SCIENTIFIC PROGRAM

Note: This program is tentative and may be modified.

WEDNESDAY 5th SEPTEMBER

9.30 UNKNOWN SESSION
Chair: VERLOES A.

THURSDAY 6th SEPTEMBER

08.45 Opening address: STUMPEL C.

09.00-11.00 FIRST SESSION: Syndrome delineation part 1
Chair: STOLL C.

09.00 C. STOLL, Y. ALEMBIK, B. DOTT AND M.-P. ROTH
Associated anomalies in cases with anorectal anomalies

09.15 M. JEANNE, N. RONCE, G. BAUJAT, S. BRETON, S. ARPIN, F. PETIT, C. VANLERBERGHE, A. DIEUX, S. MANOUVRIER, C. VINCENT-DELORME, P. KHAU VAN KIEN, J VAN GILS, C. QUELIN, L. PASQUIER, S. ODENT, F. DEMURGER, F. LAFFARGUE, D. MARTIN, A. AFENJAR, S. WHALEN, Y. CAPRI, A. DELAHAYE, J. PLAISANCIE, P. LABRUNE, A. DESTREE, I. MAYSTADT, V. CIORMA, B. ISIDOR, M. VINCENT, A. DAVID, N. JEAN MARCAIS, E. SCHAEFER, S. EL CHEHADEH, J. LESPINASSE, T. BUSA, N. PHILIP, J. AMIEL, M. RIO, C. MICHOT ,V. CORMIER-DAIRE AND A. TOUTAIN
Further delineation of the Aarskog-Scott syndrome phenotype in a series of 79 male patients with a *FGD1* mutation: recommendations for diagnosis and management

09.30 N. DI DONATO, I. NIEHAUS, S.L. LATHAM, M. H. TAFT, K. TEZCAN, B. CHUNG, L. GRAUL-NEUMANN, N. EHMKE, S. CATHEY, M.L. LYONS, K. BECKER, L. GIELDON, E. SCHROCK, A. RUMP, M. HEIDE AND D. J. MANSTEIN
Update and expanded clinical spectrum of nonmuscle actinopathies

09.45 M.R.F. REIJNDERS, K.A. MILLER, M. ALVI, C.T.R.M. STUMPEL, C. NELLAKER, H.G. BRUNNER, A.O.M. WILKIE *et al.*
De novo and inherited loss-of-function variants in TLK2: clinical and genotype-phenotype evaluation of a distinct neurodevelopmental disorder

10.00 A. MATULEVIČIENĖ, E. PREIKŠAITIENĖ, R. MATULEVIČIŪTĖ, N. KRASOVSKAJA, I. KAVALIAUSKIENĖ, R. MEŠKIENĖ, L. AMBROZAITYTĖ, V. KUČINSKAS AND A. UTKUS
Lithuanian cohort of 3-M syndrome

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Lithuanian cohort of 3-M syndrome

10.15 A.I. MIDRO, N. TOMMERUP, J. BORYS, B. KOSZTYLA- CHOJNA, R. ZALEWSKA, D. MOSKAL, E. TARASÓW, L. COOPER S.E. SCHERER, B. PANASIUK, R. SKOWRONSKI AND P.Ł STANKIEWICZ
Twenty-five-year follow-up of a male with the Russell-Silver syndrome-like features due to disruption of *BPTF*

10.30 C. ENGEL, C. CABROL, L. BURGLEN, A. MUNNICH, D. AMSALLEM AND L. VAN MALDERGEM
RANBP2-related autosomal dominant necrotizing encephalitis: a familial case

10.45 C. FAUTH, E. MAURER, J. ZSCHOCKE AND U. ALBRECHT
Au-Kline syndrome due to a *de novo* missense variant in *HNRNPK*

11.00-11.30 *Coffee Break*

11.30-12.30 FIRST SESSION: Syndrome delineation part 2
Chair: MIDRO A. - RAUCH A.

11.30 G. MUBUNGU, A. MUPUALA, A. LUMAKA, K. DEVRIENDT AND P. LUKUSA TSHILOBO
Parry-Romberg syndrome: clinical presentation in a Congolese patient

11.45 B. DEMEER, J. CHEVREAU, C. KLEIN, E. CLOSSET, C. GBAGUIDI, C. GONDRY-JOUET, G. JEDRASZAK, P.NAEPELS AND J. GONDRY
Prenatal diagnosis of a femoral facial syndrome and postnatal outcome

12.00 M.T. CARMINHO-RODRIGUES, M. GUIPPONI, C. BOREL, J. SARAIVA, M. ABRAMOWICZ, M. VENANCIO AND A. BOTTANI
Cabezas syndrome: report of 2 patients

12.15 L. GARAVELLI, I. IVANOVSKI, M. POLLAZZON, S. CARAFFI, M. VALLI, A. ROSSI, B. CAMPOS-XAVIER, S. UNGER AND A. SUPERTI-FURGA
Severe peripheral joint laxity is a distinctive clinical feature of *B3GALT6*- and *B4GALT7*-related disorders

AFTERNOON

14.30-16.00 FIRST SESSION: Syndrome delineation part 3
Chair: STUMPEL C. - KOHLHASE J.

14.30 M. ZENKER and members & partners of the European Network on Noonan syndrome and related disorders (NSEuroNet)
LZTR1 a new player in the complex genetic architecture of Noonan syndrome

14.45 S. EL CHEHADEH, H. CAVE, R. FAVRE, Y. CAPRI AND ALAIN VERLOES
Is *RASA2* really associated with RASopathies?

15.00 A. BAYAT, A. KNAUS, E. GARDELLA, U. KINI, R.S. MØLLER
PIGT-CDG, a disorder of the glycosylphosphatidylinositol anchor: description of thirteen novel patients and expansion of the clinical characteristics

15.15 A. VAN HAGEN, M. BRUIJN AND B. STRAVER
49,XXXXY syndrome: three extra x chromosomes leading to three classical signs: mental retardation, hypogonadism and radioulnar synostosis

15.30-16.00 SECOND SESSION: Genetic mechanisms of disease

15.30 I. PHELPS, J. DEMPSEY, D. DOHERTY AND R. BACHMANN-GAGESCU
The (not so) complex genetics of Joubert syndrome

15.45 A. VOGELS, G. VAN BUGGENHOUT, E. WEYTS, N. BRISON, G. D'HAENENS, J. VERMEESCH, M. VIÑAS-JORNET, N. BAENA , S. ESTEBA-CASTILLO, E. GABAU, N. RIBAS-VIDA*, A. RUIZ, R. NOVELL, M. GUITART, A. STRYDOM, N. BASS, K. WOLFE, A. MCQUILLIN AND J.H. THYGESEN
Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders

16.00-16.30 *Coffee Break*

16.30-17.30 SECOND SESSION: Genetic mechanisms of disease
Chair: GARAVELLI L.- ZENKER M.

16.30 S. CARAFFI, L. IVANOVSKI, E. ERRICHIELLO, M. POLLAZZON, L. GARAVELLI AND O. ZUFFARDI
AUTS2 syndrome: a severe case associated with a novel in-frame deletion restricts the minimal critical region of the disease to a histidine-rich motif

16.45 B. POPP, A. AGAIMY, C. KRAUS, K.X. KNAUP, A.B. EKICI, S. UEBE, A. REIS, M. WIESENER AND C. ZWEIER
Dissecting TSC2-mutated renal and hepatic angiomyolipomas in an individual with ARID1B-associated intellectual disability

17.00 M.-L. VUILLAUME, B. COGNE, M. JEANNE, A. BOLAND, D. UNG, D. QUINQUIS, T. BESNARD, J.-F. DELEUZE, R. REDON, S. BEZIEAU, F. LAUMONNIER AND A. TOUTAIN
Whole Genome Sequencing identifies a *de novo* 2.1 Mb balanced paracentric inversion disrupting *FOXP1* and leading to severe intellectual disability with autistic features

17.15 E. VAN HOOF, A. CORVELEYN, E. VERBEKEN, M. HOLVOET AND K. DEVRIENDT[1]
Multiple de novo mutations *in cis* in the DNMT3A gene in a boy with Tatton-Brown syndrome

21.00-23.00 UNKNOWN
Chair: VERLOES A. - DEVRIENDT K.

FRIDAY 7th SEPTEMBER

09.00-10.30 KEYNOTE LECTURE
A. PITON: Molecular genetics of intellectual disability

10.30-11.00 *Coffee Break*

11.00-12.15 THIRD SESSION: NGS: Lessons learned in prenatal, postnatal and follow-up
Chair: TOUTAIN A. - VAN MALDERGEM L.

11.00 B. RINALDI, V. RACE, A. CORVELEYN, J. BRECKPOT, E. DENAYER, I. DE RAVEL AND K. DEVRIENDT
NGS sequencing in prenatal setting: some examples of unexpected variant association

11.15 M. ISRIE, G. TAN-SINDHUNATA, A. VAN HAGEN, M. ELTING AND Q. WAISFISZ
Diagnostic investigations using next generation sequencing: lessons learnt

11.30 P. BOONSAWAT, R. ASADOLLAHI, P. JOSET, K. STEINDL AND A. RAUCH
Surprising twist in a long-lasting unknown case with syndromic primary microcephaly

11.45 K. STEINDL, M. ZWEIER, A. BEGEMANN, S.M. PAPUC, B. ONEDA, P. JOSET AND A. RAUCH
Final destination for a long-lasting unknown case with PEHO-like phenotype

12.00 E. BIJLSMA, L. DONKER KAAT, A. VAN HAERINGEN, M. HOFFER, G. SANTEN AND C. RUIVENKAMP
Follow-up of former presentations: looking for the wrong patients and the wrong gene

AFTERNOON

14.30-15.30 FOURTH SESSION: Gene first, phenotype second
Chair: VERLOES A. - BAYAT A.

14.30 S. DEMIRDAS
Cerebral palsy due to periventricular leukomalacia, or syndromic? A patient with desmosterolosis

14.45 J. KOHLHASE, E. NUNEZ ENTRENA AND E. WOHLLEBER
Undetected glycogen storage disease as a cause for sudden death. Case report and review of the literature

15.00 L. RUAUD, N. LOPEZ, S. SAMAAN AND S. PASSEMARD
AP4B1 mutations can induce hippocampal hypersensitivity to febrile seizures

15.15 P. ZANONI, P. BOONSAWAT, R. ASADOLLAHI, D. NIEDRIST, P. JOSET, J. WISSER, H. BUDKA, P.K. BODE, H. STICHT, K. STEINDL AND A. RAUCH
Whole-exome sequencing identifies novel causative variants and expands the phenotypic spectrum of PLK4-related primary microcephaly

15.30-16.15 FIFTH SESSION: Classification and treatment of genetic disorders

15.30 A. VERLOES, D. HAYE, A. TOUTAIN D. BONNEAU, I. KIBÆK NIELSEN ,I. BAY LUND, P. BOGAARD, S. LEENSKJOLD, K. KARAER, K.T WILD, K.L GRAND, M.C. ASTIAZARAN, L.A. GONZALEZ-NIETO, A. CARVALHO, D. LEHALLE, S.M AMUDHAVALLI, E. REPNIKOVA, C.SAUNDERS, I. THIFFAULT, I. SAADI, D. LI, H. HAKONARSON, Y. VIAL, E. ZACKAI, P. CALLIER, S. DRUNAT AND E.J. BHOJ
Phenotypic spectrum of SPECC1L pathogenic variants: new families and critical review of the nosology of Teebi and Opitz GBBB syndromes

15.45 A. BEYENS, R. DE RYCKE, H. SYRYN, B. FISCHER-ZIRNSAK, T. VAN DAMME, I. HAUSSER, M. DE BRUYNE, M. MORRONI, S. NAMPOOTHIRI, K. MAHESH, U. KORNAK, Z. URBAN, S. HADJ-RABIA, C. BODEMER, C. VAN RAVENSWAAIJ-ARIS, S. DE SCHEPPER, E.C. DAVIS AND B. CALLEWAERT
A clinical classification for Cutis Laxa syndromes, supported by Electron Microscopy

16.00 C. STUMPEL AND N. SCHOTT
Kabuki syndrome

16.15-16.45 *Coffee Break*

16.45-18.00 SIXTH SESSION: New genes
Chair: DEVRIENDT K. - BIJLSMA E.

16.45 J. STRAUB, E.D.H. KONRAD, J. GRÜNER, A. TOUTAIN, L.A. BOK, M.T. CHO, H.P. CRAWFORD, H. DUBBS, G. DOUGLAS, R. JOBLING, D. JOHNSON, B. KROCK, M.A. MIKATI, A. NESBITT, J. NICOLAI, M. PHILLIPS, A. PODURI, X.R. ORTIZ-GONZALEZ, Z. POWIS, A. SANTANI, L. SMITH, A.P.A. STEGMANN, C. STUMPEL AND M. VREEBURG, Deciphering Developmental Disorders Study, A. FLIEDNER, A. GREGOR, H. STICHT AND C. ZWEIER
De novo missense variants in *RHOBTB2* cause a developmental and epileptic encephalopathy in humans, and altered levels cause neurological defects in *drosophila*

17.00 V. LAUGEL-HAUSHALTER, C. STOETZEL, E. SCHAEFER, Y. ALEMBIC, V. GOEFFROY, M.E-C. MANIÈRE, H. DOLLFUS AND A. BLOCH-ZUPAN
A new homozygous missense mutation in *SLC10A7* involved in syndromic AI

17.15 L. IVANOVSKI, S.G. CARAFFI, A. FRASOLDATI, S. ROSATO, L. MATALONGA , S. BERNASCONI AND L. GARAVELLI
The first case of papillary thyroid carcinoma in a patient with syndromic form of primordial dwarfism

17.30 E. VERGAELEN
Immuno-psychiatry in the 22q11.2 deletion syndrome: Pro-inflammatory cytokines and the association with psychosis

ASSOCIATED ANOMALIES IN CASES WITH ANORECTAL ANOMALIES

Claude Stoll[1], Yves Alembik[1], Béatrice Dott[1], Marie-Paule Roth[1]

[1]Laboratoire de Génétique Médicale, Faculté de Médecine, 11 rue Humann, 67085 Strasbourg cedex, France

Email for correspondence: cstoll@unistra.fr

Anorectal anomalies (ARA) are common congenital anomalies. The etiology of ARA is unclear and its pathogenesis is controversial. Cases with ARA often have other non-ARA associated congenital anomalies. The purpose of this study was to assess the prevalence and the types of these associated anomalies in a defined population. The associated anomalies in cases with ARA were collected in all livebirths, stillbirths and terminations of pregnancy during 29 years in 387,067 consecutive births in the area covered by our population-based registry of congenital malformations. Of the 202 cases with ARA, representing a prevalence of 5.21 per 10,000, 100 (49.5%) had associated anomalies. There were 7 (3.3%) cases with chromosomal abnormalities, and 31 (15.3%) nonchromosomal recognized dysmorphic conditions including 17 cases with VACTERL association. Sixty two (30.7%) of the cases had non syndromic multiple congenital anomalies (MCA). Anomalies in the urogenital, the musculoskeletal, the cardiovascular, the digestive, and the central nervous systems were the most common other anomalies in the cases with MCA. The anomalies associated with ARA could be classified into a recognizable malformation syndrome or pattern in 38 out of the 100 cases (38 %) with associated anomalies. This study included special strengths: each affected child was examined by a geneticist, all elective terminations were ascertained, and the surveillance for anomalies was continued until 2 years of age. In conclusion the overall prevalence of associated anomalies, which was close to one in two cases, emphasizes the need for a routine screening for other anomalies in cases with ARA.

FURTHER DELINEATION OF THE AARSKOG-SCOTT SYNDROME PHENOTYPE IN A SERIES OF 79 MALE PATIENTS WITH A *FGD1* MUTATION: RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT

M. Jeanne[1], N. Ronce[1], G. Baujat[2], S. Breton[3], S. Arpin[1], F. Petit[4], C. Vanlerberghe[4], A. Dieux[4], S. Manouvrier[4], C. Vincent-Delorme[4], P. Khau Van Kien[5], J Van Gils[6], C. Quelin[7], L. Pasquier[7], S. Odent[7], F. Demurger[8], F. Laffargue[9], D. Martin[10], A. Afenjar[11], S. Whalen[11], Y. Capri[12], A. Delahaye[12], J. Plaisancie[13], P. Labrune[14], A. Destree[15], I. Maystadt[15], V. Ciorma[16], B. Isidor[17], M. Vincent[17], A. David[17], N. Jean Marcais[18], E. Schaefer[19], S. El Chehadeh[19], J. Lespinasse[20], T. Busa[21], N. Philip[21], J. Amiel[2], M. Rio[2], C. Michot[2], V. Cormier-Daire[2], A. Toutain[1].

1. Service de Génétique, CHU de Tours, France, 2. Service de Génétique Médicale, CHU Necker-Enfants Malades, Paris, France, 3. Service de Radiologie Pédiatrique, CHU Necker-Enfants Malades, Paris, France, 4. Clinique de Génétique Jean Fontaine, CHU de Lille, France, 5. Unité de Génétique Médicale, CHU de Nîmes, France, 6. Service de Génétique Médicale, CHU de Bordeaux, France, 7. Service de Génétique Clinique, CHU de Rennes, France, 8. Service de Génétique Médicale, CH de Vannes, France, 9. Service de Génétique Médicale, CHU de Clermont-Ferrand, France, 10. Service de Génétique, CH du Mans, France, 11. Unité de Génétique Clinique, CHU Trousseau, Paris, France, 12. Unité de Génétique Clinique, CHU Robert Debré, Paris, France, 13. Service de Génétique Médicale, CHU de Toulouse, France, 14. Service de Pédiatrie, CHU Antoine Béclère, Paris, France, 15 Service de Génétique, Institut de Pathologie et de Génétique, Gosselies, Belgique, 16. Service de Génétique, CHR de Metz-Thionville, France, 17. Service de Génétique Médicale, CHU de Nantes, France, 18. Centre de Génétique, CHU de Dijon, France, 19. Service de Génétique Médicale, CHU de Strasbourg, France, 20. Service de Génétique Médicale, CH de Chambéry, France, 21. Département de Génétique Médicale, CHU de Marseille, France.

Email for correspondence: mederic.jeanne@gmail.com

Aarskog-Scott syndrome (ASS), also called facio-genital dysplasia is a rare X-linked disorder first reported by Aarskog in 1970. Further cases were reported by Scott in 1971, leading to the name of the syndrome. It is characterized by distinctive facial features, moderate short stature, hands and feet abnormalities and genital anomalies. In 1994, causative mutations were identified in the *FGD1* gene mapping at Xq11.2, which codes for a GTP-binding protein that stimulates the GDP-GTP exchange of the Rho GTPase Cdc42. Since the first descriptions, many other cases have been reported with a wide clinical heterogeneity. In particular, the description of the neurodevelopmental phenotype varies widely in the literature. However, these descriptions mostly occurred before the availability of molecular analysis.

In order to better delineate the phenotypic spectrum of ASS caused by *FGD1* mutations, and to try to define specific clinical criteria for *FGD1* molecular testing and to help *FGD1* variant interpretation, we reviewed the clinical features in a large cohort of male patients with a *FGD1* mutation. A clinical questionnaire based on literature data was send to the referring physicians in order to collect relevant information. Morphological features were reviewed by dysmorphology experts and skeletal radiographs were reviewed by the team of the French reference centre for constitutional bone diseases. We present here the results of the clinical, radiological and molecular analysis of 79 male patients. Our results bring new information about growth and developmental course. Our results also refine the prevalence of morphological features and confirm the association of rare features with ASS. We also report new features of the ASS, in particular, specific and sensitive radiological features which have not been previously described.

Finally, considering the current high throughput sequencing strategy of gene analyses and the considerable development of retro-phenotyping, we propose specific criteria, not only for molecular confirmation but also adapted for the interpretation of *FGD1* variants. We also propose recommendations for management of ASS.

UPDATE AND EXPANDED CLINICAL SPECTRUM OF NONMUSCLE ACTINOPATHIES

Nataliya DI DONATO[1], Indra NIEHAUS[1], Sharissa L. LATHAM[2], Manuel H. TAFT[2], Kamer TEZCAN[3], Brian CHUNG[4], Luitgard GRAUL-NEUMANN[5], Nadja EHMKE[5], Sara CATHEY[6], Michel L. LYONS[6], Kerstin BECKER[7], Laura GIELDON[1], Evelin SCHROCK[1], Andreas RUMP[1], Michael HEIDE[8], Dietmar J. MANSTEIN[2]

1: Institute for Clinical Genetics, TU Dresden, Dresden, Germany 2: Institute for Biophysical Chemistry, Hannover Medical School, Hannover, Germany 3: Kaiser Permanente Sacramento Medical Center, Sacramento, CA, USA 4: Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, HKSAR 5: Institute of Medical and Human Genetics, Charité-Universitätsmedizin Berlin, Berlin, Germany 6: Greenwood Genetic Center, Greenwood, SC, USA 7: Medical Genetics Center, Munich, Germany 8: Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

Email for correspondence: nataliya.didonato@uniklinikum-dresden.de

Six human genes are known to encode for six highly conserved actin isoforms (>93% similarity), which are produced in a time- and tissue-specific manner. Mutations in all six genes can cause distinct human diseases. Pathologies associated with cardiac, skeletal, and smooth muscle cells are linked to the dominant actin isoform in the corresponding tissues. Heterozygous constitutive mutations in both *ACTB* and *ACTG1* encoding for nonmuscle actin isoforms have been associated with Baraitser-Winter Cerebrofrontofacial syndrome (BWCFF), a well-defined disorder with recognizable facial features, developmental disability, neuronal migration defects, hearing loss, ocular colobomas, heart and renal defects, and progressive muscle wasting. Mutations in *ACTG1* can also lead to non-syndromic hearing loss and isolated ocular colobomas. Multiple clinical entities have also been associated with *ACTB* mutations including intellectual disability due to ACTB haploinsufficiency, Becker's Nevus syndrome due to low-grade mosaic *ACTB* hotspot mutations, dystonia-deafness syndrome, and newly described *ACTB*-associated Thrombocytopenia and Microcephaly syndrome defined by us.

Here we analyzed systematically the genotype-phenotype correlation of more than 100 published and unpublished patients with *ACTB* and *ACTG1* variants. Surprisingly, we identified two novel recurrent missense mutations associated with either non-syndromic intellectual disability or syndromic neurodevelopmental disorder, both conditions have not been known before. These phenotypes are not overlapping with previously described conditions. Regarding brain malformations *ACTB* and *ACTG1* mutations appeared to have a broader spectrum of pathologies than expected. In addition to lissencephaly, which is known to be a part of the BWCFF spectrum, patients with both *ACTB* and *ACTG1* mutations presented with polymicrogyria and periventricular nodular heterotopia.

In addition, we analyzed the cytoskeletal phenotype in patient-derived fibroblasts. We observed that changes in the actin filament organization are specific to the clinical presentation of the patients and have distinct features depending on which actin isoform is affected. Moreover, the observed cytoskeletal changes appear to correlate with the severity of the patients clinical symptoms within the BWCFF cohort.

Further studies using patients' derived brain organoids demonstrated clearly a defect in the formation of the neuroectoderm with premature neuronal differentiation, indicating that actin mutations interrupt multiple developmental steps and not only neuronal migration.

DE NOVO AND INHERITED LOSS-OF-FUNCTION VARIANTS IN TLK2: CLINICAL AND GENOTYPE-PHENOTYPE EVALUATION OF A DISTINCT NEURODEVELOPMENTAL DISORDER

Margot R.F. Reijnders[1], Kerry A. Miller[2], Mohsan Alvi[3], Connie TRM Stumpel[1], Christoffer Nellaker[4,5,6], Han G. Brunner[1,7], Andrew O.M. Wilkie[2,8]*

* Many others contributed to this study. Their names will be visible on the acknowledgment slide.

1: Department of Clinical Genetics and GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, P. Debyelaan 25, Maastricht, The Netherlands.

2: Clinical Genetics Group, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK.

3: Visual Geometry Group, Department of Engineering Science, University of Oxford, Oxford, UK.

4: Nuffield Department of Women's and Reproductive Health, University of Oxford, Women's Centre, John Radcliffe Hospital, Oxford, UK.

5: Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford, UK.

6: Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK.

7: Department of Human Genetics, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands.

8: Craniofacial Unit, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, UK.

Email for correspondence: margot.reijnders@mumc.nl

Next-generation sequencing is a powerful tool for the discovery of genes related to neurodevelopmental disorders (NDDs). Here, we report the identification of a distinct syndrome due to *de novo* or inherited heterozygous mutations in Tousled-like kinase 2 (*TLK2*) in 38 unrelated individuals and two affected mothers, using whole-exome and whole-genome sequencing technologies, matchmaker databases, and international collaborations. Affected individuals had a consistent phenotype, characterized by mild-borderline neurodevelopmental delay (86%), behavioral disorders (68%), severe gastro-intestinal problems (63%), and facial dysmorphism including blepharophimosis (82%), telecanthus (74%), prominent nasal bridge (68%), broad nasal tip (66%), thin vermilion of the upper lip (62%), and upslanting palpebral fissures (55%). Analysis of cell lines from three affected individuals showed that mutations act through a loss-of-function mechanism in at least two case subjects. Genotype-phenotype analysis and comparison of computationally modeled faces showed that phenotypes of these and other individuals with loss-of-function variants significantly overlapped with phenotypes of individuals with other variant types (missense and C-terminal truncating). This suggests that haploinsufficiency of TLK2 is the most likely underlying disease mechanism, leading to a consistent neurodevelopmental phenotype. This work illustrates the power of international data sharing, by the identification of 40 individuals from 26 different centers in 7 different countries, allowing the identification, clinical delineation, and genotype-phenotype evaluation of a distinct NDD caused by mutations in *TLK2*.

LITHUANIAN COHORT OF 3-M SYNDROME

Aušra MATULEVIČIENĖ[1,2], Eglė PREIKŠAITIENĖ[1,2], Rugilė MATULEVIČIŪTĖ[3], Natalija KRASOVSKAJA[1,2], Ingrida KAVALIAUSKIENĖ[1,2], Raimonda MEŠKIENĖ[1,2], Laima AMBROZAITYTĖ[1,2], Vaidutis KUČINSKAS[1], Algirdas UTKUS[1]

1. Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University Faculty of Medicine, Vilnius University, Vilnius, Lithuania
2. Centre of Medical Genetics, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
3. Wolfson College, University of Cambridge, Cambridge, United Kingdom

E-mail for correspondence: ausra.matuleviciene@mf.vu.lt

3-M syndrome (OMIM 273750) is an autosomal recessive disorder, characterized by pre- and postnatal growth retardation, short stature and dysmorphic features. The prevalence of 3-M syndrome is unknown, and about 100 individuals with this condition have been described in the medical literature worldwide. Pathogenic variants in *CUL7* gene account for the majority of cases of 3-M syndrome. There are currently 63 *CUL7* gene mutations causing 3-M syndrome published in the Human Gene Mutation Database (HGMD). Pathogenic variants in *OBSL1* and *CCDC8* genes have also been identified as disease causing in patients with this condition.

Here we report four Lithuanian patients with homozygous NM_001168370.1:c.3293T>G (NP_001161842.1:p.L1098R) mutation (HGMD:CM053193) and one patient with compound heterozygous NM_001168370.1:c.3293T>G (NP_001161842.1:p.L1098R) and NM_001168370.1:c.3316C>T (NP_001161842.1:p.R1106X) (novel) mutations in exon 16 of *CUL7* (cullin 7 gene), accounting for their phenotypic presentation of 3-M syndrome. Both mutations identified in the DOC (Skp1-Fbx29 binding) functional domain.

3-M syndrome seems to present with a relatively similar phenotype. Dysmorphic features, including triangular face, broad prominent forehead, flat nasal bridge, long philtrum, short thorax (commonly with pectus excavatum/carinatum), present in the reported Lithuanian patients are distinct for this condition. Short stature and proximal limb shortening as well as other skeletal anomalies are also associated with this condition. The similarities in phenotype are thought to be due to the fact that interactions between OBSL1/CUL7 and OBSL1/CCDC8 proteins are required to maintain CUL7-SCF E3 ligase activity which is thought to be responsible for the pathogenicity of the condition.

NM_001168370.1:c.3293T>G variant is not detected in the Lithuanian population group with the minor allele frequency in the ExAC data of 0.0002/25. All of the patients claim to be unrelated but the common nature of the disease causing mutation in them led us to speculate about the potential founder's effect. However, further work is needed to confirm such hypothesis.

TWENTY-FIVE-YEAR FOLLOW-UP OF A MALE WITH THE RUSSELL-SILVER SYNDROME-LIKE FEATURES DUE TO DISRUPTION OF *BPTF*

Alina T. Midro[1], Nils Tommerup[2], Jan Borys[3],, Bożena Kosztyla- Chojna[4], Renata Zalewska[5], Diana Moskal,[4] Eugeniusz Tarasów[6], L. Cooper[7] S.E. Scherer[8], Barbara Panasiuk[1], Rafał Skowronski[9], Paweł Stankiewicz[7,10]

[1]Department of Clinical Genetics, Bialystok, Poland; [2]Wilhelm Johannsen Centre for Functional Genome Research Department of Cellular and Molecular Medicine (ICMM), University of Copenhagen, Denmark; [3]Clinic of Maxillo-Facial Surgery Medical University, Bialystok, Poland; [4]Department of Phonoaudiology and Logopedics Medical University, Bialystok, Poland; [5]Department of Ophthalmology Medical University, Bialystok, Poland; [6]Department of Radiology,Medical University, Bialystok, Poland; [7]Baylor Genetics, Houston, TX, USA; [8]Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA; [9]Department of Orthopaedics and Traumatology, Medical University, Bialystok; [8]Dept of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX; [10]Baylor Genetics, Houston, TX.

E- mail for correspondence : alinamidro@ gmail.com

Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (NEDDFL, OMIM 617755) was recently shown to result from haploinsufficiency of *BPTF* encoding the largest subunit of a nucleosome remodeling factor (NURF), a member of ISWI chromatin remodeling complex. We have observed similar phenotypic features in a 35-year-old male with Russell-Silver syndrome-like features and a *de novo* apparently balanced chromosomal translocation t(1;17)(q24.3;q24.2), reported in 1993 (PMID:8403458). FISH with BAC and fosmid clones and WGS revealed that the 17q24.2 breakpoint maps at chr17:65,944,420-65,955,659 (hg19) and disrupts the dosage sensitive *BPTF* (pLI=1.00). The 1q24.3 breakpoint was mapped at chr1:172,228,441-172,234,934 (hg19) 172,228,441-172,234,934 disrupting the brain specific gene *DNM3* predicted to tolerate loss-of-function (pLI=0.03). No non-polymorphic CNVs were identified by CMA. Phenotypic analyses performed according to the Munich Dysmorphology Database (MDDB) methodology revealed short stature, hemihypotrophy, microcephaly, triangular shape of asymmetric face, prominent forehead, hypertelorism, protruding eyeballs, broad palpebral fissures, divergent strabismus, long eye lashes, long nasal bridge, short philtrum, thin lips, microretrogenia, scoliosis of neck, thoracic and lumbal parts of spine. Limb anomalies include bilateral 5th finger clinodactyly, short phalanges broad big first toes. More asymmetric face, more cis-frontal profile, nose, maxilla and mandible distorted into right side of triangular face, changes of localization of ears in comparison to eyes lines, narrowing maxillar and mandible arcus, teeth anodontia, deepening scoliosis of spine were found at age of 34 years old. Intellectual disability, speech delay, muscle hypotonia, and the defect of phonemic audition have improved over the course of 25 years of observations. Our results expand the clinical spectrum of human disorders caused by ablation of chromatin remodeling complexes.

RANBP2-related autosomal dominant necrotizing encephalitis: a familial case

C. Engel[1], C. Cabrol[1], L. Burglen[2], A. Munnich[3], D. Amsallem[4], L. Van Maldergem[1]

[1]Centre de génétique humaine, Université de Franche-Comté, Besançon, France, [2]Service de génétique, GHU Armand-Trousseau, Paris, France, [3]Service de génétique, Hôpital Necker - Enfants Malades, Paris, France, [4]Service de pédiatrie, CHU, Université de Franche-Comté, Besançon, France.

Autosomal Dominant Acute Necrotizing Encephalopathy (ADANE), a condition described by Neilson et al in 2009 is characterized by occurrence of acute encephalitis during childhood, usually in the context of a viral infection. In many instances, coma and multifocal cavitation of the brain, particularly thalami, are paramount features. Acute episode is complicated by seizures and death in a number of cases. In others, partial recovery with subsequent cognitive and motor impairment is described. No more than sixty patients have been described until now, mostly of sporadic occurrence. Heterozygous mutations of *RANBP2* are at cause. This gene encodes a E3-SUMO ligase of major importance for proper sumoylation of proteins. Pathomechanism of the disease remains ill-defined. Only a limited number of familial cases have been reported. Singularly, in the unique large family hitherto described, approximately 80% of heterozygous relatives of index patients remained symptom-free. Such a low penetrance is rare among autosomal dominant conditions. It points to a role for environmental or epigenetic factors acting in addition to RANBP2 mutation that remains a prerequisite in triggering the disease. We describe a pedigree where two severely affected children aged 6 and 9 years at the time of presentation developed balance problems and frontal syndrome after recovering prolonged coma during their acute encephalitis episode . Heterozygosity for the common c.1754C>T (p.Thr585Met) *RANBP2* sequence alteration was identified in both cousins. In checking the status of relatives, 9 asymptomatic carriers were diagnosed. Of note, 4 histories of meningitis in infancy were noted in relatives that were not available for testing. Further studies are required to elucidate the underpinning mechanisms.

AU-KLINE SYNDROME DUE TO A *DE NOVO* MISSENSE VARIANT IN *HNRNPK*

Christine FAUTH[1], Elisabeth MAURER[1], Johannes ZSCHOCKE[1], Ursula ALBRECHT[2]

1: Division of Human Genetics, Medical University Innsbruck, Austria
2: Department of Pediatrics I, Medical University Innsbruck, Austria

Email for correspondence: christine.fauth@i-med.ac.at

Haploinsufficiency of *HNRNPK*, which encodes the heterogeneous nuclear ribonucleoprotein K has recently been identified as cause of a multiple malformation syndrome (Au-Kline syndrome, MIM #616580). Major findings include muscular hypotonia, psychomotor developmental delay, intellectual disability, cardiac, urogenital and skeletal abnormalities and a characteristic facial gestalt which shows some overlap with, but is distinct from Kabuki syndrome.

To date, a total of 13 patients with this disorder have been described in the literature. 12 of them have typical loss-of-function variants (9 patients have stop, frameshift or splice mutations in *HNRNPK*, 3 have microdeletions of 9q21.32 including *HNRNPK*) and a single patient carries a *de novo* missense variant in *HNRNPK*. While recurrent clinical features in patients with *HNRNPK* loss-of-function variants already have been delineated, the phenotypic consequences of missense variants still remain to be defined.

We describe a further patient with a de novo missense variant in *HNRNPK* and typical features of Au-Kline syndrome. The girl, who is now 8 years old, has moderate global developmental delay, marked speech delay, muscular hypotonia, cleft palate, a branchial cyst, hydronephrosis, vesicoureteral reflux, uterus duplex, vertebral segmentation anomalies of the cervical spine and facial dysmorphism (long, narrow face, metopic ridging, long palpebral fissures, bilateral ptosis, shallow orbits, full cheeks, accentuated cupid´s bow, down-turned corners of the mouth and dysplastic ears). Based on phenotypic similarities with the patient published by Dentici et al. (2017) Au-Kline syndrome was suspected. Sanger sequencing of the *HNRNPK* gene revealed a previously undescribed *de novo* missense variant c.146T>C [p.(Leu49Pro); NM_0021404]. This variant affects a moderately conserved amino acid (down to Danio rerio), is predicted to be pathogenic by several in silico prediction tools and locates to KH1, the first of three highly conserved K-homology RNA-binding (KH) domains which ensure sequence-specific RNA and DNA binding of HNRNPK.

Our findings suggest that missense variants in *HNRNPK* may lead to the characteristic clinically recognizable phenotype of Au-Kline syndrome.

PARRY-ROMBERG SYNDROME: CLINICAL PRESENTATION IN A CONGOLESE PATIENT

Authors: Gerrye Mubungu[1], Aimé Mupuala[1], Aimé Lumaka[1,2], Koenraad Devriendt[2], Prosper Lukusa Tshilobo[1,2]

1. Centre de Génétique Humaine, Université de Kinshasa, République Démocratique du Congo
2. Centre of Human Genetics, Catholic University of Leuven, Belgium

Email for correspondence: Prosper Lukusa Tshilobo: p.lukusat@gmail.com

Parry-Romberg syndrome is a rare and poorly understood craniofacial disorder occurring in children and young adults and characterized by slow and progressive atrophy, usually unilateral, of facial tissues including muscles, bones and skin. The skin overlying affected areas may present hyperpigmentation or hypopigmentation patches, and facial hair on the affected side may turn white and fall out. Neurologic and ophthalmologic manifestations can also occur. The etiology of this condition is not known. Possible factors that are involved in the pathogenesis are, among others, trauma, viral infections, heredity, endocrine disturbances, and autoimmunity. Females are more commonly affected than males.

The index patient of the present report is a young girl, born at term from healthy unrelated Congolese parents, with weight 3280 g. She was the oldest child of three siblings. Pregnancy and delivery were uneventful. She was referred at age of 11 years to genetic clinics for progressive upper lip narrowing observed since four months on right side. In addition, the parents had observed at the age of 4 years patches of skin hypopigmentation. There was no history of seizures or severe facial pain. On clinic examination, growth parameters were normal: weight 55.4 kg (P95), height 151cm (P75-P90) and head circumference 52cm. We noticed on the right side thinning and narrowing of hemiface, involving jaw, upper lip and chin, and resulting in mild retraction of the angle of the mouth. She presented patches of hypopigmented skin on hemiface and scapula with, additionally, a tuft of hypopigmented frontal hair. The search for antinuclear factor was negative. No additional anomaly was revealed on CT scan.

The main clinical features in this case are similar to those previously observed by our team in a Caucasian patient from Belgium, who presented on the left side hemifacial atrophy, with thinned and narrowed lip and jaw, and hair hypopigmentation. They are also consistent with the classical description of this syndrome in the literature.

The present case represents the first instance of Parry-Romberg syndrome ever reported in a Central African patient. The observed clinical presentation does not show notable differences from the characteristic features reported in the literature. We consider therefore that Parry-Romberg syndrome is a cosmopolite condition with similar clinical presentation in different ethnicities.

PRENATAL DIAGNOSIS OF A FEMORAL FACIAL SYNDROME AND POSTNATAL OUTCOME

Bénédicte DEMEER[1], Julien CHEVREAU[2], Céline KLEIN[3], Emmanuel CLOSSET[4], Cica GBAGUIDI[5], Catherine GONDRY-JOUET[6], Guillaume JEDRASZAK[7], Philippe NAEPELS[2], Jean GONDRY[8]

1. Medical Genetics Unit, CLAD Nord de France, Amiens Picardie University Hospital, France/ EA CHIMERE, Jules Verne University, Amiens, France
2. Prenatal Diagnosis Unit, Camille Desmoulins Maternity Hospital, Amiens Picardie University Hospital, France
3. Department of Pediatric Orthopaedic Surgery, Amiens Picardie University Hospital,France
4. Gynecology and Obstetrics Unit, Saint Quentin Hospital, France
5. Maxillofacial and Stomatology department, Amiens Picardie University Hospital, France
6. Neuroradiology department, Amiens Picardie University Hospital, France
7. Cytogenetics department, Amiens Picardie University Hospital, Amiens, France
8. Prenatal Diagnosis Unit, Camille Desmoulins Maternity Hospital, Amiens Picardie University Hospital, University of Picardie-Jules Verne, Amiens, France

Demeer.benedicte@chu-amiens.fr

We report the case of a 26 month old patient, prenatally suspected of FFS. Family history was unremarkable, except a mother surgery during infancy for right lower limb varus deformity (?). There is neither history of maternal prenatal or gestational diabetes, nor teratogen exposure or infection during pregnancy. The second trimester US assessment showed bilateral femoral hypoplasia, with femoral growth measurement estimated at ¼ of normal rate (10 mm), with bilateral clubfeet .A 29 GW bone CT scan confirmed the extremely poor femoral growth and normal subsequent growth, and showed abnormal sacral vertebrae, sacral deviation, and unusual position of the femoral heads. Array-CGH showed a maternally transmitted 13q31 variant of unknown significance (VUS). He was born at 39 GW; Apgar score was 8/10, BW was 2.550 kg and HW : 36 cm. Lower limb examination confirmed the bilateral femoral hypoplasia and club feet, and showed II,III right syndactyly; upper extremities showed ungueal hypoplasia, V bilateral clinodactyly, III right camptodactyly, and a proximal bilateral insertion of thumbs. Facial gestalt was noted with upslanted palpebral fissures, retrognathia and a posterior cleft palate. At 26 month old, neurological development is considered as normal. He is followed on a regular 2 months basis by the orthopedic team.

Femoral hypoplasia –unusual facies syndrome (femoral facial syndrome, FFS- OMIM 134780),first defined by Daentl et al in 1975 is a rare, sporadic multiple congenital anomaly syndrome comprising bilateral femoral hypoplasia and characteristic facial features. Other features, such as upper extremities and shoulder griddle affection, genitary anomalies, cardiac anomalies and CNS malformations are more variable. The vast majority of cases are sporadic and approximately 1/3 of those with the syndrome are examples of diabetic embryopathy. The genetics basis of this phenotype remains unknown.

Cabezas syndrome: report of 2 patients

Maria Teresa Carminho-Rodrigues[1], Michel Guipponi[1], Christelle Borel[1], Jorge Saraiva[2,3], Marc Abramowicz[1], Margarida Venâncio [2,4], Armand Bottani[1]

[1]Service of Genetic Medicine, Geneva University Hospitals, Geneva, Switzerland; [2]Medical Genetics Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [3]University Clinic of Pediatrics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [4]Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Email for correspondence: mcih@hcuge.ch

Introduction

Cabezas syndrome, first described in 2000, is characterized by intellectual disability (ID), seizures, gait abnormalities, tremor, macrocephaly, short stature, obesity, hypogonadism, and various dysmorphic features. It is an x-linked condition caused by loss of function variants in *CUL4B*. This gene encodes a scaffold protein that organizes a cullin-RING ubiquitin ligase (E3) complex in ubiquitylation.

Clinical Reports

Patient 1 is a 15-year-old boy, 2nd child of non-consanguineous healthy Portuguese parents, who was referred because of severe ID with absent speech, behavioral problems, epilepsy, tremor and ataxia. His height was 166 cm (P30), weight 47.8 kg (P10) and OFC 55 cm (P50). He had peculiar facial features, a marfanoid habitus with joint hyperlaxity, keratosis pilaris and muscular atrophy. A commercial nonspecific 4,813 genes NGS panel (Trusight One, Illumina) was performed. The diagnosis of Cabezas syndrome was established after identification of a *CUL4b* hemizygous variant c.2370dup (p.Arg791*), neither described in the literature nor present in various databases. It is inherited from his healthy carrier mother.

Patient 2 is a 21-year-old male, 2nd child of non-consanguineous healthy parents of Italian and Belgian origin, who was initially referred at the age of 6 months for failure to thrive and subsequently followed over the years for severe with ID and almost absent speech. He also developed intention tremor, but no history of severe behavioral problems or epilepsy. At last physical examination height was 160 cm (P3), weight 55.8 kg (P5), and OFC 59 cm (>P99). Most striking in his face was a macrostomia with upturned corners of the mouth ("Pitt-Hopkins-like"). After many different genetic analyses in the past, exome sequencing and bioinformatic analysis of a panel of 1,066 ID genes finally revealed a hemizygous *de novo* deletion affecting a splice donor site, c.1795+4_1795+7del in *CUL4B*. This variant is neither present in the literature nor in the publicly available databases. RNA studies on a lympoblastoid cell line showed skipping of exon 14 during splicing, leading to a deletion of 35 residues (p.Ala564_Tyr598del).

Discussion

The diagnosis of Cabezas syndrome is very difficult to suspect or make on clinical grounds, as many features such as absent speech, behavior problems, short stature, obesity are non-specific and common to a large number of ID entities. Targeted high throughput NGS in such undiagnosed ID cases plays a crucial role for an appropriate diagnosis, allowing for an accurate genetic counseling and follow-up.

SEVERE PERIPHERAL JOINT LAXITY IS A DISTINCTIVE CLINICAL FEATURE OF *B3GALT6*- AND *B4GALT7*-RELATED DISORDERS

Livia GARAVELLI[1], Ivan IVANOVSKI[1], Marzia POLLAZZON[1], Stefano CARAFFI[1], Maurizia VALLI[2], Antonio ROSSI[2], Belinda CAMPOS-XAVIER[3], Sheila UNGER[3], Andrea SUPERTI-FURGA[3]

1. Medical Genetics Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
2. Department of Biochemistry "Alessandro Castellani", University of Pavia, Italy;
3. Division of Genetic Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland

Email: livia.garavelli@ausl.re.it

Variations in genes encoding the enzymes responsible for the synthesis of the linker region of proteoglycans may result in recessive conditions known as "linkeropathies". In particular, variants in the *B4GALT7* and *B3GALT6* genes are the cause of a combined skeletal and connective tissue phenotype. *B4GALT7* variants cause a typical facial gestalt, short stature, radioulnar synostosis, osteopenia, and joint laxity (OMIM #130070). *B3GALT6* variants cause both spondyloepimetaphyseal dysplasia (SEMD) with joint hypermobility (SEMDJL1 or SEMDJL Beighton type; OMIM #271640) and a severe EDS-like disorder (OMIM #615349). Affected patients generally present clinical features of connective tissue weakness in infancy, and subsequently develop signs of skeletal dysplasia. Some patients develop life-threatening complications, such as an aortic dilatation, aneurysms and cervical spine instability.

We present the clinical features of 3 patients, one with *B4GALT7*-related "progeroid EDS", the second one with a severe *B3GALT6*-related SEMD-JL, and the third one with a *B3GALT6*-suggestive phenotype (molecular analysis ongoing).

Patient 1 had short stature with prenatal onset, rounded face, blue sclera, mild proptosis, myopia, mesomelic short upper limbs, bowed radius and ulna, radio-ulnar synostosis, ulnar deviation of fingers, 2nd finger camptodactyly and clinodactyly, congenital hip dislocation, soft, doughy and hyper-extensible skin, joint hypermobility particularly evident in the hands (Beighton score: 5 points), atrial septal defect and hypotonia. Compound heterozygosity for *B4GALT7* variants c.277_278insC/p.His93Profs*73 (maternally inherited) and c.628C> T, pHis210Tyr (paternally inherited).

Patient 2 had short stature (<<3rd centile), progressive in childhood, high forehead. blue-gray sclera, sparse thin hair, severe scoliosis, osteopenia, hip dysplasia, extreme joint laxity in the hands, with soft and doughy skin, long slender fingers, with ulnar deviation. Feet: toes overlapping, valgus first toe, with recurrent luxations on the left, extremely soft skin with evident venous reticulum. He also had bilateral megaureter, mild dilation of the aortic bulb, mild mitral valve prolapse and development delay. The variants c.925T>A/p.Ser309Thr (maternal) and c.353delA/p.Asp118Alafs*160 (paternal) were identified in the *B3GALT6* gene.

The third patient had short stature (<<3rd centile), progressive in childhood, high forehead, sparse thin hair, light blue-gray sclera, misaligned teeth, severe scoliosis, osteopenia, extreme joint laxity in the hands, with soft and doughy skin, long slender fingers, with slight ulnar deviation. Feet: talipes, hypoplastic toe nails, extremely soft skin with easy bruising. He also had hypotonia and development delay. Molecular analysis is ongoing.

The two phenotypes related to *B4GALT7* and *B3GALT6* are similar, with short stature, hypotonia and joint laxity, skeletal features, and a suggestive face with prominent forehead, thin soft tissue tissue, bulging eyes and often sparse hair. The most outstanding feature is the combination of severe connective tissue involvement accompanied by progressive skeletal dysplasia. The extreme laxity of distal joints and the soft, doughy skin on the hands and feet are rarely seen in other EDS types (except in EDS VIA) and are a good clue to the diagnosis, that can be supported by skeletal radiographs and by molecular analysis. Accurate diagnosis will help in excluding other causes of peripheral hypotonia, such as neuromuscular disorders, and allow for physiotherapeutic interventions.

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LZTR1 a new player in the complex genetic architecture of Noonan syndrome

Martin ZENKER [1] and members & partners of the European Network on Noonan syndrome and related disorders (NSEuroNet)

1: Institute of Human Genetics, University Hospital Magdeburg, Germany

Email for correspondence: martin.zenker@med.ovgu.de

Noonan syndrome is one of the most common monogenic disorders and characterized by distinct craniofacial anomalies, short stature, cardiac anomalies, ectodermal abnormalities and learning difficulties of variable degree. It is caused by mutations in various components or regulators of the RAS-MAPK pathway. More than 15 genes have been found to be mutated in Noonan syndrome and related disorders. LZTR1 is one of the most recently discovered gene for Noonan syndrome (Yamamoto et al., J Med Genet 2015). Following the first description of heterozygous *de novo* mutations in sporadic cases or families with segregation of the mutation and disease in an autosomal dominant manner, it has now become evident that an autosomal recessive form of LZTR1-related Noonan syndrome does also exist (Johnston et al., Genet Med 2018).

We present genotype and phenotype data on a large cohort of patients with LZTR1-related Noonan syndrome collected by our European Consortium. We found that dominant mutations are exclusively missense changes clustering at certain sites of the protein with many of the variants observed in unrelated families being recurrent. Recessive mutations instead are distributed over the entire gene and may also include nonsense, frameshift and splice mutations. It has been proposed that the latter cause loss-of-function, while the dominantly acting changes confer dominant negative effects. Phenotypically, patients with LZTR1 mutations are generally indistinguishable from individuals with Noonan syndrome of other genetic etiologies but very mild clinical expression of the disease was observed in some mutation carriers from families with a dominant inheritance pattern. Hypertrophic cardiomyopathy was present in about half of patients with LZTR1-related Noonan syndrome. Our data suggest that LZTR1 belongs to the five most frequently mutated genes in Noonan syndrome (after PTPN11, SOS1, RAF1, and RIT1). The co-existence of dominant and recessive inheritance as well as the variability in clinical expression make appropriate genetic counseling particularly challenging in LZTR1 mutation-positive families.

Is *RASA2* really associated with RASopathies?

Salima El Chehadeh[1], Hélène Cave[2], Romain Favre[3], Yline Capri[4], Alain Verloes[4].

[1] Service de génétique médicale, Institut de génétique médicale d'Alsace (IGMA), Centre de Référence Maladies Rares «Anomalies du développement et syndromes malformatifs», Centre de Référence Maladies Rares « Des déficiences intellectuelles de causes rares », Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre, Strasbourg, France
[2] Laboratoire de Biologie Moléculaire, Hôpital Robert Debré, Paris, France
[3] Service de gynécologie obstétrique, Hôpitaux universitaires de strasbourg, Strasbourg, France
[4] Service de Génétique Clinique, Hôpital Robert Debré, Paris, France

Corresponding author : salima.elchehadeh@chru-strasbourg.fr

RASopathies or RAS/mitogen-activated protein kinase (MAPK) syndromes, including Noonan syndrome (NS), are a group of phenotypically overlapping syndromes caused by germline mutations that encode components of the RAS/MAPK signaling pathway. Recently, through the use of whole exome sequencing and targeted sequencing of selected genes in cohorts of panel-negative RASopathy patients, novel gene variants, including in *RASA2* (RasGAP protein Ras P21 protein activator), a member of the mammalian RAS-GAP family, have been shown to be associated with RASopathies, further expanding the disease entity. However, the involvement of *RASA2* in NS, which functional role has not yet been fully elucidated, may be questionable because of the description of patients carrying variations of this gene but having a phenotype not suggestive of NS or very mildly. We report on a 1 year-old female patient who presented prenatally with a nuchal translucency, unilateral hydrothorax and an atrioventricular septal defect. She is tall (height + 2 SDS) and has no typical morphological sign of NS currently. Her mother is healthy, tall (height 1.74 m), has an atrial septal defect detected during her pregnancy, and a phenotype mildly suggestive of Noonan-like syndrome. The half-brother of the mother (father side), who is 15-years old, has an atrial septal defect and clinical signs mildly evocative of Noonan-like syndrome but is also very tall (1.97 m), which is atypical in RASopathies' spectrum. The propositus and her mother carry a novel heterozygous variant in *RASA2* (c.1885C>T). The uncle and the grandfather of the propositus, will soon be tested for this variant and heir results will be of importance for its interpretation in this family, which phenotype is not very suggestive of NS.

PIGT-CDG, a disorder of the glycosylphosphatidylinositol anchor: description of thirteen novel patients and expansion of the clinical characteristics.

Allan Bayat [1] Alexej Knaus [2], Elena Gardella [3,4], Usha Kini [5], Rikke S. Møller [3,4]

[1] Department of Pediatrics, University Hospital of Hvidovre, Hvidovre, Denmark.
[2] Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Germany.
[3] Danish Epilepsy Centre, Dianalund, Denmark.
[4] Institute for Regional Health Services Research, University of Southern Denmark, Odense, Denmark.
[5] Department of Clinical Genetics, Oxford University Hospitals NHS Trust, Oxford, United Kingdom.

PIGT-CDG, an autosomal recessive syndromic form of a glycosylphosphatidylinositol biosynthesis defect (GPIBD) with intellectual disability, has been described in several families with epileptic encephalopathy, but the full phenotypic range of this condition and the associated biochemical alterations remain unknown. *PIGT* encodes phosphatidylinositol-glycan biosynthesis class T, a subunit of the heteropentameric transamidase complex that facilitates the transfer of proteins to the GPI anchor. The GPI anchor links proteins to the cell membrane in all tissues.

We describe thirteen novel patients from eight unrelated families with homozygous (NM_015937.5: c.550G>A (p.Glu184Lys), c.709G>C (p.Glu237Gln), and c.1079G>T (p.Gly360Val)) or compound heterozygous (c.494-2A and c.1582G>A (p.Val528Met), c.1472T>A (p.Leu491His) and c.1484+2T>A, and c.1582G>A (p.Val528Met) and c.1730dupC (p.Leu578Thrfs*35)) pathogenic variants in *PIGT* of which three mutations are novel (c.494-2A>G, c.1472T>A (p.Leu491His), and c. 1484+2T>A). All patients had hypotonia, severe global developmental delay and epilepsy. Epilepsy onset ranged from first day of life to two years of age, and the severity of the seizure disorder varied from treatable seizures to severe neonatal onset epileptic encephalopathies. Abnormal body-hair distribution was observed in eight out of the thirteen patients. In addition, congenital fractures were found in one patient. In this study we provide a detailed description of the phenotype of *PIGT*-CDG and expand the known phenotype of this disease. Furthermore, we investigate the onset and severity of the epilepsy determined by the different genetic subtypes. Based on previously reported cases and our novel findings we conclude that the missense variant c.1582G>A seems to be associated with a milder phenotype i.e. treatable epilepsy.

49,XXXXY SYNDROME: THREE EXTRA X CHROMOSOMES LEADING TO THREE CLASSICAL SIGNS: MENTAL RETARDATION, HYPOGONADISM AND RADIOULNAR SYNOSTOSIS

Annet van Hagen[1], *Martijn Bruijn*[2] *and Bart Straver*[3]

1. Department of Clinical Genetics, Amsterdam University Medical Centers, Amsterdam, the Netherlands

2. Department of Pediatrics, Northwest Clinics, Alkmaar, the Netherlands

3. Department of Child Cardiology, Amsterdam University Medical Centers, Amsterdam, the Netherlands

Email for correspondence: a.vanhagen@vumc.nl

49,XXXXY syndrome is a rare sex chromosome aneuploidy occurring in 1:80.000 – 1:100.000 male births. The clinical phenotype is characterized by short stature, facial dysmorphism (hypertelorism, epicanthal folds, upslanting palpebral fissures), microorchidism and micropenis. Congenital malformations associated with 49,XXXXY syndrome are congenital heart malformations, radioulnar synostosis, cleft palate, hip dysplasia and renal dysplasia. The major endocrine issue of this aneuploidy is hypergonadotropic hypogonadism. Developmental delays are common in infancy and early childhood with speech delays (especially in expressive language) present in almost all patients.

The 49,XXXXY syndrome is thought to arise from maternal non-disjunction during both stages of meiosis, retaining the X chromosomes within the oocyte.

The 49,XXXXY syndrome differs from the Klinefelter syndrome (47,XXY) with regards to intelligence quotient (IQ) scores (mean values in patients with 49,XXXY = 20-60 vs 89-102 in patients with 47,XXY) and to the different prevalence of congenital malformations (in 49,XXXXY 50-100%; in 47,XXY + 18%). In fact each additional X chromosome confers a higher risk of congenital malformations.

We present two boys with 49,XXXXY syndrome illustrating the phenotype.

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The (not so) complex genetics of Joubert syndrome

Ian Phelps[1], Jennifer Dempsey[1], Dan Doherty[1], Ruxandra Bachmann-Gagescu[2]

1 Department of Pediatrics, University of Washington, Seattle, USA
2 Institute of Medical Genetics, University of Zurich, Schlieren, Switzerland

Joubert syndrome (JBTS) represents an iconic ciliopathy: while it is defined by a characteristic CNS malformation (the Molar Tooth Sign), 60% of patients display additional typical ciliopathy phenotypes (fibro-cystic renal disease, retinal dystrophy, polydactyly, skeletal dysplasia) in variable combinations, leading to *prominent phenotypic variability*. Moreover, JBTS also illustrates the extremely high *genetic heterogeneity* seen in ciliopathies, with >30 associated causative genes. Together, this phenotypic variability and genetic heterogeneity have led to propose non-Mendelian inheritance mechanisms grouped under the term "oligogenicity" for ciliopathies, including for JBTS.

In this work, we took a systematic approach to evaluate various "oligogenic" scenarios, including digenicity, tri-allelism and genetic modifiers. We analysed one of the largest JBTS cohorts available, comparing the identified variants in known JBTS genes in affected individuals to in-house sequenced controls, to control data from 900 exomes from the UK1958 birth cohort and to large databases such as ExAC.

Based on ExAC allele frequencies, we calculated that the likelihood of harboring rare predicted-deleterious variants (RDVs) in any 2 of 25 JBTS genes is 9%. In accordance with this, we identified RDVs in ≥2 JBTS genes in 4 and 8% of the studied control populations. In fact, the frequency of RDVs in control populations was higher than predicted by Hardy-Weinberg equilibrium based on estimated disease prevalence. Indeed, the distribution/type of RDVs in controls differed significantly from the causal alleles in affected individuals. Nevertheless, we found no recognizable association pattern between combined heterozygous RDVs or genes in affected individuals to support digenicity. We did not identify any unaffected siblings harboring bi-allelic RDVs in one JBTS gene, as would be expected for tri-allelism. Therefore, we found little support for non-Mendelian mechanisms such as digenicity or tri-allelism as clinically relevant inheritance modes in JBTS. On the other hand, we observed high rates of phenotypic discordance even among individuals sharing the same causal alleles, supporting the existence of genetic modifiers. However, the presence of RDVs in JBTS genes in addition to the causal bi-allelic mutations did not correlate with disease severity, illustrating the difficulty in identifying such modifiers.

Conclusion: Joubert syndrome remains a recessive disorder for clinical counselling purposes, even though oligogenicity can only be excluded once the genetic cause has been identified in all affected individuals. Single heterozygous variants in Joubert genes remain of unclear clinical significance and may indicate a second hit in the same gene that was missed. Genetic modifiers likely explain in part the phenotypic variability but their identification remains elusive.

Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders

Annick Vogels*, Griet Van Buggenhout*, Eddy Weyts*, Nathalie Brison*, Greet D'Haenens*, Joris Vermeesch*, Marina Viñas-Jornet**, Neus Baena ** , Susanna Esteba-Castillo**, Elisabeth Gabau**, Núria Ribas-Vidal**, Anna Ruiz**, Ramon Novell**, Miriam Guitart**,André Strydom***, Nick Bass***, Kate Wolfe***, Andrew McQuillin*** and Johan H. Thygesen***

*Department of Human Genetics, Centre for Human Genetics, University Hospitals Leuven, Leuven, Belgium
**Mental Health and Intellectual Disability Specialized Service, Institut Assistència Sanitària (IAS), Parc Hospitalari Martí i Julià, Girona, Spain
***Division of Psychiatry, University College London and Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK
***Division of Psychiatry, University College London, London, UK

Email for correspondence: Annick.Vogels@uzleuven.be

Copy number variations are established risk factors for neurodevelopmental disorders such as intellectual disability, epilepsy and psychiatric disorders including autism, schizophrenia and bipolar disorder. Most studies of CNVs are focussed on single disorder populations and/or pediatric patients. The role of CNVs in adults with intellectual disabilities and psychiatric comorbidities are less well characterised.
The GENMID (GENetics of Mental disorders in Intellectual Disability) consortium is comprised of three primary research groups based in Catalonia, Spain; Leuven, Belgium; and England, UK. A total of 599 adults with intellectual disabilities and one or more comorbid psychiatric diagnoses and/or significant challenging behaviours were recruited.
The aim was to determine: (a) the frequency of known neurodevelopmental disorder risk CNVs compared with large population cohorts including healthy controls, adults with intellectual disability, autism and/or schizophrenia (b) the overal rate of pathogenic CNVs (c) the relationship between pathogenic CNVs, level of intellectual disability and comorbid psychiatric diagnoses and (d) likely pathogenic CNVs affecting neurodevelopmental candidate genes. The yield of pathogenic CNVs was high (13%), Focusing on established neurodevelopmental risk loci we find a significant higher frequency in individuals with intellectual disability and comorbid psychiatric disorder (10%) compared with healthy controls (1.2%), schizophrenia (3.1%) and intellectual disability/autism spectrum disorders (6.5%).
Conclusion: there is a high rate of pathogenic CNVs in adults with intellectual disabilities and comorbid psychiatric disorders. This had clinical implications for the use of genetic investigations in psychiatric and/or intellectually disabled patients.

AUTS2 SYNDROME: A SEVERE CASE ASSOCIATED WITH A NOVEL IN-FRAME DELETION RESTRICTS THE MINIMAL CRITICAL REGION OF THE DISEASE TO A HISTIDINE-RICH MOTIF

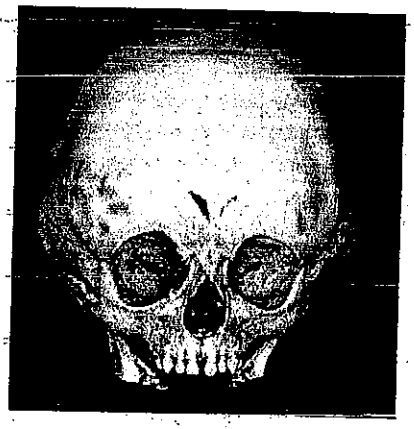
Stefano CARAFFI[1], Ivan IVANOVSKI[1], Edoardo ERRICHIELLO[2], Marzia POLLAZZON[1], Livia GARAVELLI[1], Orsetta ZUFFARDI[2]

1: Medical Genetics Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
2: Department of Molecular Medicine, University of Pavia, Pavia, Italy

Email for correspondence: stefanogiuseppe.caraffi@ausl.re.it

'AUTS2 syndrome' is a rare genetic disease mainly characterized by neurodevelopmental delay with variable ID, dysmorphic facial features, microcephaly, feeding difficulties and behavioral issues (usually autism spectrum disorder). It is caused by heterozygous defects in the *AUTS2* gene (MIM# 607270; location 7q11.22), and has usually been associated with deletions involving a large portion or the entire gene, and more rarely with intragenic loss of function variants.
AUTS2 encodes a component of the Polycomb group multiprotein complex and has a key role in promoting gene expression programs for brain development. While the 5' portion is poorly conserved, the 3' portion has been shown to originate an alternative transcript (exons 9-19) with specific nuclear functions. Accordingly, individuals harboring deletions limited to the proximal exons usually show a milder phenotype.

We report a 4-year-old child with severe ID, delayed psychomotor development, hypotonia, behavioral problems and facial dysmorphism. Speech was highly impaired and he underwent surgery for Chiari type I malformation. Whole exome sequencing revealed a novel, in-frame, *de novo* deletion of 24 base pairs within exon 9 of *AUTS2*: NM_015570.3:c.1603_1626del, NP_056385.1:p.His535_Thr542del. Both clinical and molecular findings were consistent with a diagnosis of AUTS2 syndrome.
Compared to other cases, our patient displayed a severe phenotype, with marked ID, absent language and brain abnormalities at the MRI (Chiari type I malformation and slightly dysmorphic corpus callosum). Notably, head circumference (75^{th}-90^{th} centile) did not entail microcephaly, but CT scan showed a peculiar shape of the skull, with prominent bilateral parietal bossing, craniosynostosis and large anterior fontanelle.



As expected on the basis of the in-frame nature of the variant, mRNA analysis on patient's skin fibroblasts demonstrated a stable mutant transcript, thus not subjected to degradation. According to the literature, our patient carries a unique in-frame variant removing only eight amino acid residues and perturbing a histidine-rich domain, possibly preventing AUTS2 transit or localization within nuclear speckles. Our findings imply this motif may represent the minimal critical region for the full and more severe expression of the AUTS2 syndrome.

DISSECTING TSC2-MUTATED RENAL AND HEPATIC ANGIOMYOLIPOMAS IN AN INDIVIDUAL WITH ARID1B-ASSOCIATED INTELLECTUAL DISABILITY

Bernt Popp[1], Abbas Agaimy[2], Cornelia Kraus[1], Karl X. Knaup[3], Arif B. Ekici[1], Steffen Uebe[1], André Reis[1], Michael Wiesener[3], Christiane Zweier[1]

[1]*Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany*
[2]*Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany*
[3]*Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany*

Email for correspondence: bernt.popp@uk-erlangen.de

Several subunits of the SWI/SNF chromatin remodeling complex are implicated in both cancer and neurodevelopmental disorders (NDD). Though there is no clinical evidence for an increased tumor risk in individuals with NDDs due to germline mutations in most of these genes so far, this has been repeatedly proposed and discussed. A young woman with NDD due to a de novo mutation in *ARID1B* now presented with a large renal (>19 cm in diameter) and multiple hepatic angiomyolipomas (AMLs) but no other signs of tuberous sclerosis.

We analyzed tumor and healthy tissue samples with exome and panel sequencing. Additionally to the previously known, germline *ARID1B* variant we identified a post-zygotic truncating *TSC2* variant in both renal and hepatic AMLs but not in any of the healthy tissues. We did not detect any further, obvious tumor driver events. The identification of a passenger variant in *SIPA1L3* in both AMLs points to a common clonal origin. Metastasis of the renal AML into the liver is unlikely on the basis of discordant histopathological features. Our findings therefore point to very low-grade mosaicism for the *TSC2* variant, possibly in a yet unknown mesenchymal precursor cell that expanded clonally during tumor development. A possible contribution of the germline *ARID1B* variant to the tumorigenesis remains unclear but cannot be excluded given the absence of any other evident tumor drivers in the AMLs.

This unique case highlights the blurred line between tumor genetics and post-zygotic events that can complicate exact molecular diagnoses in patients with rare manifestations. It also demonstrates the relevance of multiple disorders in a single individual, the challenges of detecting low-grade mosaicisms, and the importance of proper diagnosis for treatment and surveillance.

Whole Genome Sequencing identifies a *de novo* 2.1 Mb balanced paracentric inversion disrupting *FOXP1* and leading to severe intellectual disability with autistic features

Marie-Laure VUILLAUME[1,2], Benjamin COGNE[3,4], Médéric JEANNE[1,2], Anne BOLAND[5], Devina UNG[2], Delphine QUINQUIS[3], Thomas BESNARD[3], Jean-François DELEUZE[5], Richard REDON[4], Stéphane BEZIEAU[3,4], Frédéric LAUMONNIER[1,2], Annick TOUTAIN[1,2]

1-Service de Génétique, Centre Hospitalier Universitaire de Tours, France
2-UMR 1253, iBrain, Université de Tours, Inserm, Tours, France
3-Laboratoire de Génétique Moléculaire, Centre Hospitalier Universitaire de Nantes, France
4-CRCINA, Inserm, Université de Nantes, France
5-Centre National de Recherche en Génomique Humaine (CNRGH), Institut de Biologie François Jacob, Direction de La Recherche Fondamentale, CEA, Evry, France

annick.toutain@univ-tours.fr

The FOXP1 gene, located on chromosome 3p13, encodes the Forkhead-box protein P1, one of the four forkhead transcription factors which repress transcription by forming active homo- and heterodimers and regulate distinct patterns of gene expression crucial for embryogenesis and normal development. FOXP1 mutations, mostly truncating, have been described in patients with mild to moderate intellectual disability (ID), autism spectrum disorder (ASD), and speech and language impairment (MIM #613670).

Here, we report a patient with severe ID, ASD, seizures in whom a small de novo heterozygous balanced inversion of 2.1 Mb located at 3p14.1p13 and disrupting the genes FAM19A4 and FOXP1, was identified by Whole Genomic Sequencing (WGS). This patient also had very unusual vascular anomalies which have not been described in the clinical spectrum of FOXP1 mutations.

We show that the neurodevelopmental phenotype observed in the patient most likely results from FOXP1 haploinsufficiency as this heterozygous inversion leads to a 60 to 85 percent decrease of FOXP1 mRNA levels and to the complete absence of FOXP1 full-length protein. The role of FOXP1 haploinsufficiency or of FAM19A4 disruption in the occurrence of the vascular anomalies of the patient remains unsolved at the moment.

In conclusion, this report, in addition to expanding the molecular spectrum of FOXP1 mutations, emphasizes the emerging role of WGS in identifying small balanced chromosomal rearrangements responsible for neurodevelopmental disorders and not detected by conventional cytogenetics.

MULTIPLE DE NOVO MUTATIONS *IN CIS* IN THE DNMT3A GENE IN A BOY WITH TATTON-BROWN SYNDROME

Evelien Van Hoof[1], Anniek Corveleyn[1], Eric Verbeken[2], Maureen Holvoet[1], Koen Devriendt[1]
[1]Center for Human Genetics, [2]Department of Pathology, University Hospital Leuven, KU Leuven, Belgium. Koenraad.devriendt@uzleuven.be

The index is the only child of healthy, unrelated parents. There was one miscarriage. Family history is negative with regard to developmental disorders. At the time of conception, maternal age was 29 yrs, paternal age 30 yrs.

Pregnancy was uneventful, and he was born at gestational age of 38 weeks 6 days. Birth weight was 5090g, length 53cm and head circumference 36.8 cm.
He has congenital interstitial lung disease. A suspected diagnosis of neuro-endocrine cell hyperplasia could not be confirmed on a lung biopsy. He is on nocturnal oxygen supply. There was a small ASDII. His development was delayed, and he was diagnosed with autism spectrum disorder and intellectual disability. He follows special school for children with moderate intellectual disability.

Clinical examination at age 9.5 years revealed weight p90, length p90-97, head circumference p97. The overgrowth syndrome and facial characteristics evoked the diagnosis of DNMT3A-related overgrowth syndrome.

Molecular testing by means of Sanger sequencing and NGS in white blood cells confirmed this diagnosis. He carries a predicted splice mutation 3' of exon 11 (1429+2) in 50% of the reads, predicting a loss-of-function of the gene. A splice defect was demonstrated on mRNA level. In addition, we detected mosaicism for three additional variants in white blood cells: exon 16 Val470Phe (1864G>T) in 30% of the reads, exon 16 Val470Ile (1864G>A) in 15% of the reads and exon 11 Ile622Phe (1408A>T) in 30% of the reads. These variants are absent from the population databases and were not detected in the parents, meaning they arose de novo in the index patient.

We hypothesized that his interstitial lung disease might be related to a biallelic mutation of the DNMT3A gene in a proportion of cells. Mutations analysis in urinary cells, buccal mucosa and DNA extracted from the lung biopsy revealed the same mutations, to the same degree of mosaicism as observed in the white blood cells. mRNA analysis revealed that all variants are in cis, located on the same (paternal) allele.
Given the loss of function effect of the splice mutation, present in all cells, it is unlikely that the phenotype of this boy is influenced by the additional variants, if they should have a functional effect.

However, in the literature, only very few cases are reported with a similar complex pattern of mutations. We will discuss the different possible explanations.

NGS sequencing in prenatal setting: some examples of unexpected variant association

Berardo Rinaldi[1], Valerie Race[2], Anniek Corveleyn[2], Jeroen Breckpot[2], Ellen Denayer[2], Thomy de Ravel[2], Koen Devriendt[2]

1: Katholieke Universiteit Leuven, Leuven, Belgium;
2: Universitair Ziekenhuis Leuven, Leuven, Belgium

Email for correspondence: berardo.rinaldi@student.kuleven.be

Next-generation sequencing (NGS) has considerably incresead the diagnostic yield of individuals with genetic diseases. However, it strongly relies on phenotypical data to reach a correct diagnosis. In such a context fetal pathology remains a great challenge, the foetus being evaluable only by ultrasounds. As physical traits of different syndromes may overlap during fetal life, the research of specific diagnostic handles is rather puzzling. Moreover, the prenatal genotypic variability has not been fully explored yet, making variants interpretation more difficult. A multidisciplinar approach involving gynaecologist, fetal pathologist and radiologist is then recommended to improve the phenotypical description and support data analysis. On the other hand, a gene-driven approach may turn out to be rather efficient when considering the time constraint typical of pregnancy, fertility or newborns with severe distress.

We present a selection of fetal cases firstly referred for ultrasound abnomalities. As first-tier diagnostic mean we performed array-CGH on fetal DNA, which in these families turn out to be normal or not contributive. Whole exome sequencing was then carried out in the trio, considering only variants in OMIM genes. For each family we discuss the results, the pregnancy management and clinical actionability of the findings.

DIAGNOSTIC INVESTIGATIONS USING NEXT GENERATION SEQUENCING: LESSONS LEARNT

Mala ISRIE[1], Gita TAN-SINDHUNATA[1], Annet VAN HAGEN[1], Mariet ELTING[1] and Quinten WAISFISZ[1]

[1] *Department of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands*

Email for correspondence: m.misra@vumc.nl

Within the last decade, the use of next generation sequencing (NGS) has undergone an exponential growth. The current study is meant to highlight a few peculiar cases where the emphasis is put on the combination of NGS data analysis and a thorough clinical genetic examination.

Patient 1 was referred for evaluation of developmental delay and behavioral problems. After routine diagnostics, a whole-exome sequencing (WES) trio analysis revealed no *de novo* pathogenic variants. However, a maternally inherited nonsense variant was identified and ultimately interpreted as the causal variant with reduced penetrance in the mother.

Patient 2 was referred for genetic evaluation of developmental delay, suspicion of seizures and dysmorphic features. The clinical presentation raised the impression of Cornelia de Lange syndrome, but the eventual WES analysis resulted in a completely different diagnosis, with important implications for treatment.

Patient 3 was a pregnant lady with fetal anomalies detected by ultrasound. Routine analysis of amniotic fluid through a SNP-array was normal. Subsequent WES analysis initially yielded no mutations. However, specific re-analysis of the data did reveal the cause of the anomalies, with important consequences for the recurrence risk.

In conclusion, this study confirms the genetic diagnosis in the three cases, but – more importantly – highlights the challenging (re-)interpretation of NGS and clinical data, sometimes leading to rather unexpected results.

SURPRISING TWIST IN A LONG-LASTING UNKNOWN CASE WITH SYNDROMIC PRIMARY MICROCEPHALY

Paranchai Boonsawat, Reza Asadollahi, Pascal Joset, Katharina Steindl, Anita Rauch

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

Email for correspondence: anita.rauch@medgen.uzh.ch

We followed a 15 years old boy with primary microcephaly (-3.9 SDS at birth), cerebellar hypoplasia, progressive bilateral atrophy of optical nerves, growth retardation, moderate intellectual disability, facial anomalies and bilateral hearing loss who developed distal spasticity and steroid resistant focal segmental glomerulosclerosis. A variety of genetic tests including high-resolution chromosomal microarray studies and trio whole exome sequencing did not reveal an obvious disease cause. After observation of a very similar case we were able to diagnose both, although with different disease mechanisms.

FINAL DESTINATION FOR A LONG-LASTING UNKNOWN CASE WITH PEHO-LIKE PHENOTYE

Katharina Steindl, Markus Zweier, Anaïs Begemann, Sorina M. Papuc, Beatrice Oneda, Pascal Joset, Anita Rauch

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

Email for correspondence: steindl@medgen.uzh.ch

This 10.5-year-old female is the only child of healthy unrelated parents. She was born at term after uneventful pregnancy with birth measurements within the normal range. At age 2.5 months she presented with epileptic encephalopathy unresponsive to anticonvulsant treatment. Her cognitive and motor development was severely delayed and she developed quadriplegic hypotonic-ataxic cerebral palsy. Her head growth decelerated and her head circumference was below 3rd percentile at age 10 months. Facial dysmrophism included a round face, sparse eye lashes, deep-set eyes with mildly upslanting palpebral fissures and mild telecanthus, short nose, anteverted nares, short mouth, thin lips, and large ears with attached ear lobes. She had a high and narrow palate, a wide mammillary distance, tapering fingers with joint laxity and edemas of the skull, hand and feet. The initial MRI at age 4 months showed widened subarachnoid spaces bifronto-temporal and was considered to reflect beginning microcephaly. Repeated cranial MRI at the age 5 years showed cerebral and cerebellar atrophy more pronounced than previously. A clinical diagnosis of PEHO syndrome was considered. Chromosomal microarray analysis revealed a de novo 372 kb deletion affecting the coding region of DNM3 in 1q24.3, which was initially classified as VOUS. Recently trio-whole exome sequencing was performed and solved

FOLLOW-UP OF FORMER PRESENTATIONS: LOOKING FOR THE WRONG PATIENTS AND THE WRONG GENE

Emilia BIJLSMA, Laura DONKER KAAT, Arie VAN HAERINGEN, Mariëtte HOFFER, Gijs SANTEN, Claudia RUIVENKAMP

Dept. of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

Email for correspondence: e.k.bijlsma@lumc.nl

In 2011 at this meeting, we called for patients similar to our case of a 12-year old male, referred because of autism spectrum disorder, sleeping problems, dysmorphic features and mild mental retardation. His clinical features were suggestive of Smith-Magenis syndrome. In 2012 we presented him at this meeting as one of three examples of small deletions that pointed to the involvement of (part of) a specific gene. In the two cases this information helped to interpret the clinical problems, in the former case we had high hopes to have found a candidate gene for Smith-Magenis (like) syndrome. However, we could not confirm this finding in other patients and eventually decided to wait for input from next generation sequencing.

Unexpectedly, this case was linked to one of the patients that we presented at this meeting in 2013. That presentation regarded two cases with a non-Kabuki syndrome phenotype in association with missense mutations in exon 48 of the *MLL2* gene, now known as *KMT2D*. The cases were thought to represent a new genetically allelic condition.

Both patients turned out haploinsufficient for the same gene. Two series of patients with mutations in this gene have recently been described. Although the patients share phenotypic features, the diagnosis is probably mainly made after whole exome sequencing. In the past few months, two other patients have been diagnosed in our centre.

CEREBRAL PALSY DUE TO PERIVENTRICULAR LEUKOMALACIA, OR SYNDROMIC?A PATIENT WITH DESMOSTEROLOSIS

S. Demirdas, MD PhD (resident in training)
Clinical Genetics department,
Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands
s.demirdas@erasmusmc.nl

Introduction

Desmosterolosis is an inborn error of metabolism in which desmosterol cannot be degraded due to a deficiency of the enzyme 24-dehydrocholesterol reductase. Desmosterolosis occurs due to mutations in the *DHCR24* gene (1p32.3) encoding 3-beta-hydroxysterol delta-24-reductase. This enzyme catalyzes the conversion of desmosterol (the cholesterol precursor) to cholesterol, which is highly involved in embryonic development and morphogenesis. Reduced enzyme activity leads to the accumulation of desmosterol and a lack of cholesterol, disrupting antenatal and postnatal development. Desmosterolosis presents at birth with growth restriction, spasticity with variable degrees of hand contractures, either microcephaly or relative macrocephaly, facial dysmorphism and microretrognathia. Optic atrophy, corpus callosum agenesis and loss of white matter are frequently noted. To date only 9 patients have been described in medical literature. Here I describe a new case, with a novel homozygous missense mutation in the *DHCR24* gene.

Patient description

Our patient is a 6-year-old girl born from consanginous parents after a full-term pregnancy without perinatal complications and a good start. She presented at our clinic because her mother wondered why her daughter had a short stature. Medical history of the patient showed that at the age of 6 months she was found to have microcephaly (-2 SD) and spasticity of the lower extremities (predominantly of the hamstrings). MRI of the brain at the age of 1 year and 3 months old showed hypoplasia of the corpus callosum, an insufficiently voluminous center semiovale, a wide supratentory ventricular system, irregularly limited ventricular walls and periventricular leukomalacia: this all fits with a diffuse lack of brain matter. At a later age she developed short stature (length -2.3 SD), a valgus position of the right hip (with trouble walking), a psychomotor developmental delay, obesity and strabismus of the left eye. The patient was initially misdiagnosed to have cerebral palsy due to periventricular leukomalacia obtained due to perinatal asphyxia.

Laboratory results

Molecular testing using whole genome sequencing showed a novel homozygous missense mutation in the *DHCR24* gene (c.1424A>G, p. (Tyr475Cys)). Biochemical testing in blood of the patient showed a severe increase in desmosterol: 434 µg/mL (norm 0-7 µg/mL).

Discussion

Our patient was previously diagnosed with cerebral palsy due to perinatal asphyxia. Because antenatal and perinatal history seemed uneventful, and because of several hallmarks of a problem in brain development (hypoplasia of the corpus callosum, white matter loss and microcephaly) we were triggered to perform whole exome sequencing in search of a genetic cause for her phenotype. Cholesterol biosynthesis defects often present with brain malformations and other congenital anomalies. The found novel mutation in the *DHCR24* gene in our patient was proven to be pathogenic using biochemical cholesterol analysis (desmosterol was severely increased) and by matching the phenotype of our patient with the 9 patients reported in medical literature. We were able to both find an explanation for our patients (neurological) phenotype, and to answer the question of the mother as to why her daughter had a short stature. Unfortunately there is no curative therapy for desmosterolosis patients, but genetic counseling was now possible.

UNDETECTED GLYCOGEN STORAGE DISEASE AS A CAUSE FOR SUDDEN DEATH
CASE REPORT AND REVIEW OF THE LITERATURE

Jürgen Kohlhase[1], Encarnacion Nunez Entrena[3], Eva Wohlleber[1]

[1] SYNLAB Center for Human Genetics, Freiburg, Germany

Email for correspondence: jkohlhase@humangenetik-freiburg.de

We report the case of an 8 year old girl, who suddenly died with no obvious cause identified by autopsy. Pregnancy had been unremarkable. At 5 months of age she was hospitalized due to acute respiratory distress syndrome and was found to have muscular hypotonia. Neuropediatric examinations at 7 months lead to the suspicion of a mitochondrial depletion syndrome, but molecular testing revealed no causative mutation. At the age of 6 years, a developmental delay was obvious, especially regarding speech development, but also attention and fine motor skills were affected. She visited school and received continuous help for her learning difficulties. At age 8 years and 3 months, she suddenly collapsed during a family celebration and died. Prior to this event, she had felt weaker than usual, and someone had to carry her bag on the way to school. Since no obvious cause of death had been identified upon autopsy, molecular testing initially focussed on cardiac arrhythmias, but revealed normal results. Consanguinity of the parents prompted us to analyse a clinical exome for homozygous mutations in genes with likely effects on cardiac and muscular function. We detected a homozygous *GYS1* frameshift mutation, which we regard as disease causing in this patient. We will discuss this case with respect to the literature.

AP4B1 MUTATIONS CAN INDUCE HIPPOCAMPAL HYPERSENSITIVITY TO FEBRILE SEIZURES

Lyse Ruaud[1,2], Lopez Nathalie[3], Simon Samaan[4], Sandrine Passemard[1,2,3,4]

[1]Service de Génétique Clinique, CHU Robert Debré, France
[2]Université Paris Descartes, Paris, France
[3]Service de neurologie pédiatrique, CHU Robert Debré, Paris, France,
[4]Service de génétique moléculaire, CHU Robert Debré, Paris, France

Email for correspondence: lyse.ruaud@aphp.fr

The *AP4B1* gene located on chr1p13.2 encodes for a subunit of a heterotetrameric adapter-like complex 4, involved in targeting proteins from the trans-Golgi network to the endosomal-lysosomal system. To date, 25 patients from 19 families were reported with pathogenic homozygous or compound heterozygous variants in *AP4B1*. Psychomotor delay, hypotonia, febrile seizures prior age 1, then progressive hereditary spastic paraplegia with loss of the ability to walk alone after age 4 and ultimately, moderate intellectual disability, are the key features of this rare neurodevelopmental disease. Brain imaging usually shows thin corpus callosum, delayed myelinisation and ventriculomegaly.

Here, we report a boy with an evocative clinical course: severe neurodevelopmental delay, febrile seizures beginning at 9 months of age followed by the occurrence of a spastic paraplegia at age 8. Using multi-gene panel sequencing, we identified a new nonsense homozygote variant c.985A>T (p.Lys329*) in exon 5 of *AP4B1* confirming our clinical diagnosis. Surprisingly, repeated brain MRI showed an obvious bilateral hippocampal mesial sclerosis that appeared between age 4 and 6. Nothing was known about association between *AP4B1* mutation and hippocampal mesial sclerosis. Most reported patients had febrile seizures (12/25 patients), some evolving in partial or generalized tonico-clonic or myoclonic epilepsy. Classical febrile seizures including those associated with Dravet syndrome do not induce hippocampal mesial sclerosis. Up to now, no molecular causes have been related to hippocampal mesial sclerosis. Our patient developed an obvious hippocampal mesial sclerosis over time suggesting a high sensitivity of hippocampus to febrile seizures in a context of *AP4B1* mutation. This suggests that *AP4B1* mutations can induce hippocampal hypersensitivity to febrile seizures and cause hippocampal mesial sclerosis.

WHOLE-EXOME SEQUENCING IDENTIFIES NOVEL CAUSATIVE VARIANTS AND EXPANDS THE PHENOTYPIC SPECTRUM OF PLK4-RELATED PRIMARY MICROCEPHALY

Paolo Zanoni[1], Paranchai Boonsawat[1], Reza Asadollahi[1], Dunja Niedrist[1], Pascal Joset[1], Josef Wisser[2], Herbert Budka[3], Peter K. Bode[4], Heinrich Sticht[5], Katharina Steindl[1], and Anita Rauch[1]

1 Institute of Medical Genetics, University of Zurich, Schlieren-Zurich, Switzerland
2 Department of Obstetrics, University Hospital Zurich, Zurich, Switzerland
3 Institute of Neuropathology, University Hospital Zurich, Zurich, Switzerland
4 Institute of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland
5 Institute of Biochemistry, University of Erlangen-Nuremberg, Erlangen, Germany

Email for correspondence: zanoni@medgen.uzh.ch

Loss-of-function variants in PLK4, encoding a key regulator of centriole duplication, cause autosomal recessive microcephaly and chorioretinopathy 2 (MCCRP2). Currently, only 13 cases from six families have been reported harboring four recessive variants. Following whole-exome sequencing analysis in 61 microcephalic cases, we identified novel causative PLK4 variants in two aborted sib fetuses and an additional unrelated child. In the two fetuses, we found a nonsense variant and a serine substitution in compound heterozygous (CH) state, which the latter likely creates an additional phosphorylation site in the phosphodegron element of PLK4, leading to reduced protein level via accelerated autodestruction. Autopsy examination of the fetuses revealed white matter neuronal heterotopia and cerebellar vermis hypoplasia in one, and absence of corpus callosum in the other, apart from facial dysmorphism and microcephaly. Additional physical anomalies included 2-lobed right lung and accessory spleen, which have not been previously reported in MCCRP2. Furthermore, we identified (likely) pathogenic CH variants in the unrelated child, presenting with primary microcephaly, facial dysmorphism and moderate speech delay. Brain MRI showed simplified cortical gyri, dysplastic corpus callosum, and novel finding of large cerebellum-brain stem relative to the supratentorial region. Considering our cases and those previously reported, we consistently observed simplified gyri, abnormal corpus callosum and neuronal heterotopia, suggesting the importance of PLK4 in the regulation of neuronal migration. Moreover, we report a novel MRI finding as well as additional organ anomalies in MCCRP2, and describe the first deleterious missense variant located in the phosphodegron element outside the main PLK4 domains.

Phenotypic spectrum of SPECC1L pathogenic variants: new families and critical review of the nosology of Teebi and Opitz GBBB syndromes

Alain Verloes[3], Damien Haye[3], Annick Toutain[4], Dominique Bonneau[5], Irene Kibæk Nielsen[6], Ida Bay Lund[6], Pauline Bogaard[7], Stine Leenskjold[8], Kadri Karaer[9], Katherine T Wild[1], Katheryn L Grand[1], Mirena C. Astiazaran[10], Luis A. Gonzalez-Nieto[10], Ana Carvalho[11], Daphné Lehalle[12], Shivarajan M Amuanavalli[13], Elena Repnikova[14], Carol Saunders[14], Isabelle Thiffault[14], Irfan Saadi[15], Dong Li[4], Hakon Hakonarson[2], Yoann Vial[3], Elaine Zackai[1], Patrick Callier[11], Séverine Drunat[3], Elizabeth J. Bhoj[1,2]

1. Department of Genetics, Children's Hospital of Philadelphia; 2.Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA, United States; 3. Department of Genetics, APHP-Robert DEBRE University Hospital, Sorbonne Paris-Cité University, and INSERM UMR 1141, Paris; 4. Bretonneau University Hospital, Tours; 5. Department of Biochemistry and Genetics, and UMR CNRS 6015 INSERM 1083, University Hospital, Angers, France; 6. Department of Clinical Genetics, ;7. Department of Pathology, and 8. Department of Gynecology and Obstetrics, Aalborg University Hospital, Aalborg, Denmark; 9. Dr Ersin Arslan Research and Training Hospital, Department Of Medical Genetics, Gaziantep, Turkey; 10. Genetics Department, Research Unit-Genetics Department, Institute of Ophthalmology, Conde de Valenciana, Mexico City, Mexico.; 11. Clinical Genetics Department, Coimbra Paediatric Hospital, Coimbra PORTUGAL 12. Children University Hospital, Dijon, France; 13. Division of Clinical Genetics, Children's Mercy Hospital, University of Missouri Kansas City, School of Medicine, Kansas City, ; 14. Center for Pediatric Genomic Medicine, Department of Pathology and Laboratory Medicine, Children's Mercy Hospital, University of Missouri Kansas City, School of Medicine, Kansas City, MO, United States; 15. Department of Anatomy and Cell Biology, University of Kansas Medical Center, Kansas City, KS, United States

Email for correspondence: alain.verloes@aphp.fr

The SPECC1L protein plays a role in adherens junctions involved in cell adhesion, actin cytoskeleton organization, microtubule stabilization, spindle organization and cytokinesis. It modulates PI3K-AKT signaling and controls cranial neural crest cell delamination during facial morphogenesis. SPECC1L causative variants were first identified in individuals with oblique facial clefts. Recently, causative variants in SPECC1L were reported in a pedigree reported in 1988 as Opitz GBBB syndrome. Six families with SPECC1L variants have been reported sofar. We report here eight further pedigrees with SPECC1L variants, including a three-generation family, and a further individual of a previously published family.

We discuss the nosology of Teebi and GBBB, and show that SPECC1L syndrome is clinically like Teebi syndrome. Although the phenotype of individuals with SPECC1L mutations shows overlap with Opitz syndrome in its craniofacial anomalies, the canonical laryngeal malformations and male genital anomalies are not observed. Instead, individuals with SPECCL1 variants have branchial fistulae, omphalocele, diaphragmatic hernias, and uterus didelphis. We also point to the clinical overlap of SPECC1L syndrome with mild Baraitser-Winter craniofrontofacial syndrome: they share similar dysmorphic features (wide, short nose with a large tip, cleft lip and palate, blepharoptosis, metopic ridging and retrognathia), although intellectual disability, neuronal migration defect, and muscular problems remain largely specific to Baraitser-Winter syndrome.

In conclusion, we suggest that patients with pathogenic variants in SPECC1L should not be described as "dominant (or type 2) Opitz GBBB syndrome", as they lack certain key features of GBBB, and instead should be referred to as "Teebi or SPECC1L-related syndrome".

A clinical classification for Cutis Laxa syndromes, supported by Electron Microscopy

A. Beyens[1,2], R. De Rycke[3], H. Syryn[1], B. Fischer-Zirnsak[4], T. Van Damme[1], I. Hausser[5], M. De Bruyne[3], M. Morroni[6], S. Nampoothiri[7], K. Mahesh[8], U. Kornak[4], Z. Urban[9], S. Hadj-Rabia[10], C. Bodemer[10], C. Van Ravenswaaij-Arts[11], S. De Schepper[2], E.C. Davis[12], B. Callewaert[1]

1: Center for Medical Genetics Gent, Ghent University Hospital, Belgium; 2: Department of Dermatology, Ghent University Hospital, Belgium; 3: Department of Biomedical Molecular Biology, Ghent University, Belgium, 4: Institute of Medical Genetics and Human Genetics, Charité-Universitätsmedizin, Berlin, Germany, 5: Institute of Pathology, Universitatsklinikum, Heidelberg, Germany, 6: Department of Experimental and Clinical Medicine, Section of Neuroscience and Cell Biology, School of Medicine, Univeristà Politecnica delle Marche and Electron Microscopy Unit, United Hospitals, Ancona, Italy, 7: Department of Pediatric Genetics, Amrita Institute of Medical Sciences and Research Center, Cochin, Kerala, India, 8: Department of Pediatric Cardiology, Amrita Institute of Medical Sciences and Research Center, Cochin, Kerala, India, 9: Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA, 10: Service de Dermatologie, Hopital Universitaire - Necker, Enfants Malades, Paris, France, 11: Department of Genetics, University medical center of Groningen, 12: Department of Anatomy and Cell Biology, McGill University, Montréal, Québec, Canada

Bert.Callewaert@Ugent.be

Background

Cutis laxa (CL) syndromes are a heterogeneous group of multisystem disorders that share a loose, redundant skin as a common feature reflecting elastic fiber (EF) deficiency. The pathogenesis of each of the CL subtypes is different but affects elastogenesis. However, light microscopy of the dermis is non-discriminative and the recently observed vast molecular heterogeneity mitigates the clinical validity and practicality of the current classification, based on the mode of inheritance and systemic involvement.

Aims

We aim to classify the CL subtypes by means of a simple flowchart and to evaluate correlations between EF ultrastructural morphology (as evaluated by transmission electron microscopy) and clinical presentation.

Results

Following literature review, we developed a 7-step flowchart to classify the CL subtypes. As a proof of principle, we systematically evaluated 86 CL patients from our in-house database and could allocate 95% of patients to the right gene. We performed transmission electron microscopy in skin biopsies of all CL subtypes and found discriminative and specific findings that correlate with the main presenting symptoms (emphysema, arterial tortuosity, skeletal defects/mental disability with or without intrauterine growth retardation/cataract). Moreover, EF ultrastuctural morphology reflects the involved molecular pathogenesis and provides new insights in elastic fiber biogenesis.

Conclusion

Our novel nosology of the CL syndromes provides a practical approach to the broad differential diagnosis of CL syndromes. The classification forms a basis to integrate the clinical presentation with the pathogenesis and ultrastructural EF defects and might bode for new management guidelines and therapeutic approaches (Grant Reference BOF01N04516).

KABUKI SYNDROME

Connie Stumpel[1] and Nina Schott[2]

[1] *Department of Clinical Genetics and GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands.*
[2] *Department of Pediatrics, Zuyderland Medical Center, Heerlen, the Netherlands*

Email for correspondence: c.stumpel@mumc.nl

Kabuki syndrome (KS) was first described as a distinct syndrome by Niikawa et al [1981] and Kuroki et al [1981], and has over the course of time become a well-recognized multiple congenital anomaly/intellectual disability syndrome. Hallmarks in clinical recognition in an individual are/were early hypotonia, developmental delay/intellectual disability and facial features with long palpebral fissures and eversion of the lateral lower eyelid.
In 2010 heterozygous pathogenic variants in *KMT2D* (NM_003482.3; previously known as *MLL2*) were reported as a cause of KS. Two years later *KDM6A* (NM_001291415.1) was identified as a second gene.

The Maastricht UMC is recognized national Expertise Center for Kabuki syndrome.

Over the last couple of years part of our research focused on growth and the effect of Growth Hormone (GH) treatment. We studied the linear growth in as much male and female individuals with the syndrome. Postnatal growth retardation was a clinical feature in most cases. Studying the body proportions in KS revealed that these children had larger heads and longer arms proportional to their trunks and longer upper arms proportional to their tibia length and feet. Sitting height versus height was equal to the normal population.

We also looked at growth hormone stimulation tests in relation to the IGF-I values. Twenty-eight percent of the KS children had a lack of GH response, but none of these children had an abnormal IGF-I level. Although, GHD in KS is described in the literature, this seems not to be the main course of the short stature.

The growth response after one-year GH treatment in prepubertal KS children showed an increase in height standard deviation score (SDS) for the whole group from -2.40 to -1.69 ($P<0.05$). The mean IGF-I SDS increased from -0.70 (± 1.07) to 1,41 (± 0.91) ($P<0.05$) after 12 months. These results justified GH treatment in KS children.

Observing the metabolic effects of GH treatment, energy expenditure and body composition was measured. The Total Energy Expenditure (TEE) showed a significant increase ($P<0.01$) already after 6 weeks of treatment. Similar increases were also evident with the fat free mass rising from 15.9 (±6.4) kg to 17.1 (±5.8) kg ($P = 0.01$). Children with a reduced GH secretion during GH stimulation tests had the highest increase in TEE. Concluding, our study shows that GH treatment in KS children significantly improves height, body composition and energy expenditure.

Baseline metabolic profiles demonstrate no cardiometabolic abnormalities in these children. During GH treatment this metabolic profile remained normal and showed positively influences on lipid and (apo)lipoprotein.

We saw no important side effect of the treatment and conclude that the treatment is save.

Follow up studies are pending, and further studies will be continued.

DE NOVO MISSENSE VARIANTS IN *RHOBTB2* CAUSE A DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY IN HUMANS, AND ALTERED LEVELS CAUSE NEUROLOGICAL DEFECTS IN *DROSOPHILA*

Jonas Straub[1], Enrico D.H. Konrad[1], Johanna Grüner[1], Annick Toutain[2], Levinus A. Bok[3], Megan T. Cho[4], Heather P. Crawford[5], Holly Dubbs[6], Ganka Douglas[4], Rebekah Jobling[7], Diana Johnson[8], Bryan Krock[9,10], Mohamad A. Mikati[11], Addie Nesbitt[9], Joost Nicolai[12], Meredith Phillips[5], Annapurna Poduri[13,14], Xilma R. Ortiz-Gonzalez[6,15], Zöe Powis[16], Avni Santani[9,10], Lacey Smith[13], Alexander P.A. Stegmann[17], Constance Stumpel[17], Maaike Vreeburg[17], Deciphering Developmental Disorders Study[18], Anna Fliedner[1], Anne Gregor[1], Heinrich Sticht[19], ChristianeZweier[1]

[1]Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; [2]Service de Génétique, CHU de Tours, Tours, France; [3]Department of Pediatrics, Máxima Medical Center, Veldhoven, the Netherlands; [4]GeneDx, Gaithersburg, USA; [5]Clinical and Metabolic Genetics, Cook Children's Medical Center, Fort Worth, USA; [6]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, USA; [7]Division of Clinical and Metabolic Genetics, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada;
[8]Sheffield Children's Hospital, Sheffield, UK; 9 Division of Genomic Diagnostics, The Children's Hospital of Philadelphia, Philadelphia, USA; [10]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA; [11]Duke University Medical Center, Division of Pediatric Neurology, Durham, USA; [12]Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands; [13]Epilepsy Genetics Program, Department of Neurology, Boston Children's Hospital, Boston, USA; [14]Department of Neurology, Harvard Medical School, Boston, USA; [15]Pereleman School of Medicine, University of Pennsylvania, Philadelphia, USA; [16]Ambry Genetics, Aliso Viejo, USA; [17]Department of Clinical Genetics and School for Oncology & Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands; [18]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK; [19]Institute of Biochemistry, Emil-Fischer Center, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; Email for correspondence: christiane.zweier@uk-erlangen.de

While the role of typical Rho GTPases and other Rho-linked proteins in synaptic plasticity and cognitive function is widely acknowledged, the role of atypical RhoGTPases such as RHOBTB2 in neurodevelopment has barely been characterized.
We now identified de novo missense variants clustering in the BTB-domain encoding region of RHOBTB2 in ten individuals with a developmental and epileptic encephalopathy, characterized by early onset epilepsy, severe intellectual disability, postnatal microcephaly, movement disorders and in several individuals by (post-ictal) hemiparesis and secondary MRI anomalies.
RHOBTB2 interacts with a cullin-dependent ubiquitin ligase complex and thus regulates auto-ubiquitination and recruits other substrates to the complex. Though direct interaction of mutant RHOBTB2 with CUL3 did not appear to be impaired by co-immunoprecipitation, we observed increased levels of mutant RHOBTB2 compared to wildtype 24 hours after transfection of HEK293 cells. Abolishing this effect by adding a proteasome inhibitor indicates decreased degradation of mutant RHOBTB2 in the proteasome, probably due to impaired ubiquitination.
Similarly, elevated levels of the Drosophila ortholog RhoBTB in vivo were associated with seizure susceptibility and severe locomotor defects, while knockdown of RhoBTB resulted in no or only very mild phenotypes. Knockdown of RhoBTB in the Drosophila dendritic arborization neurons, however, resulted in a significantly decreased number of dendrites, thus suggesting a role of RhoBTB in dendritic development.
We establish missense variants in the BTB domain encoding region of RHOBTB2 as causative for a developmental and epileptic encephalopathy and elucidate the role of atypical RhoGTPase RhoBTB in Drosophila neurological function and possibly for dendrite development.

A new homozygous missense mutation in *SLC10A7* involved in syndromic AI

Virginie Laugel-Haushalter[1], Corinne Stoetzel[1], Elise Schaefer[1,2], Yves Alembic[2], Véronique Goeffroy[1], Marie-Cécile Manière[5,6], Hélène Dollfus[1,4], Agnès Bloch-Zupan[3,5,6].

[1]Laboratoire de Génétique Médicale, UMR_S INSERM U1112, IGMA, Université de Strasbourg, Faculté de Médecine, FMTS, Strasbourg, France ; [2]Service de Génétique Médicale, Hôpitaux Universitaires de Strasbourg, Institut Génétique Médicale d'Alsace, Strasbourg, France ; [3]Université de Strasbourg, Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), INSERM U1258, CNRS- UMR7104, Illkirch, France ; [4]Centre de Référence pour les affections rares en génétique ophtalmologique, CARGO, Filière SENSGENE, Hôpitaux Universitaires de Strasbourg, 67091 Strasbourg, France ; [5]Université de Strasbourg, Faculté de Chirurgie Dentaire, Strasbourg, France ; [6]Hôpitaux Universitaires de Strasbourg (HUS), Pôle de Médecine et Chirurgie Bucco-dentaires Hôpital Civil, Centre de référence des maladies rares orales et dentaires, O-Rares, Filière Santé Maladies rares TETE COU, European Reference Network ERN CRANIO, Strasbourg, France.

Email for correspondence: v.haushalter@unistra.fr

Enamel formation requires a complex and sensitive process involving a fine regulation of gene expression, where the mutation in a number of genes can lead to enamel defects. Amelogenesis imperfecta (AI) is a heterogeneous group of rare inherited disease presenting with defects in dental enamel. More than 30 genes have been reported to be involved in AI and new genes are continuously being discovered (Smith et al. 2017). AI can be an isolated finding or occur in association with other clinical anomalies as part of a syndrome. Whole-exome sequencing was performed in a consanguineous family. The affected daughter presented with an intrauterine growth retardation, proportionate dwarfism, macrocephaly, blue sclerae, and hypoplastic AI. We identified a homozygous missense mutation in exon 11 of *SLC10A7* (NM_001300842.2: c.908C> T, p.Pro303Leu) segregating with the disease phenotype. We confirmed by *in situ* hybridization on mouse embryos that *Slc10a7* transcripts were expressed in the epithelial part of the developing tooth, in bones undergoing ossification, and in vertebrae. We show that patient phenotypes could be related to an ectopic calcium distribution in cells. We also demonstrated by western blot analysis that SLC10A7 is overexpressed in patient fibroblasts compared to controls. Splice, stop, and missense mutations in exons 3 and 4 of the *SLC10A7* gene were recently described to cause a similar syndrome mediated by GAG biosynthesis defects, but with a comparatively more severe skeletal phenotype (Ashikov et al., 2018, Dubail et al., 2018) . We reported the case of a patient with the first identified *Slc10a7* missense mutation occurring at the end of the protein. Our results show a milder phenotype compared to previously described syndromic AI when this gene is mutated. In conclusion, those findings are important to highlight that the phenotype resulting from a mutation in *SLC10A7* could vary in severity depending on the type and the position of the mutation. This information will improve diagnosis of patients affected by this syndrome.

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THE FIRST CASE OF PAPILLARY THYROID CARCINOMA IN A PATIENT WITH SYNDROMIC FORM OF PRIMORDIAL DWARFISM

IVANOVSKI Ivan[1], CARAFFI Stefano Giuseppe[1], FRASOLDATI Andrea[2], ROSATO Simonetta[1], MATALONGA Leslie[3], BERNASCONI Sergio[4], GARAVELLI Livia[1]

[1]Medical Genetics Unit, Maternal and Child Health Department, AUSL-IRCCS of Reggio Emilia, Italy [2]Endocrinology Unit, AUSL-IRCCS of Reggio Emilia, Italy [3]CNAG-CRG, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology (BIST), Barcelona, Spain. [4]Pediatric Department, University of Parma, Italy

Email for correspondence: ivan.ivanovski@ausl.re.it

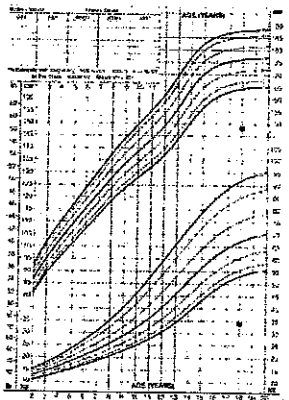
Dr Alsazia M Money (Alsazia – the Italian word for Alsace, former region in Eastern France) is an anagram of a rare form of autosomal recessive microcephalic primordial dwarfism.[1] To date, no more than 15 cases have been reported, the majority of them of Saudi Arabian origin. The condition is characterized by short stature, intellectual disability and distinct dysmorphic facial features (coarse face, short down-slanting palpebral fissures, thick everted lips, micrognathia, and microcephaly). Other reported features include skeletal findings (e.g. scoliosis), involuntary hand movements, hypersensitivity to stimuli and behavioral problems, such as anxiety.

The third child of non-consanguineous Italian parents presented with low birth weight and cryptorchidism. At the age of 9 months, he developed a tremor of the hands and feet, which remains present to date. He presented coarse face, delayed psychomotor development (autonomous walking at 2 years, poorly developed language), intellectual disability, behavioral disturbances and short stature. His final height and weight are well below 3° centile.

At the age of 15 years, he was operated on for papillary thyroid carcinoma (PTC).

Whole exome sequencing and subsequent segregation analysis revealed two variants in compound heterozygosity in the *7PRAL* (anagram!) gene: paternally inherited c.[892_895dupAGCA] p.(Ser299Lysfs*4), and maternally inherited [1087_1091delCATAA](His363Argfs*4). None of the variants have been reported to date.

In accordance with early development of PTC in our patient, a Chinese group recently published an article in which they reported significantly downregulated expression levels of *7PRAL* (anagram!) in a series of PTC tissues and cell lines.[2]



	Litearature	Our patient
Motor developmental delay	14/14	+
ID	14/14	+
Short stature	13/14	+
Microcephaly	7/14	-
Low weight	11/13	+
Facial features		
Triangular face	11/13	+
Prominent forhead	14/14	+
Deep-seated eyes	13/13	+
Narrow palpebral fissures	9/13	-
Sparse eyebrows	10/12	-
Broad nose	14/14	+
Low-set ears	7/13	+
Wide mouth	11/13	+
Full lips	9/13	+
Widely spaced teeth	10/13	+
Malar hypoplasia	11/13	+
Strabismus	4/12	-
Scoliosis	3/12	+

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Participants 29th European Dysmorphology Meeting 2018

Name	First name	E-mail address
BACHMANN-GAGESCU	Ruxandra	Ruxandra.bachmann@imls.uzh.ch
BAYAT	Allan	allan.bayat@regionh.dk
BIJLSMA	Emilia	E.K.Bijlsma@lumc.nl
CALLEWAERT	Bert	Bert.Callewaert@Ugent.be
CARAFFI	Stefano	stefanogiuseppe.caraffi@ausl.re.it
CARMINHO-RODRIGUES	Maria Teresa	mtcarminho@gmail.com
DEMEER	Bénédicte	Demeer.Benedicte@chu-amiens.fr
DEMIRDAS	Serwet	s.demirdas@erasmusmc.nl
DEVRIENDT	Koen	Koen.Devriendt@med.kuleuven.be
DI DONATO	Natalyia	Nataliya.DiDonato@uniklinikum-dresden.de
EL-CHEHADEH	Salima	salima.elchehadeh@chru-strasbourg.fr
FAUTH	Christine	Christine.Fauth@i-med.ac.at
FLEISCHER	Nicole	nicole@fdna.com
GARAVELLI	Livia	livia.garavelli@ausl.re.it
HAUSHALTER	Virginie	v.haushalter@unistra.fr
ISRIE	Mala	m.misra@vumc.nl
IVANOVSKI	Ivan	ivan.ivanovski@asmn.re.it
JEANNE	Mederic	mederic.jeanne@gmail.com
KOHLHASE	Jürgen	jkohlhase@humangenetik-freiburg.de
LUKUSA TSHILOBO	Prosper	p.lukusat@gmail.com
MATULEVICIENE	Ausra	ausra.matuleviciene@mf.vu.lt
MIDRO	Alina	alinamidro@gmail.com
PITON	Amélie	amelie.piton@igbmc.fr
POPP	Bernt	bernt.popp@uk-erlangen.de
RAUCH	Anita	anita.rauch@medgen.uzh.ch
REIJNDERS	Margot	Margot.reijnders@mumc.nl
RINALDI	Berardo	berardo.rinaldi@unimi.it
RUAUD	Lyse	lyse.ruaud@aphp.fr
STEINDL	Katharina	steindl@medgen.uzh.ch
STOLL	Claude	cstoll@unistra.fr
STUMPEL	Connie	c.stumpel@mumc.nl
TOUTAIN	Annick	annick.toutain@univ-tours.fr
VAN HAGEN	Annet	a.vanhagen@vumc.nl
VAN MALDERGEM	Lionel	vmald@hotmail.com
VERGAELEN	Elfi	elfi.vergaelen@upckuleuven.be
VERLOES	Alain	alain.verloes@gmail.com
VOGELS	Annick	Annick.Vogels@uzleuven.be
ZANONI	Paolo	zanoni@medgen.uzh.ch
ZENKER	Martin	martin.zenker@med.ovgu.de

ZWEIER	Christiane	Christiane.Zweier@uk-erlangen.de