. [8]Institute of Biomembranes, Bioenergetics and Molecular Biotechnologies, Centro Nazionale delle Ricerche, Bari, Italy. [9]Servizio grandi strumentazioni e core facilities, Istituto Superiore di Sanità, Rome, Italy. [10]Centro di riferimento per la medicina di genere, Istituto Superiore di Sanità, Rome, Italy. [11]Pediatric Neurology, Neurogenetics and Neurobiology, Meyer Children's Hospital, Florence, Italy. [12]Confocal Microscopy Core Facility, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. [13]Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy. [14]Super Computing Applications and Innovation, CINECA, Casalecchio di Reno, Italy. [15]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. [16]Mariani Center for Fragile Children Pediatric Unit, ASST Lariana, Como, Italy. [17]Department of Laboratories Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy. [18]Genetic Medicine, Dept of Pediatrics, University of California San Francisco, Fresno, San Francisco, USA. [19]Medical Genetics, ASST Papa Giovanni XXIII, Bergamo, Italy.

Email for correspondence: fclementina.radio@opbg.net; marco.tartaglia@opbg.net

Vesicle biogenesis, trafficking and signaling via Endoplasmic reticulum-Golgi network support essential developmental processes and their disruption lead to neurodevelopmental disorders and neurodegeneration. We report that *de novo* missense variants in *ARF3*, encoding a small GTPase regulating Golgi dynamics, cause a developmental disease in humans. Affected subjects showed variable degrees of DD/ID associated with brain and skeletal anomalies. No characteristic craniofacial gestalt was noted, with only minor craniofacial features reported in single patients, mainly related to microcephaly. In particular, two subjects showed microcephaly, profound DD/ID, absence of speech and language development, progressive diffuse cortical atrophy with diminished white matter, thin corpus callosum, progressive pontocerebellar hypoplasia sparing the cerebellar vermis, hypotonia, microsomia, and consistent skeletal defects. A comparable but less severe condition was observed in an additional individual, who manifested hypotonia, severe DD/ID, delayed speech, post-natal microcephaly, thinning of the corpus callosum and milder skeletal defects. The remaining two subjects showed a milder phenotype with DD/ID and delayed speech with or without early-onset seizures, corpus callosum abnormalities and milder skeletal involvement. Microcephaly-associated *ARF3* variants affect residues within the guanine nucleotide binding pocket and variably perturb protein stability and GTP/GDP binding. Functional analysis demonstrates variably disruptive consequences of ARF3 variants on Golgi morphology, vesicles assembly and trafficking. Disease modeling in zebrafish validates further the dominant behavior of the mutants and their differential impact on brain and body plan formation, recapitulating the variable disease expression. In-depth in vivo analyses traces back impaired neural precursors' proliferation and planar cell polarity-dependent cell movements as the earliest detectable effects. Our findings document a key role of ARF3 in Golgi function and demonstrate its pleiotropic impact on development.

09:30 BIALLELIC LOSS-OF-FUNCTION VARIANTS IN VOLTAGE-GATED CALCIUM CHANNEL REGULATOR CACHD1 CAUSE NEURONAL DYSFUNCTION AND MULTISYSTEM DEVELOPMENTAL ABNORMALITIES

Presenting author: Marcello Scala

Marcello Scala[1,2,3] Kamal Khan[4] Claire Beneteau[5,6,7] Rachel G. Fox[8], Sandra von Hardenberg[9], Ayaz Khan[4], Madeleine Joubert[6,10], Lorraine Fievet[11], Marie Musquer[6,10], Claudine Le Vaillant[12], Julie Korda Holsclaw[11], Derek Lim[13,14], Ann-Cathrine Berking[9], Andrea Accogli[1], Thea Giacomini[1,15], Lino Nobili[1,15], Pasquale Striano[1,2], Federico Zara[1,3], Annalaura Torella[16,17], Vincenzo Nigro[16,17], Benjamin Cogné[5,18], Max R. Salick[19], Ajamete Kaykas[19], Kevin Eggan[20], Valeria Capra[3], Stéphane Bézieau[5,18], Erica E. Davis[4,21], and Michael F. Wells[8,20]

1: Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy; 2: Pediatric Neurology and Muscular Diseases Unit, IRCCS Istituto Giannina Gaslini, University of Genoa, 16147 Genoa, Italy; 3: Medical Genetics Unit, IRCCS Giannina Gaslini Institute, Genoa, Italy; 4: Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL 60611, USA; 5: CHU Nantes, Department of Medical Genetics, CHU Nantes, 9 quai Moncousu, 44093 Nantes, France; 6: CHU Nantes, UF of Fœtopathology and Genetics, 9 quai Moncousu, 44093 Nantes, France; 7: CHU de Bordeaux, Service de Génétique Médicale, F-33000, Bordeaux, France; 8: Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095; 9: Department of Human Genetics, Hannover Medical School, 30625 Hannover, Germany; 10: CHU Nantes, Department of Anatomical Pathology, 9 quai Moncousu, 44093 Nantes, France; 11: Center for Human Disease Modeling, Duke University Medical Center, Durham, NC 27701, USA; 12: CHU Nantes, Department of Obstetrics and Gynecology, quai 38 bd Jean Monnet, 44093, Nantes, France; 13: Department of Clinical Genetics, Birmingham Women's and Children's NHS Foundation Trust & Birmingham Health Partners; 14: Department of Medicine, University of Birmingham, Birmingham, UK; 15: Child Neuropsychiatry Unit, IRCCS G. Gaslini Institute, Genoa, Italy; 16: Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy; 17: Telethon Institute of Genetics and Medicine, Pozzuoli, Italy; 18: Nantes Université, CHU de Nantes, CNRS, INSERM, l'institut du thorax, F-44000 Nantes, France; 19: Insitro, South San Francisco, CA 94080, USA; 20: Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA; 21: Department of Pediatrics and Department of Cell and Developmental Biology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

Email for correspondence**:** Marcello Scala, mscala.md@gmail.com

Voltage-gated calcium (CaV) channels are essential components and functional regulators of excitable cells. Neuronal N-type (CaV2.2) and P/Q-type (CaV2.1) channels are critical for presynaptic neuro-transmitter release. CaV α1 subunits form the channel pore, whereas the β and α2δ subunits are crucial regulators of trafficking and bio-physical properties of channel complexes. The putative cache (Ca^{2+} channel and chemotaxis receptor) domain containing 1 (CACHD1) protein structurally mimics α2δ proteins and modulates CaV2 and CaV3 channel activity and expression. *CACHD1* is widely expressed in the central nervous system but its specific function and role in neurodevelopment and/or human disease are poorly understood. We assembled a cohort of six affected individuals from four unrelated families presenting with a complex multisystem developmental syndrome characterized by facial dysmorphism, mild cognitive deficits, oculo-auricular malformations, genitourinary abnormalities, and anorectal malformations. Exome sequencing (ES) identified biallelic putative loss-of-function variants in *CACHD1* segregating with disease in all pedigrees. To establish relevance to human phenotype, we generated stable *cachd1* zebrafish mutants on a transgenic cartilage reporter line and we observed mandibular patterning defects in homozygous mutant larvae compared to wild type, a phenotype used as a proxy for dysmorphic facial features in humans. To probe the role of CACHD1 in neurodevelopment, we established two- and three- dimensional human stem cell-derived neural models and detected abnormalities in neural proliferation and differentiation in CACHD1 depleted cells. These findings support biallelic *CACHD1* loss of function variants as the cause of a novel neurodevelopmental syndrome and expand the clinical spectrum of voltage gated calcium channel effectors.

09:45 IMPAIRED ACTIVITY OF THE FUSOGENIC MICROPEPTIDE MYOMIXER CAUSES MYOPATHY RESEMBLING CAREY-FINEMAN-ZITER SYNDROME

Presenting author: Andres Ramirez-Martinez

Andres Ramirez-Martinez [1], Marie-Jose van den Boogaard [2], Inge Cuppen [3], Maarten P Massink [2], Richard H van Jaarsveld [2], Eric N Olson [1]

[1] Department of Molecular Biology and Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [2] Department of Genetics, University Medical Center Utrecht, Utrecht, Netherlands [3], Department of Neurology, University Medical Center Utrecht, Utrecht, Netherlands Utrecht

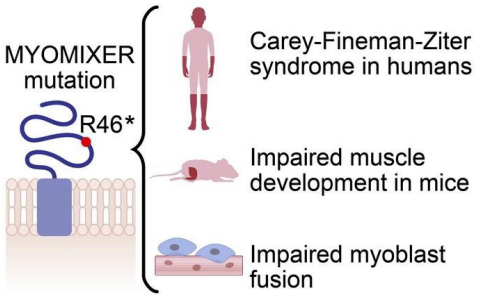
Email for correspondence: m.j.h.vandenboogaard@umctrecht.nl

Carey-Fineman-Ziter syndrome (CFZS; OMIM #254940) is a craniofacial syndrome displaying an array of abnormalities, including Robin sequence, Moebius sequence, hypotonia, myofiber size disproportion, and growth defects. Previous studies showed hypomorphic bi-allelic variants in MYMK causative for the congenital myopathy underlying this syndrome.

Two individuals, a brother and a sister, presented in our clinic with a phenotype highly reminiscent of CFZS. However, no pathogenic variants could be identified in MYMK. Open-exome analysis revealed that both patients carried a homozygous C-to-T variant in codon 46 of MYMX on chromosome 6, resulting in conversion of Arg46 to a termination codon (NM_001315494.2 [MYMX]: c.136C>T [p.(Arg46*)]).

To assess muscle abnormalities in vitro, skeletal muscle cells were differentiated from iPSCs derived from gingival fibroblasts from the male patient. To model the muscle abnormalities associated with the MYMX R46* variant, we genetically engineered mice with this mutation by CRISPR/Cas9–mediated genome editing.

Conclusion: We identified MYMX as a novel recessive, monogenic human disease gene involved in CFZS, and provide new insights into the contribution of myoblast fusion to neuromuscular diseases (PMID: 35642635). Confirming MYMX as a cause of a craniofacial syndrome, of which Robin sequence might be an early recognizable feature.



10:00 AUTOSOMAL RECESSIVE LIVER FAILURE, ABSENT EYEBROWS AND EYELASHES

Presenting author: Sally Ann Lynch

Authors Sally Ann Lynch[1,3] John Coleman[1] Audrey Dillon[2] Conor Hensey[3]

1: CHI@Crumlin, 2 St Vincent's Hospital Dublin and CHI @Temple street Dublin (s)

Email for correspondence: Sally.lynch@ucd.ie @annnlynch

We present two siblings born to consanguineous parents from Northern Iraq (Yazidi origin) with liver failure and absent eyebrows, eyelashes and scarce body hair.
The oldest sibling is a 22 yo male. He presented to Ireland with chronic liver failure with decompensated liver cirrhosis. The liver failure began in later childhood years. He also has signs of bone marrow failure and coagulopathy. He never attended school (because of political situation in Iraq) but never have any or cognition issues. He met all of his developmental milestones appropriately.
He has bone marrow failure and there are lung changes on CT. He is on a liver transplant list although the severity of his hepatopulmonary syndrome might preclude liver transplantation. He is still quite active despite significant hypoxia, maintaining some muscle mass with high oral nutritional supplements and diuretic controlled ascites, with persistent jaundice ~120.

Clinically, he has sparse eyebrows, eyelashes and scarce body hair since early infancy, predating the liver failure. He has a normal anterior hairline. He has evidence of Scleral icterus (Jaundice). He does not look particularly similar in facial appearance to his sister apart from the eyebrows.
His Younger sister is 13 years old and currently showing signs of early liver dysfunction and portal hypertension. She is developmentally appropriate. She has absent eyebrows, absent eyelashes and absent body hair with a high anterior hairline and. She had some mottling of her lower limbs. She is pre-pubertal and she has no obvious jaundice.
Investigations include Telomere studies and Quad exome analysis normal

10:15 BIALLELIC NPR1 LOSS OF FUNCTION VARIANTS ARE RESPONSIBLE FOR NEONATAL SYSTEMIC HYPERTENSION

Presenting author: Yline Capri

Yline CAPRI,[1,2] Theresa KWON,[3] Olivia BOYER,[4] Lucas BOURMANCÉ,[2] Noé TESTA,[2] Véronique BAUDOUIN,[3] Ronan BONNEFOY,[5] Anne COUDERC,[4] Chakib MEZIANE,[6] Elisabeth TOURNIER-LASSERVE,[7] Laurence HEIDET,[4] and Judith MELKI[2]

[1]Département de Génétique, Assistance publique-Hôpitaux de Paris, APHP-Nord, Hôpital Robert Debré, Paris, 75019, France
[2]Institut National de la Santé et de la Recherche Médicale (Inserm) UMR-1195 and University Paris Saclay, Le Kremlin Bicêtre, 94276, France
[3]Nephrology Department, Robert Debré University Hospital- APHP, Paris, 75019, France
[4]Service de Néphrologie Pédiatrique, Centre de Référence des Maladies Rénales Héréditaires de l'Enfant et de l'Adulte (MARHEA), Hôpital Necker-Enfants Malades, APHP-centre, Université Paris Cité, 75015, Paris, France; Laboratoire des Maladies Rénales Héréditaires, Inserm UMR 1163, Institut Imagine.
[5]Service de Cardiologie Pédiatrique, APHP-Nord, Hôpital Robert Debré, Paris, 75019, France
[6]Service de Néonatologie, Groupe Hospitalier Sud Ile-de-France, 77000, Melun, France
[7]Université de Paris, INSERM U1141, AP-HP, Service de Génétique Moléculaire Neurovasculaire, Hôpital Saint-Louis, Paris, France

Email for correspondence: yline.capri@aphp.fr

Background: Early onset isolated systemic hypertension is a rare condition of unknown genetic origin. Renovascular, renal parenchymal diseases or aortic coarctation are the most common causes of secondary systemic hypertension in young children and neonates. We investigated the genetic bases of early onset isolated systemic hypertension.
Methods: Whole exome sequencing was followed by variant filtering and Sanger sequencing for validation and familial segregation of selected variant in a large consanguineous family. mRNA expression was performed to evaluate the impact of the predicted pathogenic variant on gene expression. Whole exome sequencing or Sanger sequencing was performed in additional unrelated affected individuals.
Results: In one consanguineous family with 4 children presenting with isolated neonatal onset systemic hypertension, we identified homozygous stop gain variant in the *NPR1* gene (NM_000906.4:c.1159C>T

[p.Arg387Ter]) in the affected individuals. This variant leads to a dramatic reduction of NPR1 RNA levels. *NPR1* gene analysis of additional families allowed the identification of another family with two affected children carrying homozygous frameshift variant in *NPR1* (NM_000906.4:c.175del [p.Val59TrpfsTer8]).
Conclusion: We show for the first time that biallelic loss of function of *NPR1* is responsible for isolated neonatal onset systemic hypertension in humans, which represents a new autosomal recessive genetic cause of infantile systemic hypertension or cardiogenic shock. This is consistent with studies reporting early onset systemic hypertension and sudden death in Npr1-deficient mice. *NPR1* gene analysis should be therefore investigated in infants with early onset systemic hypertension with or without cardiogenic shock of unknown origin.

Keywords: neonatal systemic hypertension, cardiogenic shock, whole exome sequencing, *NPR1* gene

Session 8 – Syndrome delineation

11:00 INVITED TALK: KRYSTYNA CHRZANOWSKA, NBS (NIJMEGEN BREAKAGE SYNDROME) AND RELATED CHROMOSOMAL INSTABILITY DISORDERS

11:45 NOVEL DE NOVO MISSENSE VARIANT IN VPS4A ASSOCIATED WITH A SEVERE NEURODEVELOPMENTAL PHENOTYPE WITH MICROCEPHALY, DYSMORPHISM, AND DISTINCTIVE BRAIN ABNORMALITIES

Presenting author: Valeria Capra

Valeria Capra[1], Elisabetta Amadori[2], Mariasavina Severino[3], Francesca Madia[4], Ferruccio Romano[4], Pasquale Striano[2], Francesca Faravelli[1], Federico Zara[4], Marcello Scala[4]

1: U.O.C. Genomica e Genetica Clinica, IRCCS Istituto Giannina Gaslini, 16147 Genova, Italy; 2: Pediatric Neurology and Muscular Diseases Unit, IRCCS Istituto Giannina Gaslini, University of Genoa, 16147 Genoa, Italy; 3: Neuroradiology Unit, IRCCS Giannina Gaslini Institute, 16147, Genoa, Italy; 4: Unit of Medical Genetics, IRCCS Giannina Gaslini Institute, 16147, Genoa, Italy

Email for correspondence: Valeria Capra, valeriacapra@gaslini.org

The endosomal sorting complexes required for transport (ESCRTs) are multifunctional membrane modeling machineries that play essential role in multiple membrane modeling and membrane-independent cellular processes. These complexes are crucial for the modulation of membrane fission or constriction in cellular processes involving cellular membrane topology change. The *VPS4A* gene (MIM * 609982) encodes for the vacuolar protein sorting 4 homolog A (VPS4A), a critical enzyme implicated in the regulation of ESCRT function. *De novo* variants in *VPS4A* have been associated with CIMDAG syndrome (MIM # 619273), consisting of a variable association of severe congenital microcephaly, profound cognitive impairment, cataracts, dystonia, dyserythropoietic anemia, and growth retardation. Most reported variants affect the microtubule interacting and trafficking domain (MIT) or the ATPase family associated with various cellular activities domain (AAA). Through trio-exome sequencing, we identified a very rare *de novo* variant in the *VPS4A* gene in a patient with severe congenital microcephaly, profound psychomotor and cognitive impairment, dysmorphic features, hypotonia, strabismus, and behavioral disturbances. Of note, brain MRI revealed cerebellar hypoplasia, diffuse delayed myelination, and corpus callosum thickening, that has never been reported in *VPS4A* patients. Exome sequencing led to the identification of the (NM_013245.3): c.356T>A, p.(Met119Lys) variant in *VPS4A*. No other variants in known disease genes were detected and CGH-array testing yielded negative results. The p.(Met119Lys) variant is absent in the gnomAD database and

affects a very conserved residue (GERP score = 6.17) in close proximity to the low complexity region domain (LC) of the protein, possibly affecting protein folding. Variants in this region of the protein have never been associated with human disease so far. Overall, our study expands the knowledge on the genotype and phenotype of the emerging *VPS4A*-related disorder, suggesting that this condition is characterized by variable expressivity and a broad phenotype spectrum.

11:48 MOSAIC ANGELMAN SYNDROME: EXPANDED PHENOTYPE SPECTRUM OF ANGELMAN SYNDROME CAUSED BY MOSAIC IMPRINTING DEFECT

Presenting author: Boglarka BANSAGI

Boglarka BANSAGI[1], Wim WUYTS[2], Kathelijn KEYMOLEN[1], Boyan I. DIMITROV[1]

1. Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Research group Reproduction and Genetics, Centre for Medical Genetics
2. Department of Medical Genetics, Antwerp University Hospital (UZA)

Email for correspondence: Boglarka.Bansagi@uzbrussel.be

Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by loss of function of the imprinted *UBE3A* gene. Deficient expression of the maternal *UBE3A* allele - due to deletions, paternal uniparental disomy, mutations or imprinting defect - leads to the typical phenotype. The main clinical features include severe developmental delay, intellectual disability, language impairment, movement disorders, microcephaly, seizures and a happy demeanor.

The majority of the imprinting defects are sporadic epimutations. Thirty-forty % of these occur post-zygotically resulting in somatic methylation mosaicism with hypomethylation of the maternal allele. The affected individuals have a partial loss of *UBE3A* expression which leads to an atypical mosaic Angelman syndrome (mAS) phenotype. The clinical features of mAS are overall less severe in contrast with typical AS. The developmental delay is obligate but milder, all patients achieve walk, movement disorders are less likely and there is ability to communicate verbally and participate in self-care. The neurobehavioral profile is similar to AS with regard to the happy demeanor and hyperexcitability but in mAS hyperactivity and anxiety are of major concern. Hyperphagia and obesity are common overlapping symptoms with Prader Willi syndrome (PWS). Epileptic seizures and microcephaly in mAS are less likely.

We present a 3-year-old boy with a neurodevelopmental delay showing markedly disharmonic developmental profile. There is a considerable discrepancy between his average range receptive and significantly delayed expressive language skills. Concentration difficulties are pronounced. He has a general happy demeanor with refusal behaviour and high level of anxiety. He had initial feeding difficulties and failure to thrive followed by a food seeking behaviour and overweight with BMI above 97 centile.
Genetic testing with methylation-specific MLPA of the 15q11-q13 region detected a decreased methylation level on the maternal allele compatible with a mosaic methylation defect. Deletion and uniparental disomy were excluded by SNP array. An imprinting defect leading to somatic methylation mosaicism was concluded manifesting with the clinical features of mAS.

The diagnosis of mAS has to be considered in patients with mild to moderate non-specific intellectual disability, discrepancy between receptive and expressive language skills with retained speech, uncharacteristically happy demeanor especially if PWS symptoms are also present.

11:51 IDENTIFICATION OF A NOVEL PATHOGENIC VARIANT IN BCL11A GENE – PHENOCOPIES IN NEURODEVELOPMENTAL DISORDERS AND THE ADVANTAGES OF TRIO-BASED WES ANALYSIS

Presenting author: Catarina Macedo

Macedo C.[1], Moldovan O.[1], Sousa A.B.[1]

[1]Serviço de Genética, Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar e Universitário Lisboa Norte, Lisboa, Portugal

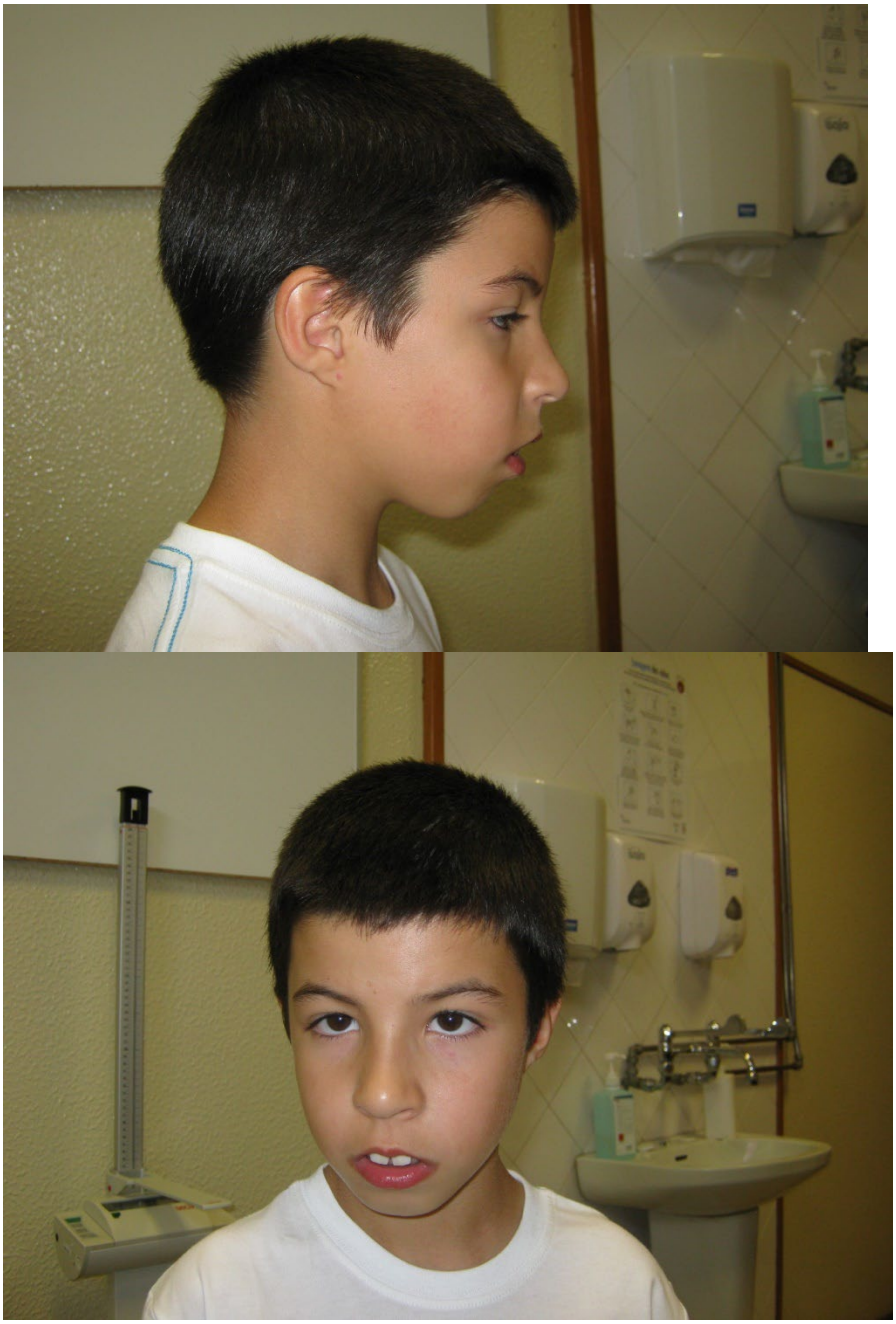
Correspondence to: catarina.macedo@chln.min-saude.pt

We present a 17-year-old boy who is the second son of distant cousins. He has a healthy older sister. His younger maternal half-brother had developmental delay (DD) and communication and social deficits. Pregnancy was complicated by placental abruption. At his first Genetics evaluation, aged 8, he had moderate DD/intellectual disability (ID), short stature, strabismus, and unspecific facial dysmorphisms (epicanthus, fleshy nose tip, hypoplastic earlobes, thin upper lip, everted lower lip, incisor macrodontia, and retrognathia). Brain MRI, neurometabolic investigation, array-CGH, and *FMR1* molecular analysis were normal.

Whole exome sequencing (WES) in trio (proband, mother and maternal half-brother) identified an hemizygous variant of uncertain significance (VUS) in *MID2* gene in both brothers: c.668G>A, p.Arg223His. Deleterious variants in *MID2* gene are associated with X-linked mental retardation type 101. The clinical significance of this variant was unclear, thus periodic clinical reevaluation was recommended.

At the last follow-up appointment, our proband maintained moderate ID, while his half-brother evolved with much less severe cognitive impairment and different facial features. Reanalysis of the data from trio-WES identified a heterozygous variant in *BCL11A* gene in our proband alone: c.142T>C, p.Cys48Arg, classified as VUS. Pathogenic variants in *BCL11A* gene cause the recently described Dias-Logan syndrome, characterized by DD/ID of variable severity, neonatal hypotonia, microcephaly, facial dysmorphisms, behavior problems, and asymptomatic fetal hemoglobin persistence. Our patient's subsequent serum hemoglobin dosage revealed fetal hemoglobin persistence (12%). Unfortunately, his father was not available for testing. Dias et al. reported a different pathogenic missense change in the same amino acid residue[1]. Taking all in consideration, the variant in *BCL11A* gene was reclassified as likely pathogenic and a diagnosis of Dias-Logan syndrome was made.

Figure 1 - Facial characteristics of our patient at age 8 showing epicanthus, strabismus, fleshy nose tip, hypoplastic earlobes, thin upper lip, everted lower lip, incisor macrodontia, and retrognathia.



Our case illustrates the importance of clinical and molecular follow-up of syndromic neurodevelopmental disorders presenting with less specific phenotypes. WES, allowing periodical data reanalysis, has proved to be cost-effective in the molecular diagnostic investigation of these conditions.

11:54 FURTHER DELINEATION OF THE KDM2B-ASSOCIATED NEURODEVELOPMENTAL SYNDROME

Presenting author: Renske Oegema

Amber van OIRSOUW[1], Claire CORNIPS[1], Michael HADDERS[2], Richard VAN JAARSVELD[1], Renske OEGEMA[1]

1. Department of Genetics, UMC Utrecht, the Netherlands
2. Oncode Institute and Center for Molecular Medicine, UMC Utrecht, The Netherlands

Email for correspondence: r.oegema@umcutrecht.nl

KDM2B (lysine-demethylase 2B, OMIM 609078) encodes for a well-studied component of the epigenetic machinery. The canonical, full-length KDM2B protein acts by demethylating lysine residues K4, K36 and K79 of Histone 3. This catalytic activity is provided for by the JmjC-domain, which is conserved from yeast to human. The DNA binding CxxC-domain directs KDM2B to promotor regions by binding unmethylated CpG dinucleotides. This DNA binding capacity has been linked to recruitment of the Polycomb repressive complex 1 (PRC1) to developmental genes and protection against DNA hypermethylation.
We have recently delineated a novel neurodevelopmental syndrome caused by heterozygous KDM2B variants. Affected individuals present with developmental delay and/or intellectual disability, autism, ADD/ADHD, congenital organ anomalies mainly of the heart, eyes, and urogenital system, and subtle facial dysmorphism (PMID 36322151).
We continuously expand our patient cohort and have now collected data on 25 individuals with pathogenic KDM2B sequence variants or 12q24.31 deletions spanning KDM2B. Also, we collected data on 10 variants of unknown significance. I will present data on clinical presentation, facial features and genotype-phenotype correlations.
Genotype-phenotype analysis suggests that missense variants, clustering in the CxxC domain cause a more severe phenotype compared to loss-of function variants. This is also reflected in the KDM2B episignature, which shows a strong subsignature in the samples with CxxC variants. We have set up a functional assay to assess DNA binding activity of the CxxC domain of KDM2B, using an electrical mobility shift assay (EMSA). For this, we use a bacterial expression vector containing the CxxC domain and PHD domain and test for DNA binding with EMSA using a fluorescently labeled CpG probe. Most of the tested variants showed decreased DNA binding compared to wildtype, which could suggest a dominant negative effect of these variants.
Furthermore, we observe a trend towards a sex-related difference in severity, with females being more severely affected than males. A sex-difference was previously observed in a *Kdm2b* mouse model. We plan to study this further by expanding our clinical cohort and in parallel developing a cellular model by the differentiating induced pluripotent stem cells (iPSCs) expressing either wild type or mutant KDM2B, to neuronal cells.

11:57 EXPANDING THE PHENOTYPE OF CATEL MANZKE SYNDROME IN AN AFFECTED WOMAN

Presenting author: Emanuele Micaglio

Micaglio E, Lo Rito M, Moresco G, Fontana L, Giamberti A, Miozzo M, Pappone C

Catel–Manzke syndrome is a very rare disease characterized by microretrognatia, orofacial cleft with hyperphalangy and clinodactyly of the index finger. Either homozygous or compound heterozygous pathogenic variants in *TGDS* gene have been demonstrated to be causative for Catel–Manzke syndrome. We describe herein a 38 years old Italian female with molecularly confirmed Catel–Manzke syndrome who presented with a complex phenotype. This phenotype was characterized by microretrognatia, vertebral schisis of the first cervical vertebra, bilateral cataract, recurrent infection of throat and inner ear, complex congenital heart malformation (interventricular heart defect and pulmonic stenosis) both surgically corrected and hyperphalangy. She underwent a careful genetic testing including *TGDS* genetic analysis and Whole Exome Sequencing to rule out other possible genetic causes of such phenotype. Only the homozygous c.298G>T in *TGDS* gene has been demonstrated, a common mutation in Catel–Manzke syndrome. We compared the aforementioned clinical phenotype with the all published patients harboring pathogenic variants in *TGDS*. According to us, this case expands the phenotype of Catel Manzke syndrome suggesting that bilateral cataract and vertebral schisis might be important clinical signs.

Session 9 – Syndrome delineation

14:00 INVITED TALK: DAVID GERMANEAU, FETAL ALCOHOL SYNDROME

14:45 CLINICAL AND GENETIC ANALYSIS OF PATIENTS WITH OVERGROWTH SYNDROMES (OGs) IN LITHUANIAN – POLISH COHORT

Presenting author: Ausra Matuleviciene

BEATA ALEKSIŪNIENĖ[1], KAMILĖ ŠIAURYTĖ[1], KAROLIS BARONAS[1], ALGIRDAS UTKUS[1], JOANNA KARWOWSKA[2], KLAUDIA BERK[2], RENATA POSMYK[2], AUŠRA MATULEVIČIENĖ[1]

[1]Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[2] Department of Clinical Genetics, Medical University of Białystok, Bialystok, Poland

Email for correspondance: Ausra.Matuleviciene@mf.vu.lt

Introduction: Overgrowth syndromes (OGs) are highly heterogeneous. Patients with OGs usually have increased height, dysmorphic features, and intellectual disability, as well as increased neoplasia risk. Such risk makes the precise and timely diagnosis crucial for cancer prevention.
Results: 108 patients with OGs from Lithuanian-Polish cohort participated in this study. Nosological units in this cohort featured: Sotos (OMIM 614753), Simpson – Golabi – Behmel (OMIM 312870), Weaver (OMIM 277590), Tatton-Brown-Rahman (OMIM 615879), Beckwith-Wiedemann (OMIM 130650) and other syndromes. Main clinical features included: lower extremity growth asymmetry (80%), psychomotor development delay or intellectual disability (64%), and congenital defects of different organ systems (45%). More than half (58%) of patients had a positive family history of cancer; with some patients also diagnosed with various neoplasias including breast cancer, Wilms tumor, hepatoblastoma, themselves. WES of the part of the cohort identified mutations in *NSD1, GPC3, EZH2, DNMT3A* genes.
Conclusions: Phenotypically this cohort mostly shares "classic" OGs features, in line with the literature. Mutations identified with WES are reflective of both clinical OGs diagnoses and cancer history of the study participants. Further analysis of molecular pathways associated with these genes is ongoing.
Funding: The study is funded by the Research Council of Lithuania (No. S-LL-21-5) and Polish National Science Center (NCN/1/DA/21/001/1106).

15:00 DECIPHERING DEVELOPMENTAL DISORDERS IN AFRICA (DDD-AFRICA): CLINICAL CHARACTERIZATION IN A CENTRAL AFRICAN SETTING

Presenting author: Prince Makay

Prince MAKAY[1,2,3], Gerrye MUBUNGU[1,2,3], Dahlie TSHIKA[1,2], Nadja LOUW[4], , Helen V. FIRTH[6,7], Matthew E. HURLES[6], Nadia CARSTENS[4,5], Amanda KRAUSE[4], Zané LOMBARD[4], Prosper LUKUSA[1,2,3], Koenraad DEVRIENDT[3], Aimé LUMAKA[1,2,8] for DDD-Africa as members of the H3Africa Consortium

[1]Faculty of Medicine, Center for Human Genetics, University of Kinshasa, Kinshasa, DR Congo
[2]Faculty of Medicine, Department of Pediatrics, University of Kinshasa, Kinshasa, DR Congo
[3]Center for Human Genetics, University Hospitals, University of Leuven, Leuven, Belgium
[4]Division of Human Genetics, National Health Laboratory Service & School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[5]Genomics Centre, South African Medical Research Council, Tygerberg, Cape Town, South Africa
[6]Human Genetics Programme, Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton CB10 1RQ, UK
[7]East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK

[8]Service de Génétique Humaine, CHU de Liège, Liège, Belgium
Email for correspondence : prince.makaybamba@kuleuven.be

Developmental Disorders (DD) affect about 1-3% of children globally. Clinical and genetic data related to DD in Central Africa are scarce. The aim of this study was to recruit and clinically characterize 150 families with at least 1 individual with unexplained DD in DR Congo, as part of the DDD-Africa project (A collaborative project between South Africa and DR Congo aimed to recruit and analyze 500 individuals with unexplained DD). Patients were recruited through the collaborative network of the Centre for Human Genetics of the University of Kinshasa, DR Congo. Four inclusion categories were used: (A) Isolated moderate to profound DD/ID, (B) Multiple major anomalies in 2 or more systems, (C) One major malformation with dysmorphism, (D) Mild to moderate DD/ID with dysmorphism. We excluded patients with clinically recognizable syndromes or strong suspicion of acquired causes. A total of 149 probands were recruited, including 97 males and 52 females, recruited as Trio (n=79), Duo (n=56), Extended Duo (n=9), and Extended Trio (n=5). The mean age was 7.84±5.84 years (range 0-38.6) with 74, 10, 5 and 60 probands respectively included in category A, B, C, and D. 130 cases (87.2%) were sporadic and 19 (12.8%) familial in whom autosomal recessive and x-linked inheritance were each suspected in six cases while autosomal dominant inheritance was suspected in seven cases. Most patients had moderate DD/ID (n=72), motor delay (n=66), and speech/language impairment (n=115). Patients were also assigned to clinical groups as follows: non-syndromic ID (n=6), overgrowth (n=15), growth retardation (n=36), severe microcephaly (n=16), seizures (n=44), skeletal dysplasia (n=4), hearing impairment (n=7), visual impairment (n=8), structural brain anomaly (n=10), heart defects (n=10), renal defects (n=10). Behavioral abnormalities included mostly hyperactivity (n=53), stereotypies (n=34), aggressive behavior (n=28), and self-injurious behavior (n=16). Clinical information is deposited in Decipher using HPO terms.
This well-phenotyped cohort of 149 families with DD/ID patients illustrates the very broad DD phenotypes in patients from Central Africa. Further genotyping by exome analysis will constitute a strong basis for genotype-phenotype correlation of DD in Central Africa.
Keywords: *DDD-Africa, Developmental disorders, phenotype, DR Congo*

15:15 DYSMORPHIC FEATURES IN A PATIENT WITH GLYCOGEN STORAGE DISEASE TYPE 4: A RARE PHENOTYPIC VARIATION

Presenting author: Marija Rozevska

Marija ROZEVSKA [1], Agnese ZARIŅA [1], Ieva MIČULE [1]

1: Medical Genetics and Prenatal Diagnostics Clinic, Children's Clinical University Hospital, Riga, Latvia

Email for correspondence: marija.rozevska@bkus.lv

Glycogen storage disease type 4 (GSD4) is a rare autosomal recessive disorder caused by a deficiency of glycogen branching enzyme (GBE). The *GBE1* gene provides instructions for making glycogen branching enzyme, which is involved in the final step of glycogen production. Glycogen is the main source of stored energy in the body.
Pathogenic variants of *GBE1* causes accumulation of abnormal glycogen in various tissues, especially the liver, skeletal muscle, heart, skin, and central nervous system.
The neuromuscular subtype of GSD4 is characterized by early onset muscle weakness and wasting. While dermatologic manifestations have been previously reported in GSD4, dysmorphic features are not typically associated with this condition.

We report a case of a patient with GSD4 neuromuscular subtype who exhibits dysmorphic features, including a webbed neck, low set ears, and increased hair growth on the back of the neck. The patient was

examined at the Medical Genetics and Prenatal Diagnostics Department of Latvian Children's Clinical University Hospital, where genetic testing was performed using new generation sequencing.

29-year-old patient came to the Genetic consultation with complaints about gait and coordination problems. The patient experiences symptoms since the early childhood – her childhood diagnosis – arthrogryposis. Patient started walking at the age of 5. Intelligence is normal. From the age of 22 patient started to notice a decrease in muscle strength, followed by depression, which further aggravated the symptoms. Now, the patient walks about 400m a day, then experiences joint pain and muscle stiffness. During the last year, the progression of the disease has been more pronounced. Additionally, memory disturbances have appeared. Similar symptoms had not been observed in the family history.

Genetic testing revealed two likely pathogenic variants in the *GBE1* gene, confirming the diagnosis of GSD4: *GBE1* c.1259del, p.(Cys421AlafsTer15) and *GBE1* c.784G>A, p.(Arg262His). In gnomAD both of the variants are located on different haplotypes, these two variants are likely compound heterozygous (in trans). While patient's neurological symptoms are strongly correlated with the known phenotype of the disease, dysmorphic features are not typically associated with GSD4 and it is unclear whether they are directly related to the genetic variants or represent an unrelated condition.

This is the second case that describes a patient with GSD4 neuromuscular subtype who also has dysmorphic features – webbed neck and increased hair growth on the back of the neck. While the association between GSD4 and dysmorphic features is unclear, this case highlights the importance of considering this possibility in patients with GSD4. The identification of two likely pathogenic variants in the *GBE1* gene through new generation sequencing confirms the diagnosis of GSD4 in this patient. Further monitoring and management of the patient's symptoms are warranted

15:18 SET-RELATED AUTOSOMAL DOMINANT INTELLECTUAL DEVELOPMENTAL DISORDER - CHROMATINOPATHY WITH EXTENDED PHENOTYPIC-PHARMACOLOGICAL CORRELATIONS

Presenting author: Malgorzata Pawlowicz

Malgorzata Pawlowicz[1,2)], Agnieszka Pollak[3)], Piotr Stawinski[3)], Joanna Kosinska[3)], Rafal Ploski[3)]

[1)] *Department of Pediatric Neurogenetics and Rare Diseases, Prof. dr Stanislaw Popowski Regional Specialized Children's Hospital, Olsztyn, Poland, ERN-ITHACA Member*
[2)] *Department of Clinical Pediatrics, Medical Faculty of Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland*
[3)] *Department of Medical Genetics, Warsaw Medical University, Warsaw, Poland*

Email for correspondence: mpawlowiczconti@gmail.com

Objective: Eight from eleven published cases (73%) of *SET*-related autosomal dominant intellectual developmental disorder are caused by truncating DNM. We present the next two cases of 8- and 3-year-old girls of Polish origin carrying *de novo* heterozygous truncating variants c.167_170del (p.Arg57Leufs*10) and c.128_131del (p.Arg44LeufsTer10) in the *SET* gene in comparison to previously published phenotypes. We also compared the *SET*-related phenotype with phenotypes of well-known autosomal dominant ID genes belonging to the *SET* gene reactome (*EP300*, *CREBBP*, *SETBP1*, *KMT2A*, *RAC1*, *CTCF*).
Methods: Presented patients were qualified for WES analysis under the program of complex ID diagnosis in the Warmia-Mazury Region (North Poland) in 2020-2022. WES analysis was performed using Illumina platform and verified by Sanger sequencing. Analysis of variant segregation in family confirmed de novo status of *SET* variants identified in probands. Classic syndromes associated with clinical signs observed in patients and caused by chromosomal rearrangements were excluded.
Results: Localization of variants in the I helix domain (association with dimerization process) was dominated in patients with DNM in the *SET* gene – 70% (including 2 presented patients). The most common recurring lesion observed in one presented and 5 published patients was the *SET* c.167_170del variant. Previously

unreported symptoms were observed in our patients: abnormal tooth eruption, optic nerve hypoplasia, localized cortical thickening, non-epileptic myoclonus, early-onset epilepsy with focal seizures, persistent startle response with good response to benzodiazepines, hypersensitivity to valproic acid as HDAC inhibitor. Comparative analysis of the *SET* gene phenotype extended with new symptoms (19 features in total) with phenotypes from reactome showed the closest correlation with the Menke-Hennekam type 1 and Wiedemann-Steiner syndromes (11 shared features), and in the case of neurodevelopmental phenotype with the *RAC1*-related autosomal dominant intellectual developmental disorder (8 shared features).
Conclusions: *SET*-related disorders can be considered a chromatinopathy with some hot-spots located in protein domains associated with dimerization process and hypersensitivity to HDAC inhibitors. In differential diagnosis, strict interference between phenotypes from the *SET* gene reactome should be taken into account.

Keywords: *SET* gene, helix domains, histone modification reactome, histone deacetylases inhibitors (HDAC inhibitors), de novo mutation (DNM), intellectual disability (ID)

15:21 ACTB CLINICAL SPECTRUM OR A COMPLEX CONDITION?

Presenting author : Mencarelli Maria Antonietta

Mencarelli Maria Antonietta[1], Carrer Anna[1 2], Maffeo Debora[2], Bruttini Mirella [1 2], Galimberti Daniela[3], Tomasini Barbara[4], Renieri Alessandra [1 2]

1 Genetica Medica, Azienda Ospedaliero-Universitaria Senese, 53100, Siena, Italy
2 Medical Genetics, University of Siena, Siena, Italy
3 Pediatria, Azienda Ospedaliero-Universitaria Senese, 53100, Siena, Italy
4 Terapia Intensiva Neonatale, Azienda Ospedaliero-Universitaria Senese, 53100, Siena, Italy

The proband was the first newborn boy of healthy non-consanguineous parents, born with a full-term pregnancy with gestational diabetes.
A low risk of fetal chromosomal disorder was highlighted from non-invasive prenatal screening (NIPT).
The weight was 2690g (8 percentile) at birth. Physical examinations revealed upper limb hypoplasia with mild hypotonia, arachnodactyly of fingers with lateral deviation, low set thumbs, absent grasp reflex, left clubfoot. Distinct facial features included squared faces, high forehead, straight eyebrows, bulbous nasal tip, thin chin.
Upper limbs X-ray, ophthalmologic examination, echocardiogram, brain and abdomen ultrasound did not reveal anomalies.
It is noted that the patient also displayed thrombocytopenia in the first day of life.
Whole exome sequencing analysis revealed a *de novo* missense variant in the last exon of *ACTB* gene(c.1090G>A, (p.(Glu364Lys)))).
This variant was already reported and associated with moderate intellectual disability, abnormal white blood cell counts, and thrombocytopenia (Nunoi et al., 1999).
To date, the spectrum of clinical conditions associated with *ACTB* variants is very wide and includes intellectual disability due to *ACTB* haploinsufficiency, Becker's Nevus syndrome due to low-grade mosaic *ACTB* hotspot mutations, Baraitser-Winter Cerebrofrontofacial syndrome from constitutive missense mutations in exons 2–4, and a distinct condition with mild developmental disability, microcephaly, and thrombocytopenia with platelet anisotropy linked to missense mutation in exons 5 and 6 (Latham et al., 2018).
To our knowledge, limb abnormalities, as evidenced in our patient, are not previously reported in the *ACTB*-associated clinical syndromes. We would like to discuss whether this characteristic can be part of the disease spectrum or if there is a different genetic explanation that can be suspected.

15:24 A NOVEL UPF3B VARIANT IN ASSOCIATION WITH PREVIOUSLY UNREPORTED BRAIN ANOMALIES: A CLINICAL SPECTRUM EXPANSION

Presenting author: Maria Francesca Di Feo

Ferruccio Romano[1], Marcello Scala[2-3], Monica Traverso[2-3], Mariasavina Severino[4], Maria Derchi[5], Francesca Faravelli[1], Valeria Capra[1],

e-mail for correspondence: ruccio1991@gmail.com

[1]Clinical Genetics and Genomics Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[2]Medical Genetics Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[3]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy
[4]Neuroradiology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[5]Cardiology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Hemizygous variants in the *UPF3B* gene are described in association with a wide spectrum of neuropsychiatric issues (MIM: 300676), including intellectual disability, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia/ childhood onset schizophrenia (COS). *UPF3B* encodes the Regulator of nonsense transcripts 3B protein, a core-member of the nonsense-mediated mRNA decay (NMD) pathway, protecting the cells from the potentially deleterious actions of transcripts with premature termination codons (PTCs).
However the understanding of the mechanisms by which *UPF3B* loss of function variants lead to the clinical manifestations still remains elusive. Poor is known about possible clinical consequences in other districts, such as the heart, and the kidney. Moreover the number of patients reported to date is limited, in some cases lacking an extensive description, especially from a neuroradiological point of view.
Here we report the case of a boy with developmental delay, intellectual disability, persistent limb stiffness, persistent hypotonia, brain malformations (corpus callosum hypoplasia/dysgenesis, anterior commissure agenesis, olfactory bulbs agenesis, choroidal plexus cysts, and a developmental venous anomaly), choanal stenosis, and tetralogy of Fallot.
Whole Exome Sequencing (WES) analysis identified the new *de novo* c.619A>T variant, (p.Lys207*), in the *UPF3B* gene. Some of the clinical features showed by the patient are not included in the classical phenotypic *UPF3B* spectrum, such as the brain malformations and the choanal stenosis. We discuss the possible role of the variant in the patient's clinical issues, suggesting an expansion of the phenotypic spectrum.

15:27 A NOVEL INSIGHT INTO THE CLINICAL AND SKELETAL SPECTRUM OF ZMIZ1-RELATED DISORDER

Presenting author: Livia Garavelli

Irene Ambrosetti[1,2], Stefano Giuseppe Caraffi[1], Francesca Peluso[1], Roberta Zuntini[1], Susanna Rizzi[3], Teresa Grimaldi[4], Antonella Crisafi[5], Alessandra Terracciano[6], Francesca Clementina Radio[7],
Carlo Fusco[3], Marco Tartaglia[7], Antonio Novelli[6], Livia Garavelli[1]

1: Medical Genetics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy. 2: Department of Medical and Surgical Science, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy 3 : Child Neurology Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy. 4 : 5 : Pediatrics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, 6: Molecular Genetics and Functional Genomics, Bambino Gesù Children's Hospital, IRCCS, 00146 Rome, Italy. 7: Translational Cytogenomics Research Unit, Laboratory of Medical Genetics, Bambino Gesù Children's Hospital, IRCCS, 00146 Rome, Italy

Email for correspondence: livia.garavelli@ausl.re.it

ZMIZ1 is a transcriptional coregulator of the Protein Inhibitor of Activated STAT (PIAS)-like family and a coactivator of several transcription factors, including p53, the androgen receptor and NOTCH1. The gene *ZMIZ1* was mapped to chromosome 10q22.3 and contains 21 exons encoding a 1067 amino acid protein. Carapito *et al*. in 2019 (PMID 30639322) identified pathogenic variants in the gene *ZMIZ1* in a cohort of 19 patients with developmental delay, intellectual disability and other associated features including growth failure, feeding difficulties, microcephaly and various congenital anomalies—cardiac, genitourinary, ocular and skeletal. To date, variants in the *ZMIZ1* gene have been reported in 32 patients with this autosomal dominant neurodevelopmental disorder also referred to by the acronym NEDDFSA (OMIM #618659). Here we describe a patient with a novel, *de novo* pathogenic variant c.850_867del in *ZMIZ1* (NM_020338.4).
The patient was referred to our service due to developmental delay, motor clumsiness, bladder diverticulum (operated), congenital heart disease with bicuspid, dysmorphic and thickened aortic valve, severe supravalvular aortic stenosis (operated), sternal resynthesis surgery for severe sternal diastasis following sternotomy, episodes of stiffness in the neck and spine, malformation of the craniocervical joint with cleft of the posterior arch of C1, dysmorphism of the foramen magnum, squat appearance of the odontoid apophysis in the absence of neuroradiological signs of instability of the craniocervical junction, brachydactyly A4 on hand X-rays, right cryptorchidism, hypertension. At the age of 8 years he had flat face, high forehead, low-set and posteriorly rotated ears, delayed tooth eruption (no upper incisors erupted), pectus excavatum, dimples in the scapular area. Hands: 2nd finger proximal interphalangeal joints hyperextension and distal interphalangeal joint hyperflexion, stiffness of the proximal interphalangeal joint and metacarpophalangeal joint of the 5th finger. Feet: hypoplastic nails. Height and weight were 130 cm (50th-75th percentile) and 22 Kg (3rd-10th percentile), head circumference was 53 cm (75th-90th percentile). Pubertal stages: A0P1B1. CGH-Array analysis was normal.
The *de novo* pathogenic variant c.850_867del, identified through WES, removes six amino acids p.(Val288_Ala293del) in the Alanine-rich domain of the ZMIZ1 protein. To date, only missense variants which modify protein sequence and structure have been described in this domain.
Our report adds some hitherto unreported molecular and clinical features and expands the phenotypic spectrum, highlighting some clinical signs that are useful as a diagnostic tool for suspecting and diagnosing this condition. Finally, we are planning a call for patients to further clarify the clinical and skeletal aspects of the disease.

Session 10 – Syndrome delineation

16:10 A PATIENT WITH BECKWITH-WIEDEMANN SYNDROME *AND* MLID WITH SNRPN:TSS-DMR HYPOMETHYLATION

Presenting author: Alma Kuechler

Alma Kuechler, Deniz Kanber, Sandra Ueberberg, Sabine Kaya, Christina Lich, Frank J. Kaiser, Jasmin Beygo

Institute of Human Genetics, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Beckwith-Wiedemann syndrome (BWS, OMIM #130650) is an overgrowth associated imprinting disorder caused by genetic and epigenetic disturbances of one or both imprinting control regions (ICR) on chromosome 11p15.5. In about one-third of BWS cases due to an imprinting defect of the *KCNQ1OT1*:TSS-DMR (ICR2), patients also show disturbed methylation at additional imprinted loci, a so called multi-locus imprinting disturbance (MLID). Additional phenotypic features normally attributed to the affected loci are usually not present in the MLID patients. Interestingly, the imprinted loci show a highly variable susceptibility

for MLID. That is, while in addition to the loci on chromosome 11, loci on chromosomes 6, 7, and 20 are frequently affected, chromosome 15 seemed to be an exception.
Here we describe a patient with BWS due to a mosaic hypomethylation of the *KCNQ1OT1*:TSS-DMR (ICR2) and MLID. He was born at term with normal measurements, but showed lateralised overgrowth of the right leg and the right side of the tongue. Additionally, an umbilical hernia was present. His psychomotor development is normal.
First molecular genetic analyses were performed shortly after birth on DNA from buccal swab samples of the right and left side separately. MS-MLPA of chromosome 11p15 (ME030, all MRC Holland) and chromosome 7 (ME032) as well as *CDKN1C* sequencing yielded normal results. Later on, a blood sample was obtained and MS-MLPA showed a mosaic hypomethylation of the *KCNQ1OT1*:TSS-DMR confirming BWS in the patient. Subsequent analyses for MLID also performed via MS-MLPA (ME034) in blood showed a mosaic hypomethylation of the *PLAGL1*:alt-TSS-DMR on chromosome 6q24 and, surprisingly, also a mosaic hypomethylation of the *SNURF*:TSS-DMR and the *MAGEL2*:TSS-DMR on chromosome 15q11.2. We confirmed these results with the specific MS-MLPAs for these loci (ME032 and ME028) and also on DNA from blood of an independent sample of this patient. For all three affected loci, the *KCNQ1OT1*:TSS-DMR, *PLAGL1*:alt-TSS-DMR and *SNURF*:TSS-DMR, the degree of hypomethylation was in the same range of about 25%.
To investigate if a variant in a maternal effect gene could be responsible for the MLID in the patient we conducted whole exome sequencing in his mother. This did not reveal any potential pathogenic variant.
Taken together, we describe one of the very rare patients with BWS and a MLID involving the DMRs on chromosome 15 but with no additional clinical features to date.

16:25 EPISIGN: EXAMPLES OF THE USE OF GENOME-WIDE OR TARGETED DNA METHYLATION ANALYSIS IN DIAGNOSTICS

Presenting author: Emilia Bijlsma

Emilia K. BIJLSMA [1], Daniela Q.C.M. BARGE-SCHAAPVELD [1], Emmelien ATEN [1], Esther A.R. NIBBELING [1], Mariette J.V. HOFFER [1], Claudia A.L. RUIVENKAMP [1]

1: Department of Clinical Genetics, Leiden University Medical Center, Leiden, The *Netherlands*

E-mail for correspondence: e.k.bijlsma@lumc.nl

Genetic defects in patients with neurodevelopmental disorders may disrupt genomic DNA methylation. DNA methylation is an epigenetic modification, resulting in changes in structural and chemical properties of the DNA, impacting molecular mechanisms such as chromatin assembly and gene transcription. Several groups have demonstrated that individuals among a growing number of rare disorders exhibit DNA methylation 'episignatures' (EpiSigns) as highly sensitive and specific DNA methylation biomarkers (1).
As of May 2023, these genome-wide DNA methylation profiles include over 70 rare disorders in association with more than 75 genes, and can be gene domain, gene level, as well as protein complex specific. As DNA methylation episignatures are detectable in peripheral blood and both highly sensitive and specific, they represent effective biomarkers for the testing of patients with a broadening range of neurodevelopmental genetic conditions. Also, they may be used as a functional test for patients with ambiguous genetic test findings or clinical phenotypes.

We will discuss several cases in which the diagnostic process was supported by adding Episign to our genetic toolbox. The examples concern:
- variants of uncertain significance in a known gene
- pathogenic variants in known genes in patients not fitting the phenotype of the specific syndrome

- cases that were diagnosed after an ‘open’ Episign

(1) Sadikovic et al. Clinical epigenomics: genome-wide DNA methylation analysis for the diagnosis of Mendelian disorders. Genetics in Medicine 2021; 23 (6),1065-74. https://doi.org/10.1038/s41436-020-01096-4.

16:40 CLINICAL PHENOTYPE OF FOXP1 SYNDROME: PARENT-REPORTED SIGNS AND SYMPTOMS IN 40 INDIVIDUALS

Presenting author: Saskia Koene

Saskia KOENE [1], Fabienne G. ROPERS[2], Dagmar BERGHUIS[2], Angela MORGAN[3], Ruth BRADEN[3], Maria Del Pilar TRELLES[4], Gijs W.E. SANTEN[1]

1: Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands.
2: Department of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands.
3: Murdoch Children's Research Institute, Parkville, VIC, Australia.
4: Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, USA

Email for correspondence: s.koene@lumc.nl

Pathogenic variants in the *FOXP1*-gene are associated with neurodevelopmental delay, autism spectrum disorder, dysmorphic features and cardiac and urogenital malformations.
This study uses a parent-reported questionnaire to assess the medical signs and symptoms associated with FOXP1 syndrome, and identify which manifestations were reported to have the highest impact patients and their family.
Patients were recruited through social media, via patient organizations and via their treating physicians.
Forty individuals were included, 20 female and 20 male. Mean age at assessment was filled out was 13.2 years (range 2 – 54 years). Seven adults were included. Thirty participants were from Europe (26 Dutch-speaking and 4 German-speaking); 10 individuals were from Northern America.
The most prevalent medical signs and symptoms include hypermetropia, strabismus, sacral dimple, cryptorchidism, abnormal muscle tone and frequent infections. Parents report a high prevalence of repetitive behavior, including the need for “security objects” in the hands, a complex sensory profile with both easy overstimulation and sensory seeking, auditory hyperreactivity, attention deficit, hyperactive behavior, and obsessive and compulsive behavior. The most bothersome consequences of FOXP1 syndrome according to parents are intellectual disability, communication difficulties, behavior problems, lack of self-reliance/independency, concentration deficit and anxiety. According to parents, patients themselves have quite similar priorities, although diurnal enuresis, obsessions, and a difficult sensory profile have a higher ranking.
Strengthened by a recent study showing high consistency between parent-reported phenotype and medical files (Engwerda et al. 2023), this study shows the potential of parent-reported medical phenotyping in patients with rare disorders. Future studies should be focused on the symptoms rated as most bothersome, including enuresis and sensory processing.

16:55 WBP11-RELATED PSEUDO-VATER SYNDOME IN 2 GENERATIONS WITH CEREBELLAR INFARCT : CHANCE OCCURRENCE OF PHENOTYPIC EXPANSION

Presenting author: Alain Verloes

Xenia LATYPOVA[1], Agnès GUET[2], Rania BENMEFTA[3], Magalie LODIN[1], Laurence PERRIN[1], Yline CAPRI[1] Corinne COLLET[1], Alain VERLOES[1]

[1]Dept of Genetics, APHP-NUP Robert Debré, Dept of pediatrics, APHP-Louis MOURIER Hospital, Paris, and [3]Pediatric dept, Pontoise General Hospital, Pontoise, France

Email for correspondence: alain.verloes@aphp.fr

WBP11, also known as WW domain binding protein 11, is a splicing factor be involved in the process of pre-mRNA splicing, a crucial aspect of gene expression regulation. Additionally, its roles in DNA damage repair and oncogenesis have been reported.
WBP11, a nuclear protein, is part of the spliceosome, a complex that is vital for the processing of pre-mRNA into mature mRNA molecules, a key aspect of gene expression (Bai, R., Wan, R., Yan, C., Lei, J., & Shi, Y. (2018). Structures of the fully assembled Saccharomyces cerevisiae spliceosome before activation. Science, 360(6396), 1423-1429). Mutations in WBP11 can affect the function of the spliceosome, leading to alternative splicing patterns and ultimately abnormal development (Staley, J.P., & Kim, P.S. (2018). Splicing gets a hold on WBP11. Molecular Cell, 69(5), 725-726).
Following DNA damage, WBP11 binds to p53, which leads to the stabilization of p53 and activation of DNA repair pathways (Luo, J., Solimini, N.L., & Elledge, S.J. (2009). Principles of cancer therapy: oncogene and non-oncogene addiction. Cell, 136(5), 823-837). High levels of WBP11 expression have been associated with poor prognosis in several types of cancers, such as breast and ovarian cancers (Koedoot, E., Fokkelman, M., Rogkoti, V.M., Smid, M., van de Sandt, I., de Bont, H., Pont, C., Klip, J.E., Wink, S., Timmermans, M.A., van der Vegt, B., Mieke, D., Martens, J.W., van de Water, B., & Fodde, R. (2019).
WBP11 is highly expressed during embryogenesis (Tanackovic, G., Ransijn, A., Thibault, P., Abou Elela, S., & Klinck, R. (2011). Differential regulation of SR proteins during mammalian embryogenesis. Nucleic Acids Research, 39(10), 4027–4037). WBP11 is involved in the Notch signaling pathway, which is crucial for the regulation of somitogenesis, the process by which the presomitic mesoderm is segmented into somites (Chapman, D. L., & Papaioannou, V. E. (1998). Three neural tubes in mouse embryos with mutations in the T-box gene Tbx6. Nature, 391(6668), 695-697). Specifically, WBP11 has been associated with vertebral segmentation defects. Mutation in WBP11 in humans can cause spondylocostal dysostosis, WBP11 mutation disrupts the normal alternative splicing of mRNA for key proteins involved in somite segmentation, leading to the vertebral defects observed in spondylocostal dysostosis (Sparrow, D. B., Chapman, G., Smith, A. J., Mattar, M. Z., Major, J. A., O'Reilly, V. C., ... & Dunwoodie, S. L. (2013). One study identified a homozygous missense mutation in WBP11 in a family with SCD, suggesting that WBP11 plays a critical role in the proper segmentation of the vertebral column (Eckalbar, W. L., Fisher, R. E., Rawls, A., & Kusumi, K. (2012). Scoliosis and segmentation defects of the vertebrae. Wiley Interdisciplinary Reviews: Developmental Biology, 1(3), 401-423). The exact molecular mechanism by which this mutation causes SCD remains unclear, but it suggests that WBP11 could be a critical factor in vertebral development and disease.

16:58 A NOVEL HOMOZYGOUS DELETION IN CCDC32 GENE CAUSING CARDIOFACIONEURODEVELOPMENTAL SYNDROME: THE FOURTH PATIENT REPORTED

Presenting author: Rita Quental

Rita QUENTAL[1], Ana GRANGEIA[1,2], Carla PINTO MOURA[1,2,3,4]

1: Serviço de Genética Médica, Centro Hospitalar Universitário de São João, Porto, Portugal; 2: i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal; 3: Departamento de Genética, Faculdade de Medicina da Universidade do Porto, Porto, Portugal; 4: Serviço de Otorrinolaringologia, Centro Hospitalar Universitário de São João, Porto, Portugal

Email for correspondence: rita.quental@chsj.min-saude.pt

In 2020, the *CCDC32* gene was associated with a human disorder through the identification of homozygous pathogenic variants in three patients from two consanguineous families. These patients presented several clinical features, including microcephaly, cleft lip and palate, cardiac defects, brain anomalies, neurodevelopmental issues, and dysmorphic features. Since the initial description, only one additional patient has been reported, displaying a similar phenotype. The biologic function of *CCDC32* is still unknown. Studies conducted on zebrafish have suggested that ccdc32 plays a critical role in normal cilia formation, and showed that ccdc32-depleted zebrafish embryos had reduction in head size, hypoplastic cerebella and disrupted cardiac looping, resembling the human phenotype. More recently, Wainberg et al (2021) have demonstrated that CCDC32 is involved in clathrin-mediated endocytosis.
In this case report, we present a female patient who was born to consanguineous parents and whose pregnancy was inadequately monitored. There was no significant family history, except for a second cousin with cerebral palsy of unknown etiology. At birth, the patient was diagnosed with microcephaly and bilateral cleft lip and palate. Throughout infancy and childhood, she experienced feeding difficulties, global developmental delay, which later progressed to intellectual disability, as well as recurrent respiratory infections and otitis. Cardiac assessments revealed an atrial septal defect, and an abdominal ultrasound showed a bicornuate uterus. Brain magnetic resonance imaging was unremarkable. At the age of 15, in her most recent physical examination, the patient exhibited intellectual disability, short stature, microcephaly, craniofacial dysmorphic features (hypertelorism, thick eyebrows, upslanting palpebral fissures, a wide nasal bridge, large prominent ears), small hands, brachydactyly, nail clubbing, large halluces, and hypoplastic toenails. Clinical exome sequencing identified the likely pathogenic variant c.(244+1_245-1)_(*872_?)del in the homozygous state in *CCDC32*, thereby establishing the diagnosis of cardiofacioneuro-developmental syndrome (OMIM #619123). The patient's mother is a heterozygous carrier of the variant, whereas the father was unavailable for study.
This case report further expands the molecular and clinical spectrum of this rare and still poorly known disorder. The description of additional patients is needed to establish the complete phenotype and will provide valuable insights on the CCDC32 function and interactions in biologic pathways. To the patient´s family, molecular diagnosis allowed proper genetic counselling and informed reproductive choices.

17:01 A NOVEL FAMILIAL DNMT3A VARIANT CAUSING GLOBAL HYPOMETHYLATION AND A VARIABLE CLINICAL PHENOTYPE OF TATTON-BROWN-RAHMAN SYNDROME IN TWO ADULT PATIENTS

Presenting author: Candy Kumps

Candy KUMPS[1], Erika D'HAENENS[1], Jennifer KERKHOF[2], Haley MCCONKEY[2], Marielle ALDERS[2], Bekim SADIKOVIC[2], Olivier M. VANAKKER[1]

1: Center for Medical Genetics, Ghent University Hospital, Belgium
2: Molecular Diagnostics Program, and Verspeeten Clinical Genome Centre, London Health Sciences Centre, London, Canada

Email for correspondence: candy.kumps@ugent.be

Tatton-Brown-Rahman syndrome (TBRS) is a rare overgrowth and intellectual disability syndrome caused by pathogenic variants in the *DNMT3A* gene, a DNA methyltransferase. We here report two adult patients with a novel familial *DNMT3A* variant (c.2206C>T, p.(Arg736Cys)). The proband presented with foetal

macrosomia, postnatal tall stature (+4.5SD), macrocephaly and obesity, mental retardation, brain atrophy, epilepsy, psychiatric issues, kyphoscoliosis and extensive cardiovascular problems including cardiomyopathy, aortic root dilatation, mitral valve prolapse and arrhythmia. The father showed foetal macrosomia, postnatal macrocephaly, normal development and intelligence, lymphocytosis and a similar cardiovascular phenotype. Episign analysis on a blood sample of both the proband and his father showed a methylation signature characteristic for Tatton-Brown-Rahman syndrome, underscoring pathogenicity of this variant. We further establish the spectrum of TBRS, presenting a novel familial pathogenic *DNMT3A* variant in two adult patients exemplifying the use of a methylation signature as a generally applicable tool for clinical variant validation. Next to overgrowth, we report the presence of amongst others psychiatric and significant cardiovascular problems as well as incomplete penetrance of the intellectual disability phenotype.

17:04 A NIDOGEN MISSENSE VARIANT LOCATED IN THE LAMININ BINDING DOMAIN CAUSES AUTOSOMAL DOMINANT DANDY-WALKER MALFORMATION WITH OCCIPITAL CEPHALOCELE

Presenting author: Koen Devriendt

Koen Devriendt[1], Anneleen Bogaerts[1], Kris Van Den Bogaert[1], Gunnar Buyse[2], Sofie Dietvorst[3], Frank Van Calenbergh[3]

1.Center for Human Genetics,
2 Department of Pediatric Neurology, 3 Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium

Email koenraad.devriendt@uzleuven.be

The index, a now 14 year old boy, presented as a neonate with a midline soft tissue occipital swelling. Imaging revealed the presence of an atretic meningocele and a Dandy Walker malformation. Follow-up showed a progressive relative macrocephaly (HC +1.7SD for a height 0.1SD) and a prominent occiput. Further clinical and neurological examination was normal. He has a normal intelligence. The maternal grandfather has the same manifestations.

The clinical diagnosis of autosomal dominant Dandy-Walker malformation with occipital cephalocele (ADDWOC) was made (OMIM 61777489). The clinical course in the present family confirms previous reports of a favorable outcome in most individuals.

A loss-of-function mutation in *NID1* (Gln388*) has previously been described in two independent families (Darbro et al;, 2013),. In another family, a missense variant (T746M) in *LAMC1,* coding for a ligand of NID1 was reported.

Mutation analysis in the present family revealed a missense variant in NID1 (c.3336T>G , p.Asn1112Lys) in the index and grandfather. The variant was absent from gnomAD. Asn1112 is a highly conserved amino acid (up to Drosophila and C Elegans). The physical interaction between nidogen and laminin is crucial for the formation of basement membranes in several tissues, including the nervous system. Crystal structure of the mouse nidogen/laminin complex shows that this interaction depends on hydrogen bonds between the side chain of Asn 802 of laminin and the side chain of the Asn corresponding to human Asn1112, exactly the amino acid affected in the present family (Takagi et al., 2003). These genetic findings in this family underscore the importance of nidogen/laminin interaction in development of the cerebellum in humans.

References:

Takagi et al., Nature. 2003 Aug 21;424(6951):969-74.;
Darbro et al. Hum Mutat. 2013 Aug;34(8):1075-9;
McNiven et al. Am J Med Genet A. 2019 May;179(5):837-841

17:10 A BOY WITH CLINICAL GOMEZ-LOPEZ-HERNANDEZ SYNDROME

Presenting author: Ilona PIRUŠKA

Ilona PIRUŠKA[1], Daiga MŪRMANE [1] Gita TAURIŅA[1]

[1] Clinic of Medical Genetics and Prenatal Diagnosis, Children's Clinical University Hospital

Email for correspondence: ilona.piruska@bkus.lv

We report a three years-old male patient, second child born to healthy parents, at 40 weeks by C-section. He was born with Apgar score of 8/10/10, length on 98th percentile, weight on 59th percentile. The first 3 days, according to the mother, the child did not react to pain irritability, there was a paretic right side of the body, snoring breathing. He wasn`t able to start breastfeeding, so the food was given through the nasogastric tube since birth. Postnatal brain MRI showed positional plagiocephaly, slight enlargment of the third, lateral ventricles and subarachnoid spaces, rhombencephalosynapsis.

The child was born to non-consanguineous healthy Caucasian parents with unremarkable family history.

From the age of 1 month the child showed positive dynamics, movements on both sides of the body become symmetrical. Around 3 months boy was treated in a hospital in Germany with acute pyelonephritis, then the left-sided megaureter and double kidney were detected.

At clinical genetic evaluation at 5 month of age he presented with light axial hypotonus and craniofacial dysmorphic features. These include a brachiocephalic head shape, low set ears, dysplastic auricles, short neck, bilateral temporal/parietal alopecia areas.

SNP array showed duplication of region q33.3 of chromosome 9: (arr{GRCh38} 9q33.3(126678561_126799029)x3), which is classified as variant of unknown significance (VUS). Variant segregation revealed that the probands' mother is the carrier of the variant.

Karyotype analysis, FISH analysis for chromosome 9 were performed as well and results were normal.

Despite the results of these analyses, the clinical criteria of the patient were evaluated. Gomez-Lopez-Hernandez syndrome has been diagnosed based on the combination of the typical clinical and neuroradiological findings. Very specific changes in the brain (rhombencephalosynapsis), as well as other specific symptoms – parietal alopecia and typical signs of the face, which coincide with the clinical signs of Gomez-Lopez-Hernandez syndrome. Our patient has a clinical similarities with those patients previously reported, supporting the gestalt described and further delineating the phenotype.

SATURDAY 16/09

Session 11 Syndrome delineation

09:00 EXPANDING THE CLINICAL PHENOTYPE OF INDIVIDUALS WITH NOVEL VARIANTS IN THE X-LINKED WDR13 GENE

Presenting author : Elis Tivoja

Elis TIIVOJA[1,2], Tiia REIMAND[1,2], Eve ÕIGLANE-SHLIK[2,3], Lorena TRAVAGLINI[4], Francesco NICITA[4], Enrico BERTINI[4], Ginevra ZANNI[4], Kirsten CREMER[5], Sophia PETERS[5], Hartmut ENGELS[5], Claudia PERNE[5], Katrin ÕUNAP[1,2]

[1] Department of Clinical Genetics, Genetics and Personalized Medicine Clinic, Tartu University Hospital
[2] Institute of Clinical Medicine, University of Tartu
[3] Children's Clinic, Tartu University Hospital
[4] Bambino Gesù Children's Hospital, IRCCS, Unit of Muscular and Neurodegenerative Disorders, Rome, Italy
[5] Institute of Human Genetics, School of Medicine, University Hospital Bonn, University of Bonn, Bonn, Germany

Email for correspondence: elis.tiivoja@kliinikum.ee

Introduction: WDR13 protein is part of a large family of structurally related WD-repeat proteins, which have a diverse range of functions. Their dysfunction is linked to the development of many diseases, including neurodevelopmental disorders. In 2021, Rzońca-Niewczas et al. were the first to describe a patient with an intellectual disability and a nonsense mutation in the X-linked *WDR13* gene in depth and to study the effects of alterations in *WDR13* gene in human cells. This work aims to describe three additional cases and expand the clinical phenotype associated with variants in *WDR13* gene.

Materials and methods: We collected information on three additional cases with a novel hemizygous variant in *WDR13* gene through GeneMatcher. The patients are of Estonian, Italian and Kosovan origin. All patients are male. The variants were detected by exome sequencing.
Results: All of the patients have global development delay with intellectual disability. One of the patients has epilepsy. Other neurological symptoms include hypotonia (2/3), truncal ataxia (2/3), and spastic diplegia (1/3). Behavioural abnormalities, including autism spectrum disorder, aggression, hyperactivity and stereotypic movements, were described in all of the cases. Chronic constipation (2/3) and hernias (2/3) were also reported in these patients. Neuroimaging studies, performed in 2 cases, showed frontal atrophy, hypomyelinization and cerebellar atrophy. All three patients present dysmorphic features, including coarse facial features, brachy- and clinodactyly, thin upper lip vermilion, epicanthus inversus, and short nose (table 1).
The variants identified in the patients were: (1) Estonian patient - NM_017883.5(*WDR13*):c.1429G>A p.(Val477Ile); (2) Italian patient - NM_017883.6(*WDR13*):c.1091G>A p.(Ser364Asn); (3) Kosovan patient - NM_001347217.2(*WDR13*):c.523+68_*2393del p.(Val175Glyfs*21). All patients inherited the variant from their mothers.
Conclusion: This adds to the evidence that the *WDR13* gene could be a candidate for developmental delay in boys. Our cases extend the phenotype described by Rzońca-Niewczas et al. 2021.
Funding: Estonian Research Council grant PRG471.

Patient	**Estonian**	**Italian**	**Kosovan**
Age	7 years	4,5 years	12 years
Speech development	No speech	Language delay	Speaks a few single words
Intellectual disability	Yes	Yes	Yes
Motor development	Delayed, does not sit and walk	Walks only with support	Delayed, but walks independently
Other neurological symptoms	Tonic-clonic seizures, central hypotonia, truncal ataxia, hand stereotypies	Autistic behaviour, hypotonia, truncal ataxia	Aggressive and hyperactive behaviour, problems with sleep, spastic diplegia
Neuroimaging	Frontal atrophy; hypomyelinization	Cerebellar atrophy	Not done
Dysmoprhic features	Coarse facial features, epicanthus inversus, short nose, broad eyebrows, brachy- and clinodactyly	Coarse facial features	Postnatal macrocephaly, thin upper lip vermilion, short phalanges
Other medical problems	Umbilical hernia, chronic obstipation, gastrostome	Not reported	Umbilical and inguinal hernia, cryptorchidism, chronic constipation

09:15 PRENATAL AND POSTNATAL PHENOTYPE OF ZTTK SYNDROME: REPORT OF TWO CASES

Presenting author: Giulia Vitetta

Giulia VITETTA[1], Vera ULIANA[1], Melissa BELLINI[2], Diana CARLI[3], Benedetta PICCOLO[4], Alessandra TERRACCIANO[5], Alfredo BRUSCO[3], Enrico AMBROSINI[6], Valeria BARILI[6], Emanuela Claudia TURCO[4], Nicola VOLPE[7], Tullio GHI[7], Antonio NOVELLI[5], Antonio PERCESEPE[1 6]

1 Medical Genetics Unit, University Hospital of Parma,Parma, Italy
2 Department of Pediatrics and Neonatology, Guglielmo da Saliceto Hospital, Piacenza, Italy
3 Department of Medical Sciences,University of Torino, Turin, Italy
4 Child Neuropsychiatry Unit, University Hospital of Parma,Parma, Italy
5 Genetics and Rare Diseases Research Division, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
6 Medical Genetics, Department of Medicine and Surgery, University of Parma, Italy
7 Obstetrics and Gynecology Unit, University Hospital of Parma, Parma, Italy

Email for correspondence: giulia.vitetta@studio.unibo.it

Background: Zhu-Tokita-Takenuchi-Kim syndrome (ZTTKS) is an autosomal dominant disease caused by de novo mutations in the SON gene. ZTTKS is a heterogeneous and multisystemic neurodevelopmental disorder. Affected individuals have intellectual disability, distinct facial features and congenital anomalies that may involve different organs. We present a prenatal diagnosis and a postnatal case of ZTTKS, describing the fetal ultrasound malformations as well as the postnatal dysmorphisms and clinical findings.

Cases presentation: Case #1 was a pregnancy with a fetus showing at the 20th week of gestation a hypoplasia of the corpus callosum and a polycystic left renal dysplasia. Fetal MRI confirmed the ultrasonographic findings and described the corpus callosum as dysmorphic, short and with increased thickness, referred to as partial agenesis. After amniocentesis karyotype and CMA analysis were performed, resulting in a normal male profile. Clinical exome analysis was subsequently carried out, reporting the heterozygous de novo pathogenic variant c.1104_1111delAGCGTTGG (p.Leu370AlafsTer54) in the SON gene, consistent with the diagnosis of ZTTK syndrome. The pregnancy was terminated thereafter.
Case #2 was a 6-year-old girl presenting growth parameters below the 3rd percentile, with hypotonia, developmental delay and peculiar facial features. The child suffered from frequent respiratory infections and epilepsy, in therapy with Valproate. Brain MRI showed a mild hypoplasia of the posterior fossa, thinning of distal part of corpus callosum, slightly enlarged ventricular system. The echocardiography reported an atrial septal defect and pulmonary stenosis. Those anomalies had already been described in the second trimester ultrasound, but prenatal diagnosis was declined by the couple. Array-CGH analysis was not conclusive, whereas whole exome sequencing identified a heterozygous de novo pathogenic variant, c.2910delC (p.Tyr970*) of the SON gene.

Conclusions: In both cases Exome Sequencing identified a truncating heterozygous variant which had not been previously described in any database. Among the SON variants, loss of function mutations are the most frequently reported in ZTTKS: they are mostly located in the third exon of the gene and involve short nucleotide deletions, leading to SON haploinsufficiency. The clinical features of our cases are consistent with the broad spectrum of extra-neurological abnormalities of ZTTKS and highlight the need of a multidisciplinary management for affected patients.

09:30 FIRST PATIENT WITH COMPOUND HETEROZYGOUS VARIANTS IN ZNF526: THE COMBINATION OF A FRAMESHIFT AND A MISSENSE VARIANT COULD LEAD TO A MILDER PRESENTATION OF THE DISEASE

Presenting author: Maria Chiara Baroni

Baroni MARIA CHIARA[1,2], Peluso FRANCESCA[1], Caraffi STEFANO GIUSEPPE[1], Cavalli ANNA[3], Petracca SONIA[1], Ormitti FRANCESCA[4], Manzali ELISABETTA[5], Zuntini ROBERTA[1], Fusco CARLO[3], Garavelli LIVIA[1]

1 Medical Genetics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy.
2 Department of Medical and Surgical Science, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy.
3 Department of Pediatrics, Child Neurology Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy.
4 Diagnostic Department, Neuroradiology Unit, University Hospital of Parma, 43126 Parma, Italy.
5 Pediatrics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy.

Email for correspondence: mariachiara.baroni2@studio.unibo.it

The *ZNF526* gene encodes a Kruppel-type zinc finger protein involved in transcriptional regulation.
It is a ubiquitously expressed gene with only one long coding exon, including 13 zinc finger domains.
To date, homozygous variants in the *ZNF526* gene were reported in only seven unrelated families presenting with a neurodevelopmental disorder.

Here we describe the first patient with compound heterozygous variants in *ZNF526*. He is a 28- month-old boy, first child of non-consanguineous parents. Prenatal history was unremarkable and he was born at 41+4 weeks by operative vaginal delivery with normal anthropometry. Concerns began at 9 months of life, when he developed focal epileptic spasms, which are currently daily and drug-resistant. He pronounced his first words at 12 months but he showed slow progression (currently pronouncing about five full words); he achieved motor milestones within normal age range but has gross motor impairment. Brain MRI showed a gliotic-malacic area in the left semioval centre and a developmental venous anomaly in the right temporo-parietal region. Nodular heterotopia and focal cortical dysplasia were suspected. At the last evaluation, growth parameters were normal and he showed mild dysmorphic features. CGH-array was unremarkable. NGS epilepsy panel revealed two novel compound heterozygous variants in the *ZNF526* gene (NM_133444). The frameshift variant c.1120dup (p.Thr374AsnfsTer96) was inherited from the unaffected father. The missense variant c.656A>G, inherited from the unaffected mother, causes a histidine to arginine substitution at amino acid position 219, the last amino acid involved in the fourth zinc-finger domain.
Homozygous loss-of function variants in *ZNF526* were recently described in four patients, showing profound developmental delay, epilepsy, bilateral congenital cataract, severe microcephaly of prenatal onset and simplified gyration at brain MRI. Homozygous missense variants were reported in four consanguineous families with either syndromic or non-syndromic intellectual disability, mostly with few clinical data.
We suggest that our patient's variants are causative of his phenotype and that the combination of a frameshift and a missense variant in the *ZNF526* gene is compatible with a milder presentation of the disease. Functional studies and clinical characterization of additional patients with missense variants in *ZNF526* are needed to prove our hypothesis.

09:45 FURTHER EVIDENCE FOR A SILVER-RUSSELL-LIKE PHENOTYPE CAUSED BY TRUNCATING VARIANTS IN PLAG1

Presenting author: Anita Rauch

Anita Rauch, Olga Bürger, Angela Bahr

Institute of Medical Genetics, University of Zurich, Schlieren-Zurich, Switzerland

Silver-Russell syndrome is one of the well-established causes of intrauterine-onset failure to thrive, typically caused by imprinting defects on chromosome 11. Next to pre- and postnatal growth retardation it is characterized by relative macrocephaly, feeding difficulties, triangular face, micrognathia, limb asymmetry and fifth finger clinodactyly. Clinical overlap is observed with a variety of other genetic defects and recently few cases with dominant truncating PLAG1 variants have been described in a Silver-Russell-like phenotype. We now identified three affected individuals through prenatal trio exome sequencing in a fetus with intrauterine growth retardation. The observed fetal heterozygous truncating PLAG1 variant was also present in the mother as well as in the first child of the family. Both children and the mother were born with length and weight below the 3rd centile and normal head circumference. Nevertheless, the mother's final height was within the normal range (1.57 cm) with a small head circumference (50.5 cm) and a lean stature with small hands and feet and narrow jaw. She had normal psychomotor development and was generally healthy. Growth of the first-born child was following the 3rd centile and there were no medical problems apart from hyperopia. Our findings further support the association between PLAG1 truncating variants and growth retardation.

10:00 GENOTYPE-PHENOTYPE EXPANSION OF BCL11B-RELATED DISORDER AND IDENTIFICATION OF AN EPISIGNATURE: A SERIES OF 25 UNREPORTED INDIVIDUALS

Presenting author: Quentin Sabbagh

Quentin Sabbagh[1], Sadegheh Haghshenas[2], Juliette Piard[3], Chloé Trouvé[3], Jeanne Amiel[4], Tania Attié-Bitach[5], Mouna Barat-Houari[6], Odile Boute[7], Diana S. Brightman[8], Ange-Line Bruel[9], Nicolas Chatron[10], Corinne Collet[11], William Dufour[7], Patrick Edery[12], Vincent Gatinois[6], Evan Gouy[12], Solveig Heide[13], Aakash Joshi[14], Boris Keren[15], Marion Lesieur-Sebellin[4], Jonathan Levy[16], Claire Lozano[17], Stanislas Lyonnet[4], Henri Margot[18], Pauline Marzin[4], Haley McConkey[2], Vincent Michaud[19], Gaël Nicolas[20], Mevyn Nizard[21], Alix Paulet[4], Francesca Peluso[22], Vincent Pernin[23], Laurence Perrin[11], Christophe Philippe[9], Chitra Prasad[24], Marlène Rio[4], Sophie Rondeau[25], Valentin Ruault[1], Debbie Shears[14], Victoria Siu[24], Arthur Sorlin[9], Mylène Tharreau[6], Frédéric Tran Mau-Them[9], Julien Van Gils[18], Alain Verloes[11], Sandra Whalen[13], Marjolaine Willems[1], Kévin Yauy[1], Roberta Zuntini[22], Jennifer Kerkhof[2], Bekim Sadikovic[2], David Geneviève[1*]

1. University Hospital of Montpellier, Department of Clinical Genetics, Centre de Référence « Anomalies du Développement et Syndromes Malformatifs », Inserm UMR1183, ERN-ITHACA, Montpellier, France.
2. London Health Sciences Centre, Molecular Genetics Laboratory, London, Ontario Canada.
3. University Hospital of Besançon, Department of Clinical Genetics, Besançon, France.
4. Necker-Enfants Malades University Hospital, Department of Clinical Genetics, Paris, France.
5. Necker-Enfants Malades University Hospital, Laboratory of Cytogenetics, Embryology and Histology, Paris, France.
6. University Hospital of Montpellier, Department of Molecular Genetics and Cytogenomics, Montpellier, France.
7. University Hospital of Lille, Department of Clinical Genetics, Lille, France.
8. Cincinnati Children's Hospital Medical Center, Department of Human Genetics, Cincinnati, Ohio, United-States of America.
9. University Hospital of Dijon, Laboratory of Molecular Genetics and Cytogenetics, Inserm UMR 1231 GAD, Dijon, France.
10. University Hospital of Lyon, Laboratory of Medical Genetics, AURAGEN Platform, Lyon, France.
11. Robert Debré University Hospital, Department of Clinical Genetics, Paris, France.
12. University Hospital of Lyon, Department of Clinical Genetics, Lyon, France.
13. Pitié-Salpêtrière University Hospital, Department of Clinical Genetics, Paris, France.
14. Churchill Hospital, Department of Clinical Genetics, ERN-ITHACA, Oxford, United Kingdom.
15. Pitié-Salpêtrière University Hospital, Laboratory of Molecular Genetics and Cytogenetics, Paris, France.
16. Robert Debré University Hospital, Laboratory of Cytogenetics, Paris, France.
17. University Hospital of Montpellier, Department of Immunology, Montpellier, France.
18. University Hospital of Bordeaux, Department of Clinical Genetics, Bordeaux, France.
19. University Hospital of Bordeaux, Laboratory of Medical Genetics, Bordeaux, France.
20. University Hospital of Rouen, Department of Clinical Genetics, Rouen, France.
21. Necker-Enfants Malades University Hospital, Department of Pediatric Endocrinology, Paris, France.
22. Santa Maria Nuova Hospital, Department of Clinical Genetics, ERN-ITHACA, Reggio Emilia, Italy.
23. University of Montpellier, Department of Nephrology, Montpellier, France.
24. London Health Sciences Centre, Department of Medical Genetics, London, Ontario, Canada.
25. Necker-Enfants Malades University Hospital, Laboratory of Molecular Genetics, Paris, France.

Email for correspondence: : q-sabbagh@chu-montpellier.fr

Purpose: Rare genetic variants in *BCL11B* are responsible for *BCL11B*-related disorder (*BCL11B*-RD) with main clinical features being syndromic neurodevelopmental delay or intellectual disability associated with facial features and immune impairment. Here, we report 25 novel individuals with *BCL11B*-RD and provide characterization of genome-wide DNA methylation.

Methods: We gathered clinical data from an international collaboration for 25 individuals and compared this series with the literature. We further assessed peripheral blood DNA methylation profiles of individuals with *BCL11B*-RD in comparison to controls and other neurodevelopmental disorders.

Results and Discussion: We describe rarely documented features including Rubinstein-Taybi-like facial features, craniosynostosis, autoimmune disorders, anxiety disorder and sleep disturbance in *BCL11B*-RD. We further report 12 novel molecular variations responsible for *BCL11B*-RD. Finally, we identify a *BCL11B*-RD DNA methylation signature that could represent a new diagnostic tool of *BCL11B*-RD and assist in reclassifying variants of uncertain significance.

NETWORKS

1. Groupe Déficience Intellectuelle France - Anomalies du Développement et Déficience Intellectuelle de Cause Rare (filière AnDDI-Rares).

2. European Reference Network (ERN) - Intellectual Disability and Congenital Malformation (ITHACA).

STUDY IDs

Institutional Review Board : IRM-MTP-2020_09_202000584
ClinicalTrials.gov : NCT04541927

10:15 INDEPENDENT CONFIRMATION OF A CLINICALLY RECOGNIZABLE MULTISYSTEM SYNDROME DUE TO A RECURRENT DE NOVO NSD2 GAIN-OF-FUNCTION VARIANT

Presenting author : Alessandro Spinelli

Alessandro M. SPINELLI [1#], Carla PITTINI [2], Fernanda FORTUNATO [3], Dora FABBRO [4]

1: Regional Coordinating Center for Rare Diseases, Udine, Italy (MetabERN HCP)
2: NICU, University Hospital, Udine, Italy
3: Unit of Medical Genetics, University Hospital, Ferrara, Italy (ERN ITHACA HCP)
4: Institute of Medical Genetics, University Hospital, Udine, Italy

Email for correspondence: alessandromspinelli@gmail.com

Case report: a 2½-year-old girl, the second child of healthy unrelated parents of Southern and Northern European origin, first came to our attention for a very peculiar facial appearance since birth, marked prominence of nearly all fingertip pads of hands and feet, neurodevelopmental disorder, echocardiographic anomalies, high-grade myopia, and a history of multiple perinatal anthropometric values around +2 SD.
Occurrence was apparently sporadic. Prenatal history: increased nuchal translucency, 'negative' NIPT, pregnancy-related IGT kept under optimal control with diet alone, advanced paternal age. The baby was born early-term by spontaneous delivery; additional support in the delivery room was limited to vigorous tactile stimulation. On day 5, before discharge from hospital, the newborn experienced a short and self-limited episode of mild respiratory distress. A number of clinical findings were observed over time: mild-to-moderate global developmental delay with steady progress in acquired milestones, mild but persistent central hypotonia, childhood-onset generalized epilepsy, friendly demeanor; persistent patency of the ductus arteriosus and persistence of the Eustachian valve at 2½ years, fenestrated atrial septal aneurysm (complete spontaneous closure of the PFO occurred between 1 and 2½ years), left ventricular hypertrabeculation (seen only in the earlier scans); myopia (−8.5 to −12 dioptres) and intermittent esotropia; body weight and length and kidney length in the neonatal period and placental weight all at the upper limit of normal; pointed or globular fingertip pads, telecanthus, wide nasal bridge, prominent eyelashes, short palpebral fissures, lateral prominence of the supraorbital ridges, slightly anteverted nares, deep and slightly short philtrum, high palate, diastema of maxillary central incisors, U-shaped upper lip with thin vermilion border, everted lower lip with midline groove, full cheeks, bitemporal narrowing and apparently increased bizygomatic width, (borderline) dolichocephaly, underdeveloped-to-absent superior crus of the antihelix.
Trio-WES analysis revealed a *de novo* germline heterozygous ultra-rare missense *NSD2* variant, recently proposed to be causative of a novel syndromic disorder in two unrelated Caucasian boys (*Clin Genet. 2023 Feb;103(2):226-230*). Comparison of clinical features across the three cases showed a highly consistent pattern.
Conclusion: a single recurrent p.(Glu1099Lys) gain-of-function variant in *NSD2* is associated with a multisystem syndrome characterized by stereotypical craniofacial gestalt, NDD, cardiovascular/ocular/digital anomalies, and signs of (generalized) overgrowth in the late pregnancy and early life. Potential areas of future development are viability and effects of alternative germline or early postzygotic GoF variants in *NSD2*, cancer incidence / need for tailored surveillance, identifiability of syndrome-specific episignature(s), and therapeutic role of targeted inhibitors.

P1 A novel heterozygous variant in the *BIRC6* gene identified in a patient with early onset cerebellar ataxia

Presenting author : Piret Mertsina

Piret Mertsina[1,2], Kaisa Teele Oja[1,2], Katrin Gross-Paju[3], Sander Pajusalu[1,2], Katrin Õunap[1,2]

[1] Genetics and Personalized Medicine Clinic, Tartu University Hospital, Tartu, Estonia
[2] Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia
[3] West Tallinn Central Hospital, Neurology Centre, Tallinn, Estonia

Background:

Early onset cerebellar ataxia with retained reflexes (EOCARR) is characterised by the progressive cerebellar ataxia, brisk tendon reflexes, and sometimes profound sensory loss.

The genetic aetiology of EOCARR is very heterogeneous, and the most common genetic causes are SCA defects and Friedrich's ataxia. The *BIRC6* gene encodes a protein with a BIR (baculoviral inhibition of apoptosis protein repeat) domain and an UBCc (ubiquitin- conjugating enzyme E2, catalytic) domain (Bello et al., 2022). Here we present a case of a 26-year old female with EOCARR who carries a rare novel variant in the *BIRC6* gene.

Clinical description:

The patient's first symptom was balance disorder, which appeared at the age of 19. A MRT was performed at the age of 24, cerebellar atrophy was reported, and spinocerebellar ataxia was diagnosed. The patient has progressive dystonia, sensitivity disorder in hands (tingling/ numbness), dysarthric speech (difficulty to start conversation) and slight impairment of cognitive function. Normal trinucleotide repeat analyses results of *SCA1, SCA2, SCA3, CACNAIA* and *FXN* genes excluded the most common causes of EOCARR. Duo exome sequencing (ES) analysis did not show abnormal findings in the clinical setting (the father is deceased).

Methods:

Patient recruited into research project PRG471. Informed consent obtained for performing duo ES reanalysis, RNA sequencing and untargeted metabolomics analysis.

Duo ES data reanalysis was performed using program Seqr (Pais et al., 2022) – an open-source platform developed by Broad Institute Centre for Mendelian Genomics and implemented in Tartu University Hospital. An identified variant was validated by Sanger sequencing.

Results:

A rare missense variant c.8927C>G (p.Ser2976Trp) was detected in *BIRC6* gene (GRCh37/hg19, 2:32725072 C>G). This variant is absent in gnomAD database, and Cadd score is 23. The variant is located in a conserved region of *BIRC6* gene. RNA sequencing analysis using the OUTRIDER tool (Brechtmann et al., 2018) showed low expression levels for *ZNF160, RNPEP* and *TBC1D15* genes. No loss of function variants was detected in these genes. Metabolomics analysis in progress.

Discussion:

BIRC6 protein inhibits apoptosis by facilitating the degradation of apoptotic proteins by ubiquitination. Its tight regulation of apoptosis is essential for metazoan development and prevents diseases such as cancer and neurodegeneration. BIRC6 is highly expressed in brain, testis, lymphatic cells and secretory organs (Hauser et al., 1998), one of highest expression is in cerebellum and cerebellar hemispheres. No disease associations are available in OMIM database. Therefore, we assume this novel variant in *BIRC6* gene is a good candidate for the patient's neurodegenerative disorder.

Funding: Estonian Research Council grant PRG471

P3 FIRST CAUCASIAN PATIENT WITH *IQSEC1* MUTATIONS PRESENTING WITH SYNDROMIC INTELLECTUAL DISABILITY

Presenting author: Eliana Zacchi

Eliana ZACCHI[1,2], Tommaso PIPPUCCI[3], Federica ISIDORI[1], Enrico AMBROSINI[1], Emanuela SCARANO[4], Duccio Maria CORDELLI[5], Luca SOLIANI[5], Marco SERI[6], Giulia SEVERI[1]

1: *U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
2 : Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum Università di Bologna, Bologna, Italy
3: *S.S. Genomica Computazionale, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
4: *S.S.U.O. Malattie Rare Congenito-Malformative, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*
5 : U.O.C. di Neuropsichiatria dell'Età Pediatrica, Bologna, IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy
6: *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*

Email for correspondence: eliana.zacchi@studio.unibo.it

IQSEC1 encodes for an ADP ribosylation factor-guanine nucleotide exchange factor, which is expressed in the postsynaptic density of excitatory synapses in the brain. Its signaling pathway is involved in the regulation of cell membrane trafficking and actin cytoskeleton remodeling, and seems to be crucial for the development of dendritic spines.

Homozygous mutations have recently been associated with a neurological phenotype consisting of psychomotor developmental delay, hypotonia, intellectual disability, absent or impaired speech, behavioral problems. To date, only two consanguineous families have been described in the literature. Short stature, nonspecific facial dysmorphisms, epilepsy and vision defects were also reported. No data are available regarding additional clinical issues of these patients.

By performing trio exome sequencing, we detected two compound heterozygous variants in *IQSEC1* in a 3-year-old boy, only child of nonconsanguineous Italian healthy parents: the maternal p.Arg429Gln variant was previously reported as homozygous in four children of a consanguineous family presenting with global developmental delay, intellectual disability and severe, early onset drug resistant epilepsy, without MRI scan abnormality. The paternal p.Gly71Asp variant was never reported in clinical databases (MAF=0,0000875).

He presented with global developmental delay, behavioural problems, facial dysmorphisms and cryptorchidism. At our last evaluation at the age of 7, his stature was at the 10th centile and weight was over 97th percentile. He could speak few words and had a friendly behavior. He recently presented with a single epileptic seizure, while previous EEG controls and cerebral MRI had not detected any abnormalities.

The phenotype of this patient permits to link *IQSEC1* mutations to a syndromic autosomal recessive genetic condition, with not only a neurological involvement but with a complex systemic phenotype.

P4 A NOVEL INSIGHT INTO THE PHENOTYPIC SPECTRUM OF *ZMYND11*-RELATED DISORDER

Presenting author: Gianluca Contrò

Contrò Gianluca [1], Caraffi Stefano Giuseppe[1], Radio Francesca Clementina [2], Coccia Emanuele[1], Passarelli Chiara[3], Orlando Valeria[3], Emanuele Agolini[3], Sartori Chiara[4], Zuntini Roberta[1], Frattini Daniele[5], Fusco Carlo[5], Novelli Antonio [3], Tartaglia Marco [2], Garavelli Livia [1]

1: Medical Genetics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy. 2: Molecular Genetics and Functional Genomics, Bambino Gesù Children's Hospital, IRCCS, 00146 Rome, Italy. 3: Translational Cytogenomics Research Unit, Laboratory of Medical Genetics, Bambino Gesù Children's Hospital, IRCCS, 00146 Rome, Italy 4: Pediatrics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, 5: Department of Pediatrics, Child Neurology Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy.

Email for correspondence: contro.gianluca@gmail.com

The *ZMYND11* gene has been identified as the critical gene for 10p15.3 deletion syndrome, a condition with peculiar phenotypic features and intellectual disability. To date, 59 patients have been reported, but the phenotypic spectrum is still under definition due to the wide phenotypic heterogeneity. All patients reported show speech delay, mild to moderate ID associated with behavioral issuess, including hyperactivity, impulsivity and aggressive behavior. Facial phenotype is characterized by thick eyebrows, depressed nasal bridge with bulbous tip, thin upper lip. Brachydactyly and irregular palmar creases are other common features. Epilepsy and hypotonia have been observed as well.

Here we describe two patients carrying a *de novo* variant in the *ZMYND11.* Patient 1 shows redundant skin on the neck, low-set ears with thick helix, depressed nasal bridge, microretrognathia, fetal finger-pads and deep palmar creases. Neuro-psychological evaluation described a delayed psychomotor development and hypotonia. Furthermore, ophthalmological evaluation performed at 3 years described a hypermetropic astigmatism and left eye exotropia. Genetic tests were carried out in order to identify a possible alteration: Karyotype and array-CGH resulted normal; WES identified a *de novo*, heterozygous variant c.1799G>T (p.Arg600Leu) in *ZMYND11* (NM_006624.5).

Patient 2 was referred to our service because of his clinical picture characterized by neurodevelopmental delay, premature puberty and subclinical hypothyroidism. Physical examination revealed a prominent broad forehead with low anterior hairline, broad thick eyebrows, short nose with bulbous tip and thin upper lip. Apparently, bilateral shortening of the fifth finger with fetal finger pads and irregular deep palmar creases were detected on the hands. Left hand x-ray, performed due to the precocious puberty, showed an advanced bone age (corresponding to 17 years at the chronological age of 12 years and 10 months) associated to thin 4^{th} metacarpal, anomalies of the 4^{th}-5^{th} metacarpal bones and proximally placed pisiform bone. Fragile X and array-CGH tests were normal; WES identified a c.1588_1591del, with creation of a stop codon (p.Gln530Ter). Biological parents were unavailable, so we were not able to determine the inheritance pattern.

Our report adds some hitherto unreported features and expands the knowledge of the phenotypic spectrum, highlighting some clinical signs that are useful as a diagnostic tool for suspecting and diagnosing this condition. Finally, we are planning a call for patients to further clarify other clinical and diagnostic aspects of the disease.

P5 DIPROSOPUS: A RARE CASE OF CRANIOFACIAL DUPLICATION

Presenting author: Viola Trevisani

Viola Trevisani[1,2], Eleonora Balestri[3], Manuela Napoli[4], Anna Colonna[5], Lorenzo Iughetti[1], Giancarlo Gargano[3], Andrea Superti-Furga[6], Livia Garavelli[2]

1: Post-graduate School of Pediatrics, Department of Medical and Surgical Sciences of the Mother, Children and Adults, University of Modena and Reggio Emilia, Italy
2: Medical Genetics Unit, Department of Mother and Child, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy
3: Neonatal Intensive Care Unit, Department of Mother and Child, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy
4: Neuroradiology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Italy.
5: Department of Biomedical Technologies, School of Dentistry, University of Siena, 53100 Siena, Italy
6: Division of Genetic Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Email for correspondence: viola.tervisani@gmail.com

Introduction: The name "craniofacial duplication" describes a wide number of anomalies, ranging from less severe forms of embryo clefting of the face to diprosopus. In 1990, Gorlin et al. highlighted 4 types of cranio-facial duplications: 1) single mouth with duplication of the maxillary arch; 2) supernumerary mouth laterally placed with rudimentary segments; 3) single mouth with replication of the mandibular segments; 4) true facial duplication, namely diprosopus.

Case description: A female newborn was born at 38th week of gestation by assisted vacuum delivery in an Ethiopian hospital. At birth the adaptation to neonatal life was good, Apgar score 4-7. The parents are non-consanguineous, they have an older and healthy son. During the pregnancy, the mother did not take any drugs or "traditional medication". The pregnancy was apparently physiological. At birth, her weight was 2,800 g (18^{th} centile), length 48 cm (27^{th} centile) and head circumference 35 cm (84^{th} centile). She presented widely spaced eyes, flat nose without tip, widely spaced nostrils, two oral cavities, two palates, two tongues and a median protuberance with two pits between the two mouths (picture 1 and 2); objective examinations were, otherwise, normal as well as the female external genitalia. The following tests were carried out: brain ultrasound (figure 1), skull x-ray (figure 2), and head and neck CT scan (figure 3). They revealed a duplication of maxillary and mandible bones, agenesis of the corpus callosum, small midline lipoma, small posterior fossa with Chiari I malformation.

We were evaluating the execution of a brain MRI and surgical procedures before the sudden death owing to a respiratory complication at 1 month.

Discussion: Diprosopus, or diprosopia, is a rare congenital disorder in which the fetus is born with two faces. Usually the patient with this condition has duplicate facial features (4 eyes, 2 noses, 2 mouths and only one brain). The etiology remains unknown but the pathogenesis seems to be related to an incorrect formation of the facial bones. The incidence of this malformation is <1/1.000.000, and the rate in sex is M:F=1:1.4.

The medical literature reports almost 30 cases: all cases present facial malformation, and in 96% of cases central nervous system is affected, anencephaly is certainly the most common and severe anomaly of CNS. Other associated anomalies are cardiac malformations (86%), oral/cleft palate (63%), diaphragmatic hernia (13%), and DSD (13%); other clinical features are virtually anecdotal. Karyotype was performed in only 8 of the cases described in the literature (normal), and further investigations were not performed.

In conclusion, diprosopus is a rare congenital malformation and it is usually associated to cerebral anomalies. The embryonic development of the head involves a highly complex and delicate process guided by a large array of genetic components; it could be interesting studying this condition form this point of view.

Picture 1. Baby at birth: widely-spaced eyes, flat nose without tip, widely-spaced nostrils, two oral cavities, two palates, two tongues and a median protuberance with two pits between the two mouths

Picture 2. Baby at birth

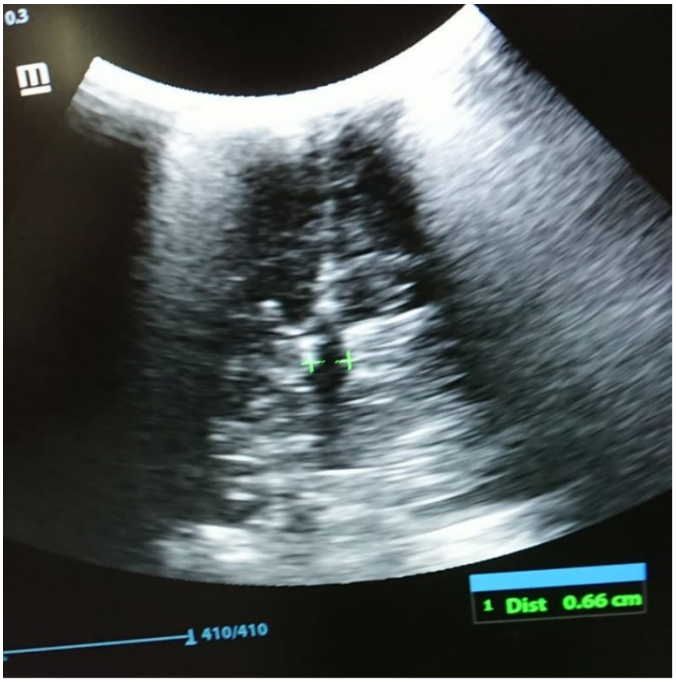


Figure 1. Brain ultrasound: Enlargement of the third ventricle; corpus callosum not detectable.

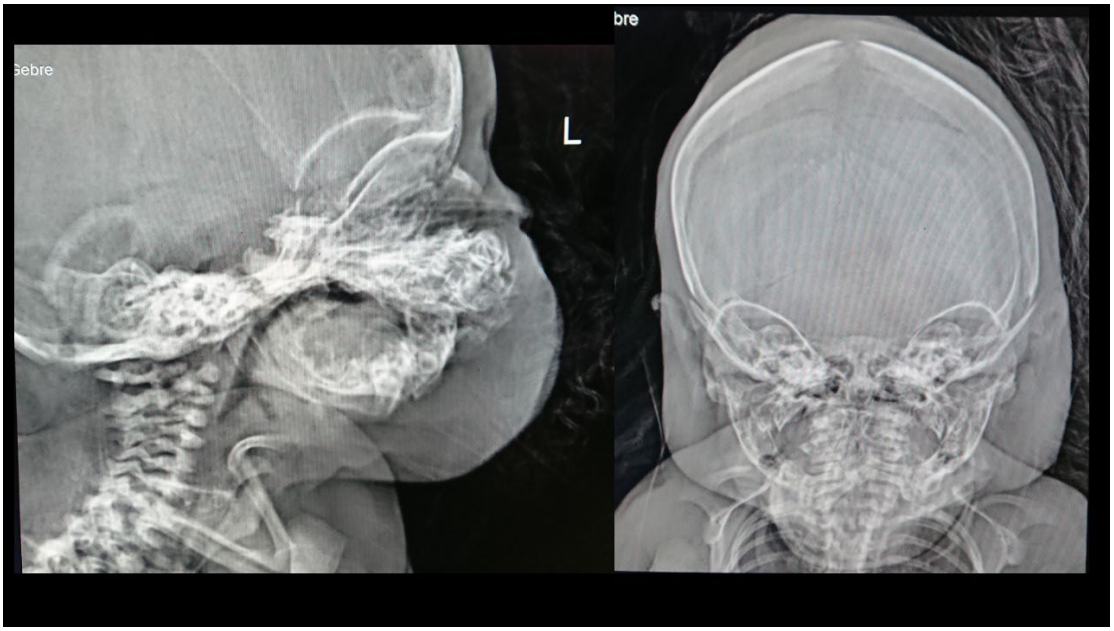


Figure 2. Skull x-ray: disorganization of the maxillary and mandible bones.

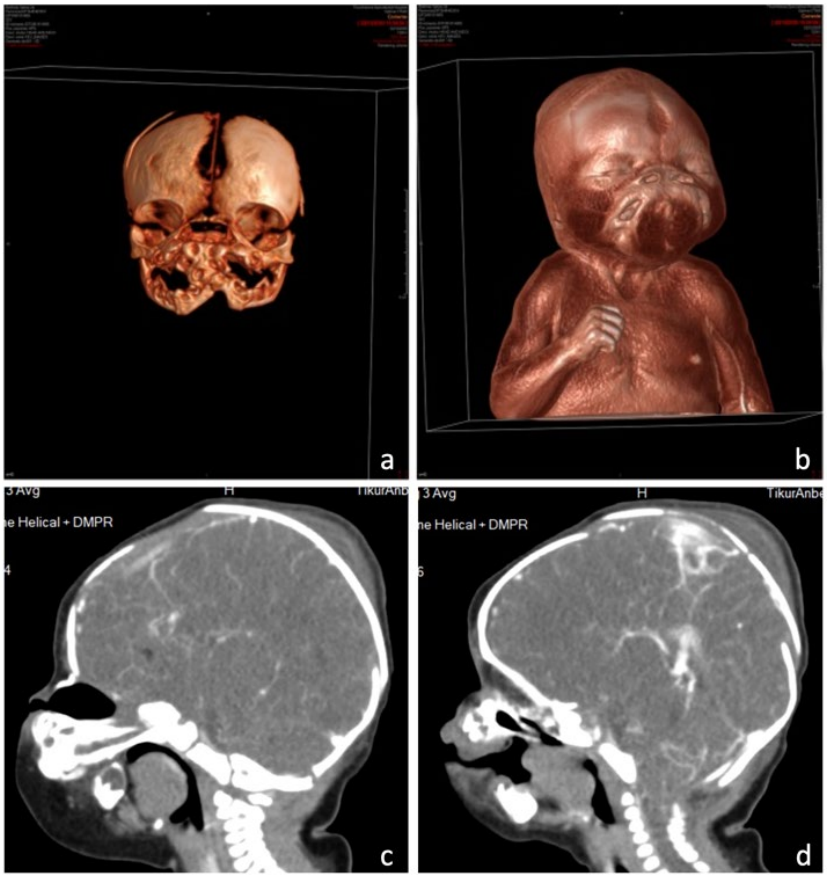


Figure 3. CT scan. VR (a-b) Duplication of the mandible and, partially, of the maxilla, double opening of the oral cavity.

(c-d) CT sagittal MPR. Agenesis of the corpus callosum (d) with a small midline anterior lipoma (c, black allow). Small Posterior fossa with cerebellar tonsillar ectopia, with extension of the tonsils below the level of the foramen magnum (d)

P6 A FAMILY CASE OF GREIG CEPHALOPOLYSYNDACTYLY

Presenting author: Joanna Karwowska

Karwowska JOANNA[1], Posmyk RENATA[1]

1: Medical University of Bialystok, Bialystok, Poland

Email for correspondence: joannbekier@gmail.com

Greig cephalopolysyndactyly syndrome (GCPS; OMIM #175700) is a rare genetic disorder caused by mutations in *GLI3* gene (*locus geni 7p14.1)* inherited in autosomal dominant manner. It is characterized by polysyndactyly, craniofacial abnormalities and autistic symptoms with usually normal or mildly affected intelligence.

We present a 6-year-old boy who was referred to genetic counselling unit at the age of 19 months due to dysmorphic features and delayed development. He was born from uncomplicated pregnancy and delivery, with length and occiput circumference above 97th percentile, hypotonia, umbilical hernia and dysmorphism: prominent forehead, hypertelorism, low-set ears, broad thumbs and toes, bilateral feet polydactyly. MRI revealed defects of corpus callosum.

Currently his psychomotor development remains delayed with intellectual disabillity – the boy is not able to speak or control his physiological needs and presents autistic features. Head circumference still persists over 97th percentile.

Genetic testing revealed a novel *GLI3* variant c.2749_2769del also detected in his mother who presents similar dysmorphic symptoms (macrocephaly, prominent forehead, polysyndactyly, broad thumbs and toes) but her intelligence is within the norm.

The family is an evidence of Greig caphalopolysndactyly variable expression among relatives. It is considered that point mutation in *GLI3* gene connects with normal or mildly affected intelligence but large deletions (especially more than 1 Mbp) may be associated with more severe phenotype. Our patient with small deletion suffers from profound psychomotor and mental development delay paralelly with autistic features.

P7 CEREBELLAR MALFORMATION IN SYNGAP1 RELATED SYNDROME: NEW ASSOCIATION OR SERENDIPITY?

Presenting author: Claudia Ciaccio

Claudia CIACCIO[1], Marco MOSCATELLI[2], Enza Maria Valente[3,4], Edoardo Errichiello[3,4], Emanuela PAGLIANO[1], Arianna DE LAURENTIIS[1], Chiara PANTALEONI[1], Stefano D'ARRIGO[1]

1. Department of Pediatric Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
2. Department of Neuroradiology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
3. Department of Molecular Medicine, University of Pavia, Pavia, Italy
4. Molecular Genetics and Cytogenetics Lab-Neurogenetics Research Center, IRCCS Mondino Foundation, Pavia, Italy

Email for correspondence: claudia.ciaccio@istituto-besta.it

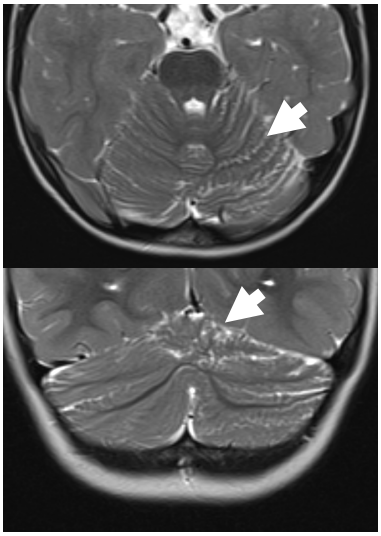
SYNGAP1-related syndrome is a condition characterized by developmental delay/intellectual disability, generalized epilepsy, and behavioral abnormalities up to autism spectrum disorder diagnosis. Additional manifestations include microcephaly, minor facial anomalies, strabismus, gastrointestinal dysfunction, and musculoskeletal disorders. Brain MRI is usually normal, even in those cases with severe ID and drug resistant epilepsy. Either *SYNGAP1* pathogenic variants or deletions of the 6p21.3 region encompassing the gene can cause the disease.

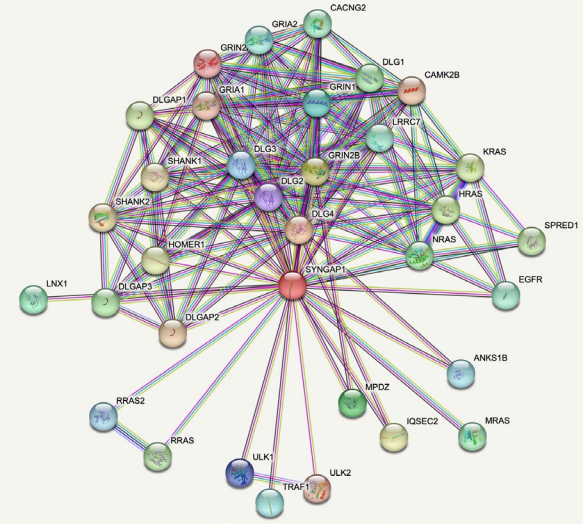
We report the case of a 2-year-old girl referred to our Center for developmental delay and gait instability. Brain MRI revealed a peculiar cerebellar malformation, with irregular foliation of vermis and hemispheres, asymmetric for left predominance (Figure 1). ArrayCGH was performed, with normal result, so that trio-WES study was also started. In the following months, the girl showed a slow improvement of language, social, and motor skills, with a reduction of gait staggering. An EEG revealed a diffuse epileptic paroxysms, configuring a hypsrahythmic pattern, so that an antiepileptc therapy with valproid acid (VPA) was introduced; at the age of 3 she starting experiencing episodes of eyelid myoclonia, resolved after VPA dose adjustment. WES results arrived, demonstrating the presence of the *SYNGAP1*:c.1167_1168del *de novo* variant; the variant determine a frameshift and creation of a STOP codon after 27 triplets (p.Gly391Glnfs*27), and it is classified as pathogenic according to ACMG guidelines.

SYNGAP1-related syndrome is recognized to be a neurodevelopmental disorder where the clinical phenotype does not have a brain MRI counterpart. To date, there is no study on the condition with a particular focus on neuroradiology, but brain MRI is reported to be normal in most patient, except for minor abnormalities, including a single case of cerebellar atrophy. The gene encodes a brain-specific synaptic Ras GTP-ase, localized to dendritic spines in neocortical pyramidal neurons. Looking at its interactions (Figure 2), the gene appears to be linked to several others whose mutation cause neurodevelopmental syndromes.

Patients with MRI finding of cerebellar atrophy have been described in three of such syndromes (caused by CAMK2B, DLG4, and GRIA2 mutations), while in Schimmelpenning-Feuerstein-Mims Syndrome (HRAS/KRAS/NRAS mutations) Dandy Walker Malformation can be present.

Given the strong expression of *SYNGAP1* in brain development and its link with genes whose mutations may cause cerebellar alterations, we can hypothesize a functional cause-effect mechanism for cerebellar hypoplasia in our *SYNGAP1* girl, but further data will be required to confirm a possible link between the gene and cerebellar malformations.





P8 TRISOMY 18 MOSAICISM IN 5-YEAR-OLD GIRL WITH ALOPECIA UNIVERSALIS, ABSENCE OF FINGERPRINTS ON BOTH HANDS AND FEET, BILATERAL RENAL HYPODYSPLASIA, NEUTROPENIA AND MICROBRACHYCEPHALY.

Presenting author: Luigi Monti

Monti Luigi[1,2], Battaglia Paola[1], Magini Pamela[1], Affronte Leonardo[2,4], Barbieri Elena[2,4], Pettenuzzo Ilaria[2,4], Soliani Luca[4], Scarano Emanuela[5], Severi Giulia[1].

1: *U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy.* 2: Alma Mater Studiorum University of Bologna, Italy, Department of Medical and Surgical Sciences, Bologna Italy. 4: U.*O.C. di Neuropsichiatria dell'Età Pediatrica, Bologna, IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy.* 5: *S.S.U.O. Malattie Rare Congenito-Malformative, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*.

Email for correspondence: luigi.monti3@studio.unibo.it

Mosaic trisomy 18 occurs when two different cell lines exist in the same individual; one cell line has two copies of chromosome 18, while the other has three copies. This type of trisomy accounts for approximately 5% of trisomy 18 cases. The phenotype can be extremely variable, from complete trisomy 18 with early death to normal appearing and reproductive adults. Furthermore, there is no apparent correlation beetween the percentage of trisomic cells in either fibroblasts or leukocytes and the individual's phenotype or intellectual findings.

Here we present the case of a 5 years-old Pakistani girl, born from non-consanguineous healthy parents. The prenatal course was complicated by oligohydramnios, prenatal growth deficiency and evidence of renal hypoplasia in the fetus. The infant was born at 34+1 weeks by cesarean section (due to previous cesarean section). Birth weight was 1.750 g, height 41.5 cm, head circumference 28.5 cm (4°pc). In the second minute of life respiratory depression requiring ventilator assistance occurred. Microcephaly, total alopecia and hypotonia were noted at birth. Therefore, some investigations were carried out: a dermatological evaluation, which confirmed the alopecia and identified a skin peeling and multiple Mongolian spots, a physiatric consultation with the finding of bilateral clubfeet and some haematological evaluation with finding of persistent neutropenia. In addition, an abdominal ultrasound confirmed bilateral renal hypoplasia with cortical hyperechogenicity and bilateral cystic formations, and a brain ultrasound revealed mild hyper-echogenicity of the white matter.

At 3 years of age, a brain MRI was performed and showed microcephaly, simplified cerebral gyral pattern, and relative frontal underdevelopment. Physical examination at 5 years confirmed harmonic short stature, low-set ears, alopecia universalis and also revealed poikilodermia of palms and gluteus and absence of fingerprints on either hands. At the neurological evaluation, the patient presented a mild delay in language development and toe walking. Remaining stages of psychomotor development in the normal range. The diagnosis was established at 5 years old by CGH-array that showed an anomaly compatible with mosaic trisomy of chromosome 18, in a fraction of cells estimated at around 40%, according to the formula published by Valli et al. (2011). Cytogenetic analysis of her skin fibroblasts showed a normal female karyotype (the search for mosaicism, performed by FISH analysis on 300 metaphase nuclei, revealed the presence of three hybridization signals corresponding to the pericentromeric region of chromosome 18 in only 2 nuclei), cytogenetic analysis of lymphocytes showed a mosaic female karyotype for the presence of a normal cell line (82%) and a line with trisomy 18 (18%).

The aim of this report is to broaden the knowledge about the clinical phenotype of Edwards syndrome by describing the peculiar phenotypic characteristics of a patient with mosaic trisomy 18 and to present the second case of trisomy 18 associated with alopecia and absence of fingerprints, supporting the possibility that the association may not be coincidental.

P9 DEVELOPMENTAL DELAY AND DYSMORPHIC FEATURES IN A BOY WITH A DE NOVO 5.5 MB DELETION OF 13 Q12.11Q12 INVOLVING ZMYM2

Presenting author: Camilla Sarli

Camilla Sarli[1,2,3], Daniele Vitale[1], Stefano Pagano[1,2,3], Elisa D'Acunto[1,2,3], Achille Iolascon[1,2,3], Michele Pinelli[1,2,3].

1.Department of Molecular Medicine and Medical Biotechnology, Federico II University, Naples - Italy.
2.CEINGE Advanced Biotechnology, Naples - Italy.
3.U.O.C. Medical Genetics, A.O.U. Federico II, Naples - Italy.

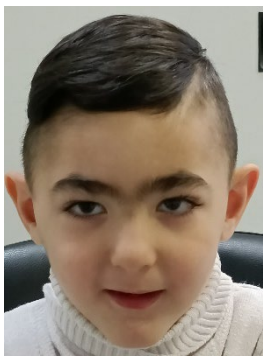
Neurodevelopmental diseases encompass a wide range of conditions that are known to have a significant genetic component. However, achieving a molecular diagnosis for these conditions is challenging due to their complex and often aspecific clinical presentations and the numerous genetic factors involved.

In this report, we present a clinical case of a male child displaying speech delay, gross and fine motor clumsiness, dysmorphic features including triangular face, bilateral epicanthus, synophrys, long eyelashes, depressed nasal root, flat philtrum and thin upper lip. These features gestaltically oriented us toward a Cornelia de Lange (CdL) syndrome, and Face2Gene also supported this suggestion (CdL ranked 2). However, the clinical phenotype lacked the microcephaly, growth restriction and other minor features often described. Therefore, we performed CGH-array at first, which has found a *de novo* 5.5 Mb deletion on the chromosomal region 13q12.11q12. This deletion has not been observed in the DGV controls and partially overlaps with deletions described in a previous case series involving children all with neurodevelopmental anomalies with variable severity and a milder malformative phenotype, except for one case (*Makiko Tominaga et al., 2019*; *Pavone et al., 2013*). At the time of the case series collection the proposed critical gene was *FGF9*.

Among the genes in the deleted region, we considered ZMYM2 as the potential critical gene since it is associated with a high haploinsufficiency score (pHaplo = 0.93 according to *Collins et al., 2022*) and has recently been discovered as causative of *Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities* (*Connaughton et al., 2020*). Still, our patient does not exhibit the kidney or heart malformations described in those patients. Similarly, we found in Decipher other cases with deletions involving ZMYM2 who were reported with neurodevelopmental anomalies and recognizable facial appearances, but not kidney or heart malformations. Using gene-matching we additionally found other patients with mutations in ZMYM2 displaying neurodevelopmental anomalies and facial dysmorphisms.

ZMYM2 (Zinc Finger MYM-Type Containing 2) is part of a chromatin-associated complex involved in transcriptional regulation. It is a component of the LSD1-CoREST complex and mutations of other components of this complex, such as KDM1A and HDAC1, are linked to neurodevelopmental disorders.

Therefore, we believe that the 13q12.11q12 variant caused the neurodevelopmental anomaly in our patient and that the critical effect is mainly due to haploinsufficiency of ZMYM2 gene. Currently, we are participating in a case series collection involving individuals with point mutations or deletions in ZMYM2 to further characterize the clinical spectrum of these patients.



P10 RADICULOMEGALY AS A KEY CLINICAL FEATURE IN OCULO-CARDIO-FACIO-DENTAL SYNDROME: A CASE REPORT

Presenting author: Clément Sauvestre

Clément SAUVESTRE[1], Marie-José BOILEAU[2], Didier GRIFFITHS[1], Nicolas CHASSAING[3], Caroline ROORYCK[1,4]

1. *CHU Bordeaux, Service de Génétique Médicale, F-33000 Bordeaux, France*
2. *Univ. de Bordeaux, UFR des Sciences Odontologiques, Centre de Compétence des Maladies Rares Orales et Dentaires, CCMR O-Rares, C.H.U Bordeaux, France*
3. *Service de Génétique Médicale, Hôpital Purpan CHU Toulouse, Toulouse, France; Centre de Référence des Affections Rares en Génétique Ophtalmologique CARGO, Site Constitutif, CHU Toulouse, Toulouse, France.*
4. *Univ. Bordeaux, Maladies Rares : Génétique et Métabolisme (MRGM), INSERM U1211, F-33000 Bordeaux, France*

Email for correspondence: clement.sauvestre@chu-bordeaux.fr

Radiculomegaly is a rare dental anomaly characterized by the enlargement of the root canals of teeth. It is usually associated with Oculo-Cardio-Facio-Dental syndrome (OCFD) due to truncating variants in BCOR (MIM*300485).

We present the case of a 21-year-old female patient who was referred to genetics for a polymalformative syndrome including bilateral glaucoma and dental anomalies especially radiculomegaly. Some others dysmorphic features were right superior lip notch, ogival palate, long philtrum, difficulty in pronation, café-au-lait spots, II-III toe bilateral syndactyly and macrocephaly. Cone-beam computed tomography confirmed radiculomegaly. Targeted genetic of *BCOR* analysis identified a heterozygous pathogenic variant c.2093del (p.Pro698Glnfs*17). We review all published radiculomegaly cases and discuss the nature of non-syndromic radiculomegaly cases.

This case report highlights the importance of radiculomegaly as a clinical sign of OCFD syndrome and emphasizes the rarity of non-syndromic radiculomegaly.

P11 A LARGE DE NOVO 11Q13.2 DELETION INCLUDING *KMT5B* IN A BOY WITH INTELLECTUAL DISABILITY, EPILEPSY, MRI ANOMALIES AND DISTINCTIVE PHENOTYPE: LOOKING BACK TO GO FORWARD

Presenting author: Francesca Peluso

Francesca PELUSO[1], Irene AMBROSETTI[2,3], Carlotta SPAGNOLI[4], Stefano Giuseppe CARAFFI[1], Carlo Fusco[4], Livia Garavelli[1]

1 *Clinical Genetics Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy.*
2. *U.O.C. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy*
3. Postgraduate School of Medical Genetics, Alma Mater Studiorum-University of Bologna, Bologna, Italy.
4. Child Neurology and Psychiatry Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy.

Email for correspondence: francesca.peluso@ausl.re.it

The boy is the first child of non-consanguineous parents, with an unremarkable family history. Antenatal ultrasound and brain MRI reported borderline ventriculomegaly, and the karyotype was normal male. Eutocic delivery or birth and normal neonatal auxological parameters were reported. He was immediately admitted to the neonatal care unit for poor suction, feeding difficulties, mild hypotonia, transient high transaminase and CPK.

The boy presented with global developmental delay, moderate intellectual disability, severe language delay with nasal speech, dyspraxia, generalized hypotonia, focal seizures with good drug response, autism, and delayed puberty. He underwent surgical correction for bilateral cryptorchidism and inguinal hernia. He also presented severe drooling, gastro-oesophageal reflux, previous eosinophilic oesophagitis, multiple hypersensitivities and atopic eczema.

MRI performed at 15 years showed hyperintensity in the periventricular white matter, ventriculomegaly, thinned corpus callosum and arachnoid diverticulum with partially empty sella. At 16 years old, his height was at 10th centile, weight at first centile, head circumference at 42nd centile. He presented with triangular face, prognatism, micrognathia, downslanting palpebral fissures, narrow mouth, small, low-set and protruding ears, long hands and 2nd-3rd right foot cutaneous syndactyly. In 2012 he performed array-CGH that revealed a 2.2 Mb de novo deletion in 11q13.2. There was no clear genotype-phenotype correlation at the time, but a new gene emerged at a recent re-evaluation, *KMT5B*, which encodes for the lysine methyltransferase 5B. *KMT5B* was recently associated with an autosomal dominant neurodevelopmental disorder with ID, autism, seizures, hypotonia, high stature, gastrointestinal issues, congenital heart defects and macrocephaly. Few missense and protein-truncating variants, two partial deletion and two small deletions encompassing *KMT5B* have been described. The limited number of patients does not allow to define an accurate genotype-phenotype correlation. Our patient is the only case with an extensive deletion encompassing multiple genes in addition to *KMT5B*. He presented distinctive face, longilinear habitus with hypotrophy and muscle mass deficit (also observed in *Kmt5b* KO mice models) and delay of puberty never previously described. It cannot be ruled out that the other genes in the deleted region may also have influenced his clinical phenotype, although further studies would be needed to determine their influence precisely.

P12 EXPANDING THE PHENOTYPIC SPECTRUM OF INTELLECTUAL DEVELOPMENTAL DISORDER-70

Presenting author: Sinem Kocagil

Sinem KOCAGİL[1], Ali Rıza KEKLİKCİ[1], Sabri AYNACI[1], Ezgi SUSAM[1]

1.Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Genetics Eskisehir / TURKEY

Introduction: Intellectual developmental disorder-70 (MRT70, OMIM#618402), a very rare phenotype with an unknown prevalance, is caused by biallelic loss-of-function variants of *RSRC1*. *RSRC1* gene encodes a Serine and arginine-rich(SR)-related protein, localized to the nuclear speckled domain. SR proteins are evolutionarily conserved co-regulators of constitutive and alternative pre-mRNA splicing. RSRC1 plays a relevant role in the second step of pre-mRNA splicing. Furthermore, it may participate in post-splicing mRNA processing and function as a transcriptional regulator.
Case report: Here, we report a 17-year-old female patient referred to our outpatient clinics for intellectual disability and dysmorphism. Her parents were 1st degree cousins. She was born at the 38th week of gestation with a birth weight of 2600 gr. She had a febrile seizure at 4 months old and has recurrent epileptic seizures since then. Her neuromotor development was delayed. She could sit unsupported at 2 years old, and walk independently at 4 years old. She could talk with few words around 3 years of age. She had physical therapy for 6 years. She had special education but never learned to read/write. She generally had a friendly nature but occasionally had tantrums. Her cranial MRI was normal. In her physical examination; her height, weight and head circumference were normal. She had mild hypotelorism, straight eyebrows, a short filtrum, small hands and feet, and bilateral flexion contractures at the elbows. Karyotype analysis was normal and at microarray analysis, there was no likely pathogenic/pathogenic variants detected. Whole-exome sequencing

revealed homozygous likely pathogenic RSRC1(NM_001271838.2):c.109C>T variant at the patient and the segregation analysis done by Sanger sequencing showed the healthy parents as carriers.
Conclusion: MRT70 is primarily characterized by variable degrees of intellectual disability. Developmental delay, mild facial dysmorphism, febrile seizures, and behavioral abnormalities have been reported in some patients. To our knowledge, approximately 25 patients have been reported in the literature and distinctive neurological features or facial dysmorphism have not been defined so far. We believe that the presented case (patient we report) will expand our understanding of this rare phenotype, and novel findings such as small hands and feet, and flexion contractures of the elbows will occur as emerging syndromic clinical phenotype.

P14 *FREM1* GENE VARIANT IN A CHILD WITH DYSMORPHIC FEATURES

Presenting author: Sarah Berrada

Sarah Berrada1, Amal Tazzite2, Fatima Maarouf1, Hind Dehbi1,2

1- Medical Genetics Laboratory, Ibn Rochd University Hospital, Casablanca, Morocco
2- Laboratory of Cellular and Molecular Pathology, Faculty of Medicine and Pharmacy, Hassan II University of Casablanca, Morocco
Email for correspondence: sarah.berrada.gen@gmail.com

FREM1 (subunit 1 of the Fraser extracellular matrix complex) variants are associated with a large phenotypic spectrum, including Manitobaoculo-tricho-anal (MOTA) and Bifid Nose with or without Anorectal and Renal Anomalies (BNAR) syndromes.

Here, we report the case of a 6-year-old Moroccan girl from a first-cousin marriage, who presented with neonatal hypotrophy (2 kg) and generalized hypotonia. Physical examination showed a short stature (98 cm), facial dysmorphia including high hair implantation, hypertelorism, bilateral palpebral coloboma and bifid nose. Renal ultrasound showed a right renal agenesis.

The whole exome sequencing showed a homozygous pathogenic variant in *FREM1* gene (NM_144966.5:c.4705C>T(p.Gln1569Ter)).

The FREM1 protein, in association with many other proteins, enables adhesion between the basement membrane and the epidermis during embryogenesis. The substitution from C nucleotide to T nucleotide at position 4705 in *FREM1* gene creates a premature stop codon, leading to a truncated protein with loss of functional domains. In the present case, this variant is responsible for deregulation of embryonic development conferring a phenotype combining features of MOTA and BNAR syndromes.

Key words: *FREM1* gene, dysmorphia, BNAR syndrome, MOTA syndrome.

P15 FRASER SYNDROME WİTHOUT CRYPOOPHTALMOS: A NOVEL VARİANT

Presenting author: Yusuf Bahap

Yusuf Bahap[1] Özge Beyza Gündoğdu Öğütlü[1], Gülsüm Kayhan[1], Ferda Emriye Perçin[1]

[1] Department of Medical Genetics, Medical Faculty, Gazi University, Ankara

Email for correspondence: yusufbahap11@gmail.com

Introduction

Fraser syndrome (FS) is an autosomal recessive syndrome which caused by pathogenic variants in the FRAS/FREM complex genes: *FRAS1, FREM2* and *GRIP1*. FS is characterized by syndactyly, cryptophthalmos, urogenital defects and laryngo-tracheal abnormalities. The diagnostic criteria still in use were designated by Van Haelst et al. According to this study, 6 major (syndactyly, cryptophthalmos spectrum, urogenital tract abnormalities, ambiguous genitalia, laryngeal tracheal anomalies, positive family history) and 5 minor criteria (anorectal defects dysplastic ears, skull ossification defects, umbilical abnormalities, nasal anomalies) was defined. Meeting 3 from 6 major (syndactyly, cryptophthalmos spectrum, urogenital tract abnormalities, ambiguous genitalia, laryngeal tracheal anomalies, positive family history), 2 major and 2 minor criteria, or 1 major and 3 minor criteria were accepted as compatible with FS. This report presents a patient with a homozygous novel variant in *FRAS1* gene which is compatible with Fraser syndrome who was presented without cryptophthalmos which is accepted as the most determining finding of FS.

Material Method:

A patient from nonconsanguineous family was applied to our clinic with surgically repaired syndactyly, renal agenesis, bilateral mixed hearing impairment, lacrimal duct aplasia. Her physical examination revealed some dysmorphic features such hypertelorism, hypodontia, hypoplastic nares, midline nasal cleavage. Clinical Exome Sequencing (CES) analysis was performed using the SOPHiA™ Genetics CESv_2 kit on the Illumina NextSeq 500 platform. Variant filtering and interpretation performed on Sophia DDM™ and classified according to the American College of Medical Genetics 2015 guideline and ACGS 2020 guideline. Population frequency was obtained from the Genome Aggregation Database (GnomAD). The missense variants were assessed using in silico tools, such as Revel, MetaLR, and Gerp.

Results and Conclusion:

The patient's clinical findings met the diagnostic criteria. CES analyses revealed a c.1108-3T>G homozygous variant in *FRAS1* (NM_025074.7) which was not in population databases nor in ClinVar database reported. This variant was interpreted as variant of unknown significance/ likely pathogenic (PM2, PP3, PM3_P, PP4). This result thought to compatible with FS. Since cryptophtalmos is the most defining finding of Fraser syndrome, only two patients with Fraser syndrome was previously reported without cryptophthalmos. This case presents a patient with Fraser syndrome with no cryptophthalmos, and harboring a novel genetic alteration. More patients are needed to be published along with their molecular alterations to develop the genotype-phenotype correlation.

P16 NEW VARIANT IN *TBL1XR1* GENE LINKED TO PIERPONT SYNDROME: CASE REPORT

Presenting author: Sara Pinho

Sara Beatriz PINHO, Juliette DUPONT, Ana Berta SOUSA

Serviço de Genética, Departamento de Pediatria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

Email for correspondence: sara.pinho@chln.min-saude.pt

Pierpont syndrome (OMIM #602342) was first described in 1998 as a rare multiple congenital anomaly syndrome characterized by moderate to severe global developmental delay, bilateral congenital plantar fat pads located anteromedially to the heels, fetal finger and toe pads, and distinctive craniofacial features. The

latter include microcephaly, broad face with high forehead and mild midface hypoplasia, narrow upward slating palpebral fissures, broad nasal bridge and tip, and long and smooth philtrum with bowed upper lip.

In 2016, the molecular basis of Pierpont syndrome was found to be a *de novo* pathogenic variant in *TBL1XR1* gene, with all but 3 patients reported in the literature so far having the same c.1337A>G (p.Tyr446Cys) missense variant. Other variants in *TBL1XR1* gene have also been associated with intellectual developmental disorder autosomal dominant-41 (MRD-41, OMIM #616944) and autism spectrum disorder (ASD), in individuals who did not present the distinctive features of Pierpont syndrome. Up until recently, these differences in phenotype were thought to be caused by distinct mechanisms of pathogenesis. The p.Tyr446Cys variant was located on one of the WD40 rings of TBL1XR1 protein, creating a dominant negative effect, while variants associated with MRD-41 and ASD led to haploinsufficiency. However, as more clinical cases with different *TBL1XR1* gene variants have been documented, it is hypothesized that the phenotypes associated with this gene may lie instead in a continuum.

We present a 10-year-old boy with intellectual disability and the typical dysmorphic Pierpont-like features. By whole exome sequencing, a different heterozygous missense variant in *TBL1XR1* gene from those previously linked to Pierpont syndrome was identified: c.734A>G (p.Tyr245Cys). Segregation analysis was negative in both parents, indicating the variant occurred *de novo*. This variant has already been described in a patient with isolated cognitive impairment and ASD.

With this case report, we hope to raise awareness for the clinical spectrum of *TBL1XR1* gene variants, and to further the current knowledge about genotype-phenotype correlations and disease mechanism.

P17 *SMC1A* MULTIPLE-EXON DELETION IN A PATIENT WITH INTRACTABLE EPILEPSY AND SEVERE DEVELOPMENTAL DELAY

Presenting author: Katalin Sakszon

Katalin Szakszon[1a], Csaba Erdész[1a], Mónika Bessenyei[1a], Zsuzsanna Szűcs[1b], Lászó Madar[1b], Anikó Ujfalusi[1b]

1. University of Debrecen, Faculty of Medicine, Clinical Centre
   a) Institute of Paediatrics
   b) Institute of Laboratory Medicince, Clinical Genetics Centre

Email: szakszon.katalin@med.unideb.hu

Background:
The SMC1A gene (MIM 300040), located at Xp11.22, encodes one of four core subunits that make up the cohesin ring. The cohesin ring plays important roles in cell division, transcription regulation, and DNA repair. *(Horsfield J et al., 2012.)* Missense variants and small in-frame deletions of the *SMC1A* gene are responsible for approximately 5% of Cornelia de Lange Syndrome (CdLS). Protein truncating mutations in *SMC1A* have been extremely rarely reported – such variants affect females and associate with drug-resistant epilepsy and severe developmental impairment *(Symonds JD. et al., 2017)*, without recognizable features of CdLS. *Jansen et al. (2016)* suggested the existence of a novel phenotypic entity - distinct from CdLS - caused by de novo SMC1A loss of function mutations.
We present a female patient with intrauterine growth restriction, multiple congenital malformations including tetralogy of Fallot, severe developmental delay and early-onset, therapy resistant epilepsy (migrating partial seizures) having a de novo multiple-exon deletion in the *SMC1A* gene. Facial features shared overlap with those seen in CHARGE association.
Methods: Array CGH was performed using Affymetrix CytoScan 750K and Chromosome Analysis Suite (ChAS) v2.0 Software (Affymetrix, Thermo Fisher Scientific, Waltham, MA, USA)

Whole Genome Sequencing (WGS) was performed on the DNBSEQ-G400 sequencer system using DNBSEQ-G400RS High-throughput Sequencing Set (FCL PE150) in paired-end mode. The MGIEasy Universal DNA Library Prep kit (MGI Tech Co., Ltd., Shenzhen) was used for library preparation.
Sanger confirmation of the breakpoints detected by genome sequencing was performed using the BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA).
Results:
Microarray analysis identified a pathogenic deletion on Xp11.22 with the following coordinates: arr[GRCh38] Xp11.22(53381985_53385009)x1 including the 3' end of the SMC1A gene (MIM 300040). WGS was performed for identification of deleted exons (exon 21-26) and exact breakpoints (53369380-53391250).
To our knowledge intragenic deletion spanning multiple exons of the *SMC1A* gene has been only reported once in the medical literature. (Hoppman-Chaney et al., 2011.)

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P18 RACHIPAGUS

Presenting author: Ivana Kavecan

Kavecan Ivana[1], Maksimovic Jadranka[2], Obrenovic Milan[3]

[1] Department of Pediatrics, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia; [2] Institute of Epidemiology, Faculty of Medicine. University of Belgrade, Belgrade, Serbia; 3 Service of Medical Genetics, Institute for Children and Youth Health Care of Vojvodina, Novi Sad, Serbia

Emails for correspondence: ivana.kavecan@mf.uns.ac.rs

Conjoined twin with or without associated congenital anomalies occurs sporadically, with estimated incidence 1/1.000.000 live births. Heteropagus is not functional. It is only partially formed parasitic mono zygotic twin, asymmetrical physically attached and completely depends for survival on the viabile dominant and primary living, well-developed twin –autosite. According fused anatomical localization Potter classified the parasitic twins by the site of connection into equal-diplopagus and unequal-heteropagus Conjoined twin joined dorsally in the vertebral column is „parasitic“ rachipagus, Greek rachi-(spine); pagus-(fixed), and is the most rare type of all conjoined twins. Types of conjoined twins depend on anatomical region and could be at inferior, mid and superior conjunction (craniopagus,thoracopagus, omphalopagus, pygopagus, ischiopagus). Conjoined twins are associated with higher incidence of congenital anomalies.

A newborn was reffered to geneticist for the evaluation of its anomalies. It was born with dorsal mass on cervico-thoracal region. On her back she had an accessory partial and hypoplastic upper limbs (arms) (3 fingers – one came-off, hypoplastic ulna, radius, humerus, 2 scapulas) completely covered with skin, that measured approximately 10 cm in diameter, soft in consistency, that showed no movement, sensitive to touch, with spectrum of associated anomalies (Fig. 1). Prenatal and family history were unremarkable. Her karyotype was normal. At the first moment it was thougt that this is the third - extra upper limb as congenital anomaly. Neverthless, further examinations such as three-dimensional Computed Tomography showed specific skeletal anomalies and MRI showed multiple anomalies: meningomielocela, ventriculomegaly, vertebral and ribs deformation and Bochdalek hernia and the diagnosis of heteropagus was established.

The aetiology of parasitic conjoined twins remains uncertain. It has been suggested that the incomplete division of the blastocyst around 2 nd week of gestation results in conjoining. One twin dies and some parts of the body continue to grow and remain attached to the parts of second twin and prevents closure of the neural tube during development and cause anomalies of living twins. Second possible mechanism is that the autosite and parasite originated as 2 dizygotic twins with subsequent early fusion, with partial resorption of parasitic twin. An appropriate clinical and imaging evaluation such as computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI) are necessary to differentiate this anomaly from others and assess further developmental anomalies in all types of conjoined twins. Surgical excision is the definitive treatment if it is possible. Outcome and prognosis depend on the extent of sharing, localization and associated anomalies.

P19 FINDING THE NEEDLE IN THE HAYSTACK: A 7-YEAR DIAGNOSTIC ODYSSEY IN AN ADOPTED CHILD WITH SEVERE DEVELOPMENTAL DELAY REVEALS A NOVEL PATHOGENIC SPLICE VARIANT IN *KDM5C*

Presenting author: Maria Francesca Di Feo

Maria Francesca Di Feo[1,2], Patrizia De Marco[3], Francesca Madia[3], Anna Allegri[4], Mariasavina Severino[5], Ferruccio Romano[3], Federico Zara[3], Francesca Faravelli[1], Valeria Capra[1]

1: Clinical Genetics and Genomics Unit, IRCCS Giannina Gaslini Institute, 16147 Genoa, Italy; 2: Folkhälsan Research Center, Helsinki; 3: Medical Genetics Unit, IRCCS Giannina Gaslini Institute, 16147, Genoa, Italy; 4: Endocrinology Unit, IRCCS Giannina Gaslini Institute; 5: Neuroradiology Unit, IRCCS Giannina Gaslini Institute, 16147, Genoa, Italy

Email for correspondence: maria.francesca.difeo@edu.unige.it

The lysine-specific demethylase 5C protein plays a crucial role in controlling gene transcription, specifically removing methyl groups from dimethylated and trimethylated histone H3 lysine 4 (H3K4). The *KDM5C* gene is located on chromosome X, and several pathogenic variants in its 26 exons have been associated with Claes-Jensen type of X-linked syndromic intellectual developmental disorder (MRXSJ). MRXSJ is relatively rare, but large-cohort studies suggest that it may represent 0.7%–2.8% of all X-linked intellectual disability cases.
J.C. first came to our attention at the age of 4. He had severe developmental delay, axial hypotonia, distal hypertonia, and epileptic encephalopathy, with the MRI showing thinning of the corpus callosum and mildly dilatated ventricles and subarachnoid spaces. He showed 11 pairs of ribs bilaterally, a slightly excavated chest, areas of alopecia in the occipital region, microcephaly, strabismus, and facial dysmorphisms. He also suffered from congenital hypothyroidism. Array-CGH 180K was carried out and found a 2.53 Mb deletion in Yp11.2; fragile X was negative. In the years that followed, NGS panels for Angelman, Rett, and Kabuki syndrome were carried out and turned out to be negative. Sequencing of *FOXP2* gene gave negative results as well. In other centers, methylation tests for Prader-Willi syndrome and sequencing of *GNS* gene were carried out, with negative results. Another pediatric unit suggested fetal alcohol syndrome as the final diagnosis.
In 2022, the patient returned to our center, showing a slight improvement in relationships, eye contact, and understanding of commands. We opted for a singleton exome, which turned out with no pathogenic variants but 6 variants of unknown significance in different genes*: SETD1A*, *ANKRD11*, *SCN1A*, *DSPP*, *KAT6A*, and *KDM5C*. All the variants were revised by the clinical genetics team and ACMG criteria were carefully checked. We found that variant *KDM5C*(ENST00000375401.8): c.3121-8G>A is a splice variant with an acceptor loss delta score of 0.95, and an acceptor gain delta score of 0.99, according to SpliceAI, thus suggesting pathogenicity. Also, CADD, Polyphen, and other predictive tools suggested a pathogenic effect on splicing. A clinical re-evaluation confirmed that the phenotype was in fact perfectly fitting. Thus, we carried out a cDNA analysis and a quantitative transcript analysis, finding that the variant causes a splice defect that leads to an almost complete absence of the transcript, probably due to mRNA nonsense-mediated decay.

We believe that diagnosing patients with MRXSJ is not only important to name the disease and give a risk of recurrence to parents, but also to create prospective cohorts in view of promising research projects. Recent studies suggested that FDA-approved SAHA (histone deacetylase inhibitor suberoylanilide hydroxamic acid) may rescue KDM5C depletion in murine neurons. Further efforts are needed to explore these potential therapeutic strategies.

P20 A TURKISH FEMALE PATIENT WITH ALAZAMI SYNDROME

Presenting author: Elvin Kazancioglu

Elvin Kazancioglu[1], Ozge Beyza Gundogdu Ogutlu[2], Gulsum Kayhan[2], E. Ferda Percin[2]

[1] Adıyaman University Education and Research Hospital, Department of Medical Genetics, Adıyaman, Turkey
[2]Gazi University, Faculty of Medicine, Department of Medical Genetics, Ankara, Turkey

Email for correspondence: kazanciogluelvin@gmail.com

Introduction: Alazami syndrome (AS), caused by biallelic pathogenic variants in *LARP7*, is characterized by primordial dwarfism, severely impaired intellectual development (ID), and distinctive facial features. Since it was first described in 2012 in a large consanguineous Arab family, 24 patients have been reported in the literature. Here, we present a 16-year-old Turkish female with short stature, failure to thrive, and developmental delay. Whole exome sequencing (WES) identified homozygous pathogenic variants in *LARP7* (NM_016648.4): c.647-2_649del, indicating a diagnosis of AS. This mutation has not been reported in the literature as homozygous and in a Turkish family.

Patient findings and methods: Patient findings and methods: A 16-year-old female patient whose parents were consanguineous to the 3rd degree was evaluated because of neurodevelopmental delay. Detailed genetic investigation revealed a history of IUGR and premature delivery. Her weight was 19.5 kg (-9.65 SDS), height was 127 cm (-6.05 SDS), and head circumference was 47.1 cm (-6.74 SDS). In her physical examination: neurodevelopmental delay, microcephaly, hypertelorism, epicanthal folds, columella belowed alae nasi, broad nasal bridge, short philtrum, macrostomia, dysplastic nails, and skeletal features (slender fingers, pectus excavatum) were observed. In addition, she had behavioral psychiatric manifestations such as self-mutilation, poor eye contact and rocking. Microarray analysis and WES analysis were performed for molecular diagnosis.

Results: Array analysis resulted as normal. WES analysis revealed homozygous pathogenic variants in LARP7. This variant was found in compound heterozygous state in a patient with AS reported by Ling and Sorrentino (2016). This variant has been reported as heterozygous in a female and a male in the gnomAD database.

Discussion: To date approximately 24 patients have been reported in the literature. Most patients are reported to have moderate to severe ID and global developmental delay, particularly delayed speech. Our patient was found to fulfill many more of the distinctive facial findings typical of AS as described in the OMIM database and in the literature. In the literature, AS patients with biallelic pathogenic mutations in the *LARP7* gene have been differentially diagnosed with many other diseases due to their prominent common features: Smith–Lemli–Opitz, Rett syndrome. When our patient first presented, Rett syndrome because of epilepsy and microcephaly, Angelman syndrome because of lack of speech and self-injurious behavior, Smith Magenis syndrome because of self-injuries behaviors, and MOPD because of dwarfism and microcephaly, were considered. In order to better understand the neurologic and dysmorphic manifestations of AS, more patients need to be reported with clinical findings.

Keywords: *LARP7*; Alazami syndrome; developmental disabilities; primordial dwarfism

P21 PIERPONT SYNDROME - A CHARACTERISTIC PHENOTYPE AND A NEW CONCERN UPON DIAGNOSIS

Presenting author : Maria Abreu

Maria Abreu1, Ana Miguel Capela1, Cláudia Falcão Reis1

1: Medical Genetics Department, Centro de Genética Médica Jacinto de Magalhães (CGMJM), Centro Hospitalar Universitário de Santo António (CHUdSA)

Email for correspondence: mariaabreu.genetica@chporto.min-saude.pt

Pierpont syndrome is a recognizable autosomal dominant entity characterized by hypotonia and developmental delay associated with seizures, and abnormal-looking skin which becomes less evident with age. Feeding difficulties have been described in some patients, generally noticeable at birth even if they may require lasting intervention.

We present a case of an infant with Pierpont syndrome diagnosis who suffered a sudden death due to food aspiration, despite having had no feeding difficulties up to 3 mo. The girl was born at 36 weeks of gestational age, to a healthy couple, with a prenatal diagnosis of unilateral kidney atrophy and oligoamnios in the second semester of pregnancy. At birth, global hypotonia and dysmorphic features were noted. She did not pass newborn hearing screening, MRI showed a thin corpus callosum and she was treated for metabolic acidosis, hypoglycemia and hypocalcemia. In the Medical Genetics consultation at 3mo, asymmetric and small palpebral features, thick nose, low-set fleshy ears, redundant skin, mild contracture of the knees and elbows, pigmented articular grooves on the knees and elbows and deep palmar and plantar grooves were noted. A WES-based gene panel was requested. The child suffered a cardiorespiratory arrest at home two weeks after, and life support attempts were unsuccessful.

Identification of a de novo pathogenic heterozygous variant c.1337A>G p.(Tyr446Cys) in TBL1XR1, established the diagnosis of Pierpont syndrome. Autopsy attributed the cause of death to food aspiration.
There are no reports of sudden death in children with Pierpont syndrome, and although features of the syndrome, such as dermal sinus and seizures, are of concern, it is not an entity which generally threatens an infant's immediate survival. We report this case to bring awareness to the severity and suddenness with which the feeding difficulties may present in a syndrome which, upon knowing its phenotype, is readily identifiable

P22 DE NOVO VARIANT IN TLK2: CLINICAL EVALUATION AND GENOTYPE-PHENOTYPE OF A NEURODEVELOPMENTAL DISORDER

Presenting author: Teresa Carrion

We report the case of a 22 year old woman, followed since infancy for genetics, psychiatry and neuropediatrics due to intellectual disability, dysmorphic symptoms and attention deficit hyperactivity disorder.

She was born of non-consanguineous parents. No history of intellectual disability or neurological diseases. Two healthy male brothers aged 29 and 26.
She was delivery at 38 weeks without complications. APGAR score 8/9. Weight 2.400 gr, T: 44 cm and PC 31 cm.
Delay in acquiring developmental milestones.Pondoestatural delay in p3 up to two years atributed to diarrhea + vomiting. Multiple studies were conducted ruling out: cystic fibrosis, celiac disease, malabsorption syndrome, food allergies.
Examination at 22-yo showed Peculiar fascies, microcephaly, broad forehead, hypertelorism. Palpebral fissures short, oblique upwards. Bilateral epicanthal folds, ears of low implantation. Large nose with bulbous tip, small mouth, with thin lips, macroglossia, broad lower jaw, short and flat filtrum, prognathism,high palate.
Recognized Degree of Disability of 66% and Degree of Dependence 1 both definitive.
Throughout years, extensive investigations were performed,metabolic studies and skeletal series were normal. CT, MRI and MR angio (09/27/02) it has a ventricular size in high limits. 2nd MRI and MR angio (05/24/05): moderate dilation of the ventricular system, in the same , which may be significant for some subcortical atrophy.
Interconsultation with infantile endocrinologist for weight-height delay: normal and subsequently slowing of puberty.
Karyotype 46 XX - X-fragile: negative.Most common microdeletion syndromes (MLPA) : normal.Molecular study to detect microdeletion in region 22q11.2 : normal.Smith-Magenis SD and congenital central hypoventilation syndrome: negative
FISH: no deletion of subtelomeric regions.
Array-CGH (60 Kb) Normal
High resolution karyotype 46XX
Microarray CGH 1000K arr 8p23.3 (1,504-084-1,509,519)x1 female karyotype with **microdeletion in 8p23.3 de novo.**
Study of family segregation: negative.
Whole exome sequencing detected LP **heterozygous variant p.** Arg546Gly **in the TLK2 gene.**
The variant found p.Arg546Gly in the patient is not found in the databases of general population consulted. It has not been described in the scientific literature or classified in databases of genetic variants of clinical relevance. However, ***in silico*** predictors indicate a deleterious effect on the protein encoded by this gene. This variant is located in a functionally relevant domain of the protein involving a "hot-spot" in which other pathogenic variants have been described. TLK2 is a protein-coding gene. It encodes a nuclear serine/threonine kinase.The encoded protein functions in regulating chromatin assembly in the S phase of the cell cycle by regulating the levels of a histone H3/H4 chaperone. Associated with repairing double-stranded breaks of DNA damage caused by radiation.
Associated diseases include autosomal dominant intellectual developmental disorder 57 and Pica disease. Among its related pathways are the regulation of miRNA, the response to DNA damage and the regulation of Chks at checkpoints.

P23 A NEW CASE OF OCULO-FACIO-CARDIO-DENTAL SYNDROME: A CASE REPORT AND REVIEW OF THE LITERATURE

Presenting author: Maria Lopes-de-Almeida

Maria Lopes-de-Almeida[1,2]

[1]Medical Genetics Unit, Hospital de Braga, Braga, Portugal; [2]Genetyca-ICM, Atrys, Porto, Portugal

Email for correspondence: marialopesdealmeida@hotmail.com

Oculo-facio-cardio-dental syndrome (OFCDS) is a very rare condition associated with multiple congenital anomalies. It is characterized by the pathognomic dental finding radiculomegaly, other dental findings such as oligodontia, fused or malocclusion teeth; ocular abnormalities as bilateral congenital cataracts, microphthalmia and regressive vision impairment, facial dismorphisms as long narrow face and curved and thick eyebrows; and congenital heart disease as septal defects, ventricular and atrial hypertrophy, benign peripheral pulmonic stenosis and mitral valve prolapse.

It will be reported a new case of a three years old girl with OFCDS, with prenatal growth restriction, neonatal hypotonia and neonatal hypoglicemy, bilateral congenital cataracts, asymmetrical microphthalmia, conical shaped teeth, pulmonar stenosis, and congenital hypothyroidism. Molecular testing identified a probably pathogenic frameshift variant in *BCOR* gene. It will also be reviewed the other literature known cases of OFCDS.

P24 *ZC4H2* HETEROZYGOUS DELETION ASSOCIATED PHENOTYPE IN A 7-YEAR-OLD ROMANIAN GIRL

Presenting author: Ioana Streata

IOANA STREATA[1, 2], ANAMARIA CHIRILAȘ[1], ANCA-LELIA COSTACHE[1, 2], F.BURADA[1, 2]

1 Regional Centre of Medical Genetics Dolj, Emergency County Hospital Craiova, 200642 Craiova, Romania
2 Laboratory of Human Genomics, University of Medicine and Pharmacy of Craiova, 200638 Craiova, Romania

Email for correspondence: ioana.streata@umfcv.ro

BACKGROUND

ZC4H2 (MIM *300897) is an X-chromosomal gene encoding zinc finger C4H2 domain-containing protein, which may play a role in neuronal development and in neuromuscular junction formation (Uniprot Q9NQZ6). Hemizygous pathogenic variants in *ZC4H2* cause Wieacker-Wolff syndrome (MIM #314580), and heterozygous pathogenic variants have been associated with female-restricted Wieacker-Wolff syndrome (WRWFFR; MIM #301041). Recent data showed that females who are carriers for loss-of-function *ZC4H2* variants present with a more severe phenotype, which is like that observed in male hemizygotes for the pathogenic *ZC4H2* missense variants. Clinical features in carrier females with a maternally inherited *ZC4H2* variant range from normal phenotype to mild flexion contractures, borderline to mild intellectual disability, and facial dysmorphism. The reported females' cases with a de novo pathogenic variant including Xq11.2 microdeletions showed high variation in clinical presentation and ranged from mildly to severely affected. The de novo variants in affected females are predicted to be loss-of-function alleles. We describe a newly diagnosed case with a de novo pathogenic loss-of-function *ZC4H2* variant and severe phenotype in a 7-year-old Romanian girl.

CASE PRESENTATION

The proband is a 7-year-old Romanian girl born from healthy, non-consanguineous parents. There was no family history of known congenital anomalies, genetic disorders, epilepsy, or intellectual disability.
She was born premature, with a birth weight of 2,780 g, length of 47 cm and occipitofrontal circumference (OFC) of 32 cm. Her developmental milestones were severe delayed. She presents significant arthrogryposis multiplex, with associated global developmental delay and multiple congenital anomalies. Her developmental delay includes fine motor delay, gross motor delay, and absent language. She has intellectual disability. She also has neuropathy and abnormal eye movement. She has atrial septal defect. Gastroenterological issues include mega-esophagus. She has bifid uvula and club foot and contractures. Dysmorphic features include limb anomaly.

The exome data analysis for rare heterozygous variants (potential de novo variants) and variants following recessive inheritance pattern identified a heterozygous deletion encompassing exon 1 of ZC4H2 gene. This deletion is estimated to cover the genomic region chrX: g.64196111_64196351del and is approximately 240 base pairs in size.

CONCLUSIONS

Our case provides a detailed clinical presentation of a girl affected with Wieacker-Wolff syndrome (WRWFFR; MIM #301041) and expands the mutational spectrum associated with this extremely rare genetic condition. This is the first case of Wieacker-Wolff syndrome identified in Romania.

P25 CASE REPORT OF WAGR SYNDROME IN A COLOMBIAN PATIENT: CLINICAL PRESENTATION AND EMBRYOLOGICAL ANALYSIS

Presenting author : Rafael Ossa

Rafael H. Ossa[1], María Lucía Gutiérrez[1,2] and Juan Carlos Prieto[1]

1. Institute of Human Genetics - School of Medicine, Pontificia Universidad Javeriana.
2. Department of Morphological Sciences, School of Medicine, Pontificia Universidad Javeriana.

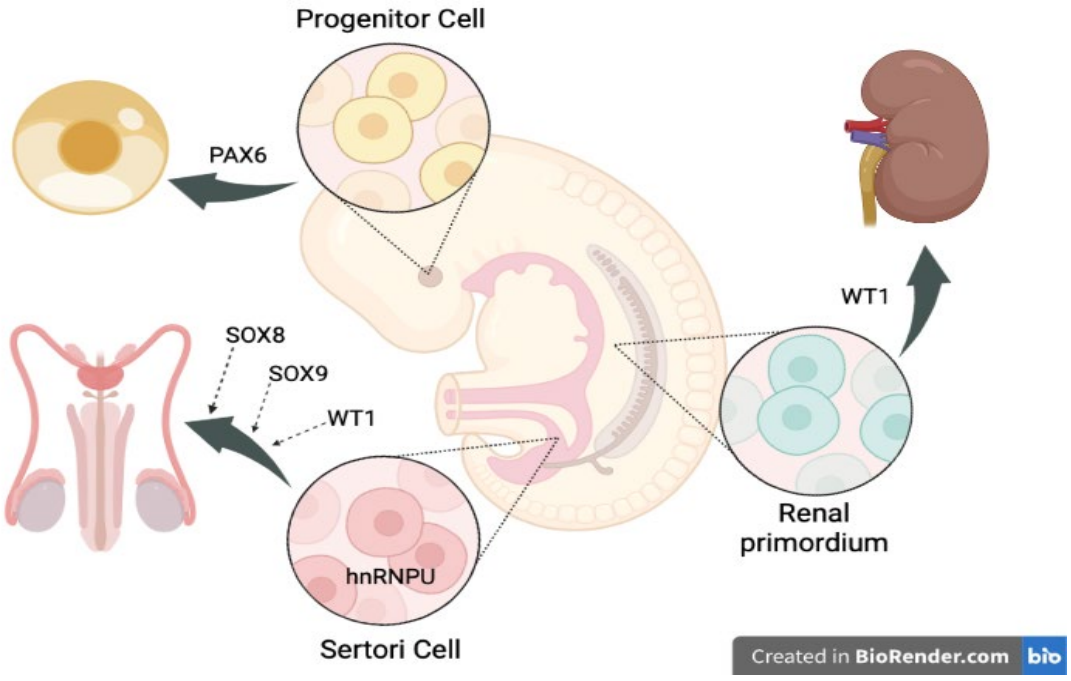
Corresponding author: Rafael Ossa : rossat@genetica.com

Wilms tumor, Aniridia, Genital anomalies and mental Retardation (WAGR) syndrome is a contiguous gene deletion disease caused by the absence of the distal portion of chromosome 11p13, deleting a group of genes with a special involvement in embryonic development like WT1 gene, which plays a role in development of the urogenital system and PAX6 a transcription factor key in eye development which are absent.

We present a case of a Colombian 10-year-old male patient attending medical genetic consultation in Bogotá-Colombia with a history of severe developmental delay associated with bilateral sensorineural hearing loss, Wilms tumor in the left kidney, cystic pulmonary malformation, anterior segment coloboma, mild hypercalciuria, and sexual differentiation disorder. A deletion/duplication study identified a loss of 7.6 Mb in bands 11p13.1,p12.

Based on this clinical case, databases were searched and focused on the 11p13 contiguous gene deletion, investigating their role during embryological development (PAX6, WT1, KCNA4, PRRG4, among others). By the end of the third week, *PAX6* expression defines the eyefield. However, in this patient embryological absence of this gene resulted in aniridia and anterior segment coloboma, both affecting the neuroectoderm. In Nephrogenesis WT1 drives metanephric mesenchyme differentiation and mesenchymal–epithelial transition; alterations in this gene have been associated with Wilms tumor, as observed in this patient only in his left kidney, as well as gonadal dysgenesis. Alteration in KCNA4 gene is related to the formation of microcephaly and intellectual disability. Last, PRRG4 gene relates to fetal neural development and consequent autistic behavior.

Syndromes, such as the WAGR syndrome highlight the importance of gene function and the special role during embryological development. In this way, the pathophysiology can be best elucidated; since other organs were affected such as the inner ear and the lung, where the aforementioned genes could have been involved. The objective of this work is to associate the gene with the possible etiology of the malformation in this patient.


Progenitor Cell
PAX6
WT1
SOX8
SOX9
WT1
hnRNPU
Renal
primordium
Sertori Cell
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Presenters' email address

Maria Abreu	maria_dabreu@hotmail.com
Akçahan Akalın	akcahanbalci@gmail.com
Irene Ambrosetti	irene.ambrosetti@studio.unibo.it
Enrico Ambrosini	enrico.ambrosini@unipr.it
Sietse Aukema	smaukema@gmail.com
Yusuf Bahap	yusufbahap11@gmail.com
Natalja Bannink	n.bannink@franciscus.nl
Boglarka Bansagi	Boglarka.Bansagi@uzbrussel.be
Maria Chiara Baroni	mariachiara.baroni2@studio.unibo.it
Cord-Christian Becker	becker@genetikum.de
Klaudia Berk	klaudia.berk@gmail.com
Sarah Berrada	sarah.berrada.gen@gmail.com
Ozge Beyza Gündogdu Ogutlu	ozgebeyzag@gmail.com
Emilia Bijlsma	e.k.bijlsma@lumc.nl
Davide Calosci	davide.calosci@studenti.unipd.it
Valeria Capra	valeriacapra@gaslini.org
Yline CAPRI	yline.capri@aphp.fr
Teresa Carrion	tcmera@gmail.com
Joana Catanho	joana.silva9@chlc.min-saude.pt
Sofia Cesarini	sofia.cesarini@studio.unibo.it
Claudia Ciaccio	claudia.ciaccio@istituto-besta.it
Francesca Clementina Radio	fclementina.radio@opbg.net
Gianluca Contrò	contro.gianluca@gmail.com
Elisa D'Acunto	elysa93@hotmail.com
Koen Devriendt	koenraad.devriendt@uzleuven.be
Maria Francesca Di Feo	maria.francesca.difeo@edu.unige.it
Christina Ringmann Fagerberg	christina.fagerberg@rsyd.dk
Diogo Fernandes da Rocha	diogo7.rocha@gmail.com
Susana Lemos Ferreira	susana.ferreira2@chlc.min-saude.pt
Romano Ferrucio	ruccio1991@gmail.com
Maria Luisa Garau	marialgarau@gmail.com
Livia Garavelli	livia.garavelli@ausl.re.it
Joyce Geelen	joyce.geelen@radboudumc.nl
David Germaneau	david.germaneau@aphp.fr
Yvan Herenger	y.herenger@genetica.ch
Ivan Ivanovski	ivan.ivanovski@medgen.uzh.ch
Behnam Javanmardi	bjav@uni-bonn.de
Silvia Kalantari	silvia.kalantari@unito.it
Joanna Karwowska	joannbekier@gmail.com
Ivana Kavecan	ivanakavecan@gmail.com
Elvin Kazancioglu	kazanciogluelvin@gmail.com

Sinem Kocagil	sinemkocagil@gmail.com
Saskia Koene	s.koene@lumc.nl
Monika Kowalczyk	monika.kowalczyk@ipczd.pl
Alma Kuechler	alma.kuechler@uk-essen.de
Candy Kumps	candy.kumps@ugent.be
Maria Lopes-de-Almeida	marialopesdealmeida@hotmail.com
Sally Ann Lynch	sally.lynch@ucd.ie
Catarina Macedo	catarina.macedo@chln.min-saude.pt
Prince Makay	prince.makaybamba@kuleuven.be
Ausra Matuleviciene	Ausra.Matuleviciene@mf.vu.lt
Alessandro Mauro Spinelli	alessandromspinelli@gmail.com
Maria Antonietta Mencarell	mar.mencarelli@ao-siena.toscana.it
Piret Mertsina	piret.mertsina@kliinikum.ee
Emanuele Micaglio	emanuele.micaglio@grupposandonato.it
Diana Mitter	mitter@zotzklimas.de
Luigi Monti	luigi.monti3@studio.unibo.it
Mariana Neves	neves.mariana3@gmail.com
Renske Oegema	r.oegema@umcutrecht.nl
Daniela Oliveira	danielaoliveira@chuc.min-saude.pt
Rafael Ossa	rossat@genetica.com.co
Derya Hazal ÖZBAKIR	hazalozbakirogu@gmail.com
Malgorzata Pawlowicz	mpawlowiczconti@gmail.com
Cristina Peduto	drcristinapeduto@gmail.com
Francesca Peluso	Francesca.peluso@ausl.re.it
Adelaide Peruzzi	adelaide.peruzzi@studio.unibo.it
Sara Pinho	sara.pinho@chln.min-saude.pt
Ilona Pirushka	ilona.piruska@bkus.lv
Ewelina Preizner-Rzucidło	e.preizner@gmail.com
Rita Quental	rita.quental@chsj.min-saude.pt
Shauna Quinn	squinn8@tcd.ie
Anita Rauch	anita.rauch@medgen.uzh.ch
Marija Rozevska	marija.rozevska@bkus.lv
Quentin Sabbagh	q-sabbagh@chu-montpellier.fr
Ana Isabel Sánchez Barbero	ana.sbarbero@quironsalud.es
Elif Saraç	elif.sarac@ogu.edu.tr
Camilla Sarli	camilla.sarli@gmail.com
Clément SAUVESTRE	clement.sauvestre@chu-bordeaux.fr
Marcello Scala	mscala.md@gmail.com
Ariane Schmetz	ariane.schmetz@hhu.de
Sarah Schuhmann	sarah.schuhmann@uk-erlangen.de
Giulia Severi	giulia_severi@aosp.bo.it
ABDULLAH SEZER	abdullahsezer25@gmail.com
Karolina Śledzinska	ksledzinska@gumed.edu.pl
Katharina Steindl	Katharina.Steindl@medgen.uzh.ch
Ioana Streata	ioana.streata@umfcv.ro

Katalin Szakszon	zakszon.katalin@med.unideb.hu
Kristi Tael	kristi.tael@kliinikum.ee
Elis Tiivoja	elis.tiivoja@kliinikum.ee
Viola Trevisani	viola.trevisani@gmail.com
Marie-José van den Boogaard	m.j.h.vandenboogaard@umcutrecht.nl
Nathalie Vanden Eynde	nathalie.vandeneynde@uzbrussel.be
Alain Verloes	alain.verloes@aphp.fr
Giulia Vitetta	giulia.vitetta@studio.unibo.it
Dorota Wicher	d.wicher@ipczd.pl
Eliana Zacchi	eliana.zacchi@studio.unibo.it