TWENTY-SIXTH EUROPEAN MEETING ON DYSMORPHOLOGY

9 – 11 SEPTEMBER 2015
LE BISCHENBERG

26th EUROPEAN MEETING ON DYSMORPHOLOGY

GENERAL PROGRAM

WEDNESDAY 9th SEPTEMBER

5 p.m. to 7.30 p.m.		Registration
7.30 p.m. to 8.30 p.m.		Welcome reception
8.30 p.m.	Dinner	
9.30 p.m.		Unknown

THURSDAY 10th SEPTEMBER

8.15 a.m.		Opening address
8.30 a.m. to 1.00 p.m.		First session
1.00 p.m.	Lunch	
2.30 p.m. to 7.00 p.m.		First and Second sessions
8.00 p.m.	Dinner	
9.00 p.m. to 11.00 p.m.		Unknown

FRIDAY 11th SEPTEMBER

8.30 a.m. to 1.00 p.m.		Second, Third and Fourth sessions
1.00 p.m.	Lunch	
2.30 p.m. to 6.00 p.m.		Fifth, Sixth and seventh sessions
7.30 p.m.	Dinner	

SATURDAY 12th SEPTEMBER

Breakfast – Departure

SCIENTIFIC PROGRAM

Note: This program is tentative and may be modified.

WEDNESDAY 9th SEPTEMBER

9.30 UNKNOWN SESSION
Chair: FRYNS J.P.

L. WOLF
Presentation Face2Gene

PEREZ-AYTES A. AND MARIN-REINA P.
Formal unknown

A. BAYAT
Formal unknown

F. DUIJKERS AND J.M. COBBEN
An unknown syndrome with abnormal laryngeal cartilage rings causing subglottic stenosis

G. MUBUNGU, A. LUMAKA, R. NGIYULU, K. DEVRIENDT, A. CORVELEYN AND P. LUKUSA TSHILOBO
DOOR syndrome: deafness, onychdystrophy, osteodystrophy, and mental retardation

THURSDAY 10th SEPTEMBER

08.15 Opening address: FRYNS J.P.

08.30-11.00 FIRST SESSION: Clinical delineation of known syndromes
Chair: STOLL C.

08.30 C. STOLL, B. DOTT, Y. ALEMBIK AND M.-P. ROTH
Associated congenital anomalies among cases with Down syndrome

08.45 D. LEDERER, V. BENOIT, B. GRISART, S. MOORTGAT, A. DESTREE, C. VERELLE-DUMOULIN AND I. MAYSTADT.
Cohort study of Kabuki syndrome, phenotype comparison of KMT2D and KDM6A mutated patients

09.00 J. BRECKPOT, T. de RAVEL, H. VAN ESCH, J.-Pi. FRYNS AND K. DEVRIENDT
The diagnostic odyssey of Kabuki syndrome: a never ending story?

09.15 R. BACHMANN-GAGESCU, J. DEMPSEY, I. PHELPS, C. ISABELLA, D. O'DAY, B. O'ROAK, J. SHENDURE, I. GLASS AND D. DOHERTY
Genetic architecture and phenotypic range in a large Joubert syndrome cohort

09.30 G. BEUNDERS, J. VD KAMP, P. VASUDEVAN, J. MORTON, K. SMETS, T. KLEEFSTRA, S.A. DE MUNNIK, J.SCHUURS-HOEIJMAKERS, B. CEULEMANS, M. ZOLLINO, S. HOFFJAN, J. SO, L. MERCER, T WALKER, L. VELSHER, M.L PARKE, A.C MAGEE, B. ELFFERS, R. F. KOOY, H.G. YNTEMA, E.J. MEIJERS-HEIJBOER AND E.A. SISTERMANS
A detailed clinical analysis of thirteen patients including six adults with AUTS2 syndrome further delineates the AUTS2 syndrome and underscores the behavioral phenotype

09.45 B. ALBRECHT, H.-J. LÜDECKE, T. STROM, H. ENGELS AND D. WIECZOREK[1]
Macrocephaly, epilepsy, and severe intellectual disability in a patient with compound heterozygous mutations in SZT2 gene

10.00 L. BOMME OUSAGER, C.R. FAGERBERG, H. HOVE, A.O.M. WILKIE AND S.R.F. TWIGG
Acromelic frontonasal dysostosis caused by mutation in ZSWIM6

10.15 C. FAGERBERG, L. KROGH, M. LARSEN, N. ILLUM, M. KIBÆK, L.W. LAULUND, M. ZOLLINO AND C. BRASCH ANDERSEN
MED13L, three cases supporting the variability of the phenotype

10.30 M.C. VAN RIJ, K.B.M. HANSSON, N.M. APPELMAN-DIJKSTRA, M. MERADJI, A.P. ORANJE AND S.G. KANT
Rothmund-Thomson syndrome in a patient formerly published with a clinical diagnosis of COPS syndrome

10.45 B.FISCHER-ZIRNSAK, N. ESCANDE-BEILLARD, J. GANESH, Y. XUAN TAN, M. AL BUGHAILI, I. SAHAI, P. BAHENA, S. CHADWICK, A.LOH, G.D. WRIGHT, J. LIU, E. RAHIKKALA, E. PIVNICK, U. KRÜGER, T. ZEMOJTEL, C. VAN RAVENSWAAIJ-ARTS, R. MOSTAFAVI, I. STOLTE-DIJKSTRA, S. SYMOENS, L. PAJUNEN, L. AL-GAZALI, D. MEIERHOFER, P.N. ROBINSON, S. MUNDLOS, C.E. VILLARROEL, P. BYERS, A. MASRI, S.P. ROBERTSON, U. SCHWARZE, B. CALLEWAERT, B. REVERSADE AND U. KORNAK
De Barsy syndrome revisited

11.00-11.30 *Coffee Break*

11.30-12.30 First SESSION (Continued)
Chair: LACOMBE D. – RAUCH A.

11.30 I. VAN DER BURGT, E. WINGBERMUHLE, R.L. ROELOFS, J.L. EGGER, D.C. VAN TRIER, E.A. CROONEN, R.J. ADMIRAAL AND J.M. DRAAISMA
Results of extensively clinical studies on cognition and hearing in Noonan syndrome

11.45 H. DRIDI, F. GUIMIOT, D. HERON, M. TILL, N. PHILIP, H. DOLLFUS, L. VERA, H. CAVÉ, A. VERLOES AND Y. CAPRI
Noonan syndrome and related disorders associated with coloboma: five case reports and review of literature

12.00 L. GARAVELLI, M. POLLAZZON, I. IVANOVSKI, D. SANTODIROCCO, E. ABDALLA, M. ADAM, S.G. CARAFFI, G. COCCHI, D.M. CORDELLI, G. CUTURILO, R. EPIFANIO, F. FARAVELLI, L. GIORDANO, M. GRASSO, A. IODICE D. LACOMBE, M. MAGGI, B.MALBORA, I. MAMMI, R. PASCARELLA, M.L. POCH OLIVE, F. RIVIERI, S. SAVASTA, A. SELICORNI, B. SOPENA, G. SORGE, L. TARANI, A. TRIMOUILLE, E. VALERA, S. SCHRIER VERGANO, N.

ZANOTTA, M. ZOLLINO, W.B. DOBYNS AND A.PACIORKOWSKI
Neuroimaging findings in Mowat-Wilson syndrome: a study of 30 patients

12.15 S. PASSEMARD, V. EL GHOUZZI, P. GRESSENS, S. DRUNAT AND A. VERLOES
A new case of TUBGCP6 mutation in a child with a MCPH phenotype

AFTERNOON

14.30-16.00 FIRST SESSION (Continued)
Chair: GARAVELLI L. – PEREZ-AYTES A.

14.30 D.P. GERMAIN, J.-B. RIVIERE, I. DABAJ, J. BATAILLE , C. JAUNY, I.E. JURCA-SIMINA, L. FAIVRE AND I. HAEGY
Clove syndrome: a case report

14.45 K. STEINDL, L. GOGOLL, P. JOSET, E. KELLER AND A. RAUCH
A novel family with Kohlschütter-Tönz syndrome

15.00 P.SEGAL AND A. RAAS-ROTHSCHILD
Patients with mucolipidosis iv: what can we learn from the parents? Aa preliminary study

15.15 O. VANAKKER AND B. CALLEWAERT
Four novel patients with tricho-hepato-enteric syndrome: clinical presentation and natural history

15.30 S. ROSATO, I. IVANOVSKI, M. POLLAZZON, D. SANTODIROCCO, M. BELTRAMI, L. GARAVELLI AND F. MALFAIT
MACS (RIN2) syndrome: the first Caucasian patient. evolution of the phenotype over time

15.45 F. DUIJKERS, A.E BROOKS, E. SMEETS, A. VAN HAERINGEN, P. TERHAL AND J.M. COBBEN
Wiedemann-Steiner Syndrome should be clinically recognizable, but apparently it is not

16.00 L. VAN MALDERGEM, M. SIMANDLOVA, J.LESPINASSE, P. STANIER AND S.B SOUSA
PTDSS1-related cutis laxa

16.15-16.45 *Coffee Break*

16.45-18.00 SECOND SESSION: Cytogenetics
Chair: STUMPEL C.- KOHLHASE J.

16.45 A. GONZALEZ-MENESES LÓPEZ.
Confirmation of haploinsufficiency of XPO1 and USP34 as causal genes of specific phenotype in 2p15 deletion syndrome

17.00 A. VOGELS, E. WEYTS, G. VAN BUGGENHOUT, R. CAEYENBERGHS, N. BRISON, L. LEEMPOELS AND G. D'HAENENS
Copy number variatons in intellectually disabled adults with catatonia

17.15 J. ROOSENBOOM, G. HENS, L. LAGAE, P. CLAES, W. DEMAEREL, A. SWILLEN, E. VERGAELEN, J. BRECKPOT, H. PEETERS, P. HAMMOND AND K. DEVRIENDT
Genotype-phenotype correlations in atypical 22q11.2 deletions: the role of TBX1

17.30 M. JEANNE, S. VONWILL, D. HAYE, N. CHELLOUG AND A.TOUTAIN.
A de novo intragenic deletion in *HIRA* (*TUPLE1*) in a patient with a 22q11.2 microdeletion phenotype

18.00 KEY-NOTE LECTURE
J.L. MANDEL
Fragile X syndrome: an overview

21.00-23.00 UNKNOWN
Chair: FRYNS J.P.

FRIDAY 11th SEPTEMBER

08.30-11.00 SECOND SESSION (Continued)
Chair: ALBRECHT B. – VERLOES A.

08.30 B. ALEKSIŪNIENĖ, R. MATULEVIČIŪTĖ, Ž. ČIULADAITĖ, A. MATULEVIČIENĖ, A. UTKUS AND V. KUČINSKAS
Coarctation of aorta with dysmorphic features in a patient with triplication of 15q26.1-q26.3: clinical and molecular analysis

08.45 A.MATULEVIČIENĖ, B. ALEKSIŪNIENĖ, L. TAMULIENĖ, A. LIUBŠYS, ŽI. ČIULADAITĖ, A. UTKUS AND V. KUČINSKAS
A novel de novo dup (4) (q28.2-qter) & del (8) (pter-p23.1) due to unbalanced translocation in a girl: clinical and molecular analysis

09.00 M. DE RADEMAEKER, A. VAN DEN BOGAERT, M. LEYDER , A. VORSSELMANS, K. KEYMOLEN
A case report of a prenatal diagnosis of a complex chromosomal rearrangement: what could be the phenotype?

09.15 Y. SZNAJER, C. BANDELIER, M. RAVOET, J. VERMEESCH, K. JANSSENS, K. VAN DEN BOGAERT, F. KOOY, A. VAN DEN BOGAERT, J. DÉSIR, A. DHEEDENE, J. MUYS, C. STAESSEN, C. VILAIN, K. KEYMOLEN, J.-S. GATOT, B. MENTEN, B. GRISARD, S. ROMBOUT, O. VANAKKER; B. BLAUMEISER, M. DE RADEMAEKER, G. SMITS, A. DE LEENER, B. PICHON, A. DESTREE; T. de RAVEL DE L'ARGENTIÈRE, S. GAILLEZ, J.H. CABERG, N. REVENCU, S. JANSSENS, S. BULK, C. MELOTTE AND K. DEVRIENDT
Evidence from adults with intellectual disability to CNV in prenatal period: how to build penetrance validation and appropriate genetic counselling ? An example with 10q11.22 duplication

09.30 C. FAUTH, B. KRABICHLER, J. ZSCHOCKE AND R. PFUNDT
FETOPLACENTAL discordance for an unbalanced subtelomeric translocation detected by postnatal CNV analysis on exome data

09.45-11.00 THIRD SESSION: New genes

09.45 F. KORTÜM, V. CAPUTO, C.K. BAUER, L. STELLA, A. CIOLFI, M. ALAWI, G. BOCCHINFUSO, E. FLEX, S. PAOLACCI, M.L. DENTICI, P. GRAMMATICO, G.C. KORENKE, V. LEUZZI, D.MOWAT, L.D.V. NAIR, T.T.M.NGUYEN, P. THIERRY, S.M. WHITE, B. DALLAPICCOLA, A.

PIZZUTI, P.M. CAMPEAU, M. TARTAGLIA AND K. KUTSCHE
Mutations in *KCNH1* and *ATP6V1B2* cause Zimmermann-Laband syndrome

10.00 A. TOUTAIN, Y. HUMEAU, D. UNG, M.-P. MOIZARD, N. LEBRUN, J.L CHELLY, G. STEVANIN AND F. LAUMONNIER.
Intellectual disability associated with spastic paraplegia and glaucoma in an Algerian family is caused by a homozygous mutation in *GRID1*, a gene encoding a subunit of glutamate receptor channels

10.15 M. ZENKER, D. SCHANZE, C.. STEVENS, F. BRANCATI, A.T. VULTO-VAN SILFHOUT, A. KARIMINEJAD, V. FERRAZ, N. ROCHE, O. BARTSCH, P. FARNDON, E. BERMEJO-SANCHEZ, L. MAZZANTI, S. MARCHEGIANI, T. DAVIS, M.C.V. MALICDAN, C.F. BOERKOEL, B.B.A. DE VRIES AND M. VAN HAELST
Ablepharon-macrostomia & Barber-Say syndromes and the spectrum of "twistopathies"

10.30 A. RAUCH AND E. BOLTSHAUSER
KDM1A mutations in intellectual disability

10.45 D. LACOMBE, E. LOPEZ, M. BERENGUER, S. MARLIN, A. TINGAUD-SEQUEIRA, S. CHARRON, H. DE BELVALET, G.MATTHIEU, FECLAD, P. BABIN, B. ARVEILER AND C. ROORYCK
A first gene involved in Goldenhar syndrome

11.00-11.30 *Coffee Break*

11.30-13.30 FOURTH SESSION: Skeletal dysplasias
Chair: BIJLSMA E. – BOMME OUSAGER L..

11.30 J.A.N. MEESTER, L. SOUTHGATE, A.-B. STITTRICH, H. VENSELAAR, S.J.A. BEEKMANS, N.E DEN HOLLANDER, E.K. BIJLSMA, A. HELDERMAN-VAN DEN ENDEN, J.B.G.M. VERHEIJ, G. GLUSMAN, J.C. ROACH, A. LEHMAN, M.S. PATEL, B.B.A. DE VRIES, C. RUIVENKAMP, P. ITIN, K. PRESCOTT, S. CLARKE, R. TREMBATH, M. ZENKER, M. SUKALO, L. VAN LAER, B. LOEYS AND W. WUYTS [1]
Heterozygous loss-of-function mutations in a new gene for Adams-Oliver syndrome

11.45 H. BUCIEK HOVE, M. DUNØ, J. DAUGAARD-JENSEN AND S. KREIBORG
Transmission of the P250R mutation of the FGFR3 gene in four generations with highly variable phenotype variable phenotype

12.00 M.T. BONATI, M. CRIPPA, S. GIANGIOBBE, C. SCACCABAROZZI, L. FATTI, F. BELLINI, L. LARIZZA, L. PERSANI AND P. FINELLI
A balanced reciprocal translocation t(10;15)(q22.3;q26.1) interrupting ACAN gene in a family with idiopathic short stature: further delineation of the aggrecan-associated phenotypes

12.15 A.T.MIDRO, K. KOZŁOWSKI E.HUBERT, J.BORYS, E. HASMANN-POZNAŃSKA E. TARASÓW, J. SKOWRONSKI, M. RYDZANICZ, A.POLLAK, P. STAWIŃSKi, B. STASIEWICZ-JAROCKA AND R. PLOSKI[7]
Progression of clinical and morphological features in man with Hajdu-Cheney syndrome during 23 years of observation

12.30 L. MACKENROTH, P. LORENZ, N. DI DONATO, A. RUMP AND A. TZSCHACH
A patient with geleophysic dysplasia-plus phenotype due to novel mutations in *ADAMTSL2*

12.45 D. HAYE, C. COLLET AND A. TOUTAIN
Camurati-Engelmann disease with torus palatinus: coincidence or clinical overlap with Worth hyperostosis ?

AFTERNOON

14.30-16.00 FIFTH SESSION: Clinical syndromology
Chair: MIDRO A. – RAAS-ROTHSCHILD A.

14.30 A. LUMAKA, N. COSMANS, A. LULEBO MAMPASI, H. PEETERS, M. HOLVOET, P. LUKUSA TSHILOBO AND K.DEVRIENDT
Detection of facial dysmorphism in Central African patients

14.45 Á. MARTÍN-RODRÍGUEZ, E.J. GARCÍA, L. CASTAÑO, A. AGUAYO AND A. GONZÁLEZ-MENESES.
Fetal Warfarin syndrome and hyperinsulinism: a possible phenotypic expansion?

15.00 K. KEYMOLEN, M. DERADEMAEKER, D. HASAERTS AND S. SENECA
When a common syndrome presents in a less common way

15.15-16.15 SIXTH SESSION: Genomics in the clinic

15.15 C. ZWEIER, K. KOCHINKE, B. NIJHOF, Mi. FENCKOVA, P. CIZEK, F. HONTI, S. KEERTHIKUMAR, M.A.W. OORTVELD, T. KLEEFSTRA, J.M. KRAMER, C. WEBBER, M.A. HUYNEN AND A. SCHENCK
SYSID: a systematic approach to the genetic and clinical heterogeneity of intellectual disability disorders

15.30 A. VERLOES, S. PASSEMARD, S. DRUNAT, C. DUPONT, M. OUACHEE, E.A CUADRO AND R. KOM
Unraveling unusual presentations of classical syndromes by exome sequencing: the case of primary microcephaly

15.45 B M. HEMPEL, T. DIEHL, M. BLOOM, P. DEINDL, E. MAHLER, T.B. HAACK, C. KUBISCH, T.M. STROM, D. LESSEL
Exome and genome analysis in Neonatal and Paediatric Intensive Care Units – the Hamburg experience

16.00 C. STUMPEL AND MANY COLLEGUES IN MAASTRICHT AND NIJMEGEN
The genome era: a clinical perspective

16.15-16.45 *Coffee Break*

16.45-18.30 SEVENTH SESSION: Reverse phenotyping: mutation first
Chair: DEVRIENDT K.. – ZENKER M.

16.45 B. DEMEER, A. DADBAN, P. VABRES, G. MORIN , B. ARAL, A. VARENTERGHEM, J. THEVENON, D. BREMOND-GIGNAC, J. ST-ONGE, J. RIVIÈRE, J. COURCET, C. THAUVIN AND L. FAIVRE;
Reverse phenotyping of a patient with CRIPT gene mutation and further delineation of the associated phenotype

17.00 J. KOHLHASE, T. NEUMANN, M. BRAUNER AND M. FEDORCAK
A novel mutation in *WDR45* in a girl with developmental delay, loss of speech and motor skills

17.15 M. MIGUET, J. THEVENON, V.LAUGEL, A. BOURCHANY, J.-B. RIVIERE, E. SCHAEFER, M.C. ANTAL, R. ABIDA, M. LEFEBVRE, A.-S. WEINGERTNER, V. KREMER, C. THAUVIN-ROBINET, P. VABRES, F.MORICE-PICARD, M.GONZALES, D. LIPSKER, S. FRAITAG, J.L. MANDEL, H. DOLLFUS, L. FAIVRE, N. CALMELS AND S. EL CHEHADEH[1].
Fetal whole exome sequencing identifies mutations in the ERCC2(XPD) gene associated with severe congenital ichthyosis and dysmorphic features

17.30 J. HENDRIKSEN, E. SMEETS, H. VLES
Neurocognitive profile in atypical *MECP2* related Rett syndrome

17.45 L. SPRUIJT, A. VERRIPS, E.J. KAMSTEEG, C. MARCELIS
HMSN Type IIc and scoliosis in patients with a TRV4-gene mutation

FORMAL UNKNOWN

A. PEREZ-AYTES AND M. REINA

Dysmorphology and Reproductive Genetics Unit, University Hospital La Fe. Valencia, Spain.

E-mail for correspondence: aperezaytes@gmail.com

C.D.S. is a 5-year-old boy. Mother 36 year old; father 36 year old, non-consanguineous Spanish couple. A healthy brother 2 year old.
Uneventful pregnancy. Delivery at 41 weeks gestation. Birth weight: 3.620 gm
At birth: Hypoplastic/dysplastic kidneys, right pre-auricular tag, hypospadias.
Evaluated for the first time in Dysmorphology clinic at 2 year old:

- Weight: 13.500 gm (50 centile) Height: 83 cm (25 centile) OFC: 43 cm (< 3 centile)
- Microcephaly. Large, normal ears (pre-auricular tag extirpated); bilateral clinodactyly of 5th finger; absence of distal interphalangeal crease in 3th-4th fingers; limitation to elbows extension. Obesity. Hypospadias. Ocular refractive defect (needs glasses). Mild speech delay, good motor skills. Is an expressive child
- Ocular fundus exam: Normal
- Cardiac echography: normal
- Array-CGH (Agilent, 70 kb range resolution): normal
- Brain MRI: No malformations
- X-ray: Hypoplastic middle phalangies 5th fingers; radial luxation

Physical examination for minimal dysmorphic features, and abdominal echography, both parents: Normal
Follow-up: Perthes disease. Chronic renal failure (Renal transplant at 4½ year old). Formal development evaluation IQ: 75. He assist normal school with special support for speech
Ay 5 year old: Weight: 16.500 gm (50 centile) Height: 103 cm (10 centile) OFC: 45.5 cm (< 3 centile)
In summary:

- Microcephaly
- Hypoplastic/dysplastic kidneys (Renal failure)
- Hypospadias
- Right pre-auricular tag
- Radial luxation
- Hypoplastic middle phalangies 5th fingers
- Absence interphalangeal crease 3-4 fingers
- Very mild developmental delay

Myopia

FORMAL UNKNOWN

A. BAYAT

Department of Clinical Genetics, Rigshospitalet, University Hospital of Copenhagen, Denmark.

Gender and age of the patient
12-year-old girl
Family history
The second-born child of healthy, non-consanguineous parents of Caucasian extraction.
Pregnancy, delivery and neonatal period
Pregnancy was normal, GA 37 weeks.
BW 3010 g, length around 50-52 cm, full Apgar scores.
Development
She started to walk about 1 year of age, has always had weakness and other complaints from the musculo-skeletal system. Contractures of the hips and hands were first described at the age 8.
Global cognitive development is normal.
Growth parameters in percentiles or standard deviations
Bone age at 6 ½ years was advanced to 7.10 years.
Length +4 SD (tall parents: mother 173 cm, father 198 cm).
Weight +3.2 SD (53 kg.
Vision and hearing
Normal hearing.
Abnormal vision: hypermetropia.
Dysmorphic features
Tall stature, long extremities.
Pectus excavatum.
Truncal obesity.
Distal contractures that progress.
Scoliosis possibly due to anisomelia.
Abnormal external ears.
Beighton score 0/9, normal skin.
Neuromuscular
Slightly reduced muscle strength.
When attempting to smile, she grimaces (but doesn't look like crying).
Perhaps positive Gowers sign.
Normal investigations
Due to suspicion of rheumatic disease relevant blood tests were done (hematology, HLA-B27, acute-phase reactants).
Normal creatine kinase.
Normal echocardiography.
Normal array.
Normal *FBN1, TGFBR1, TGFB2, SMAD3, MYH11 and ACTA2.*
SHOX gene: two copies.
De novo heterozygous mutation in *FBN2.*
Suggested diagnosis
Beals contractural arachnodactyly syndrome.

AN UNKNOWN SYNDROME WITH ABNORMAL LARYNGEAL CARTILAGE RINGS CAUSING SUBGLOTTIC STENOSIS.

F. DUIJKERS[1] AND J.M. COBBEN[1]

[1] Clinical Genetics and Pediatrics, AMC, the Netherlands.

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E-mail for correspondence: f.a.duijkers@amc.nl

History: This case concerns a preterm boy (G.C.) with multiple dysmorphic features and stridor causing breathing difficulties a few weeks after birth. Prenatal ultrasound did not show abnormalities. T.E. has a subglottic stenosis that is probably caused by plate-like laryngeal cartilage rings (laryngoscopy). A tracheostomy tube was needed for breathing support.
Family history: The mother also had a stridor from birth and had a tracheostomy tube from 8 to 14 months of age, because of aberrant subglottic cartilage rings. She had a cliteromegaly, clubfoot, clinodactyly of the 5th toe and a severe pectus excavatum. She developed a combined perceptive and conduction hearing loss and has a short stature (height 152 cm) and normal intelligence. No other affected family-members are known. No consanguinity.
Physical examination: Normal growth parameters. T.E. has. telecanthus, mild retrognatia, downslanted palpebral fissures, cryptorchism and a mild hypospadia.
Additional investigations: x-thorax: hypoplastic left 5th rib. DNA-diagnostics showed a normal DNA-profile (46,XY) by CGH-array and no mutations in the MID1-gene and 14 Noonan syndrome genes.
Discussion: This case represents a mother and son with a severe congenital subglottic stenosis probably caused by aberrant cartilage rings. We considered Aarskog syndrome and skeletal dysplasia syndromes, but did not perform additional diagnostics yet because of the low probability of these syndromes being the cause of the problems in this boy and his mother.
Conclusion: Unknown syndrome with congenital subglottic stenosis, probably fitting autosomal dominant inheritance.

DOOR SYNDROME: DEAFNESS, ONYCHDYSTROPHY, OSTEODYSTROPHY, AND MENTAL RETARDATION

G. MUBUNGU[1,2,3], A. LUMAKA[1,2,3,4], R. NGIYULU[1], K. DEVRIENDT[4], A. CORVELEYN[4] AND P. LUKUSA TSHILOBO[1,2,3,4].

[1] Département de Pédiatrie, Faculté de Médecine, Université de Kinshasa, RD Congo.
[2] Centre de Génétique Humaine, Faculté de Médecine, Université de Kinshasa, RD Congo.
[3] Institut National de Recherche Biomédicale, DR Congo.
[4] Center for Human Genetics, Catholic University of Leuven, Belgium.

We present a 20-month-old female infant referred to our genetics clinic for assessment of developmental delay and dysmorphism. She was the only child of young and unrelated parents and was born at term following an uneventful pregnancy with a birth weight of 3 kg. From the age of 5 months on, she was followed in paediatrics. At the age of 10 months, she was still hypotonic and could not sit without support.

On clinical examination at 20 months, we noticed microcephaly with somewhat depressed forehead, bitemporal narrowing, wide nasal bridge, bulbous nasal tip, hypertelorism, long philtrum, thick upper and lower lip vermilions, high-arched palate, cupped ears, short neck with redundant skin, widely spaced nipples, umbilical hernia, relatively short distal phalanges with hypoplastic nails, especially on the 4th and 5th toes and the 4th and 5th fingers. She was unresponsive to voice and hand clapping. Radiograph of the skull revealed a craniosynostosis.

These clinical findings strongly mimicked the DOOR syndrome, an acronym standing for Deafness, Onychodystrophy, Osteodystrophy, and mental Retardation (OMIM 220500). Recently, pathogenic mutations have been identified in *TBC1D24* among DOOR patients. We extracted DNA in Kinshasa and Sanger sequenced the TBC1D24 gene in Leuven. Unfortunately we did not identify a good candidate causal mutation.

Thus, no definite diagnosis could be reached so far. Nevertheless, the presence of the main clinical features of DOOR syndrome in the present patient is highly suggestive of genetic heterogeneity in DOOR syndrome. On the other hand, different additional physical features were noted in the present patient, suggesting the possibility for alternative diagnoses.

Keywords: deafness, onychodystrophy, osteodystrophy, developmental delay, TBC1D24 gene.

ASSOCIATED CONGENITAL ANOMALIES AMONG CASES WITH DOWN SYNDROME

C. STOLL[1], B. DOTT[1], Y. ALEMBIK[1] AND M.-P. ROTH[1]

[1] Laboratoire de Genetique Medicale, Faculte de Medecine, Strasbourg, France.

E-mail for correspondence: cstoll@unistra.fr

Down syndrome (DS), the most common congenital anomaly, is widely studied since at least 150 years. However, the type and the frequency of congenital anomalies associated with DS are still controversial. Despite prenatal diagnosis and elective termination of pregnancy for fetal anomalies, in Europe, from 2008 to 2012 the live birth prevalence of DS per 10,000 was 10, 2. The objectives of this study were to examine the major congenital anomalies occurring in infants and fetuses with Down syndrome.

The material for this study came from 402,532 consecutive pregnancies of known outcome registered by our registry of congenital anomalies between 1979 and 2008. Four hundred sixty seven (64%) out of the 728 cases with DS registered had at least one major associated anomaly. The most common associated anomalies were cardiac anomalies, 323 cases (44%), followed by digestive system anomalies, 42 cases (6%), musculoskeletal system anomalies, 35 cases (5%), urinary system anomalies, 28 cases (4%), respiratory system anomalies, 13 cases (2%), and other system anomalies, 26 cases (3.6%). The most common cardiac anomaly was atrioventricular septal defect (30%) followed by ventricular septal defect (22%), patent ductus arteriosus (5%), coarctation of aorta (5%), and tetralogy of Fallot (3%). Forty two (6%) of the cases had a digestive system anomaly recorded, duodenal atresia (67%), Hirschsprung disease (14%), and tracheo-esophageal atresia (10%) being the most common. Fourteen (2%) of the Down syndrome patients had an obstructive anomaly of the renal pelvis, including hydronephrosis. The other most common associated anomalies were syndactyly, polydactyly, club foot, cataract, hydrocephaly, cleft palate, hypospadias and diaphragmatic hernia.

Many studies to assess associated anomalies in DS have reported various results. There is no agreement in the literature as to which associated anomalies are most common in cases with DS and associated anomalies. In this study we observed a higher percentage of associated anomalies than in the other reported series as well as an increase in the frequency of duodenal atresia, urinary obstructive anomalies, musculoskeletal system anomalies, and lung anomalies, and a decrease in the frequency of anal atresia, annular pancreas, and limb reduction defects.

In conclusion, we observed a striking prevalence of total congenital anomalies and specific patterns of malformations associated with Down syndrome which emphasizes the need to evaluate all patients with Down syndrome for possible associated major congenital anomalies.

COHORT STUDY OF KABUKI SYNDROME, PHENOTYPE COMPARISON OF KMT2D AND KDM6A MUTATED PATIENTS

D. LEDERER, V. BENOIT, B. GRISART, S. MOORTGAT, A. DESTREE, C. VERELLE-DUMOULIN AND I. MAYSTADT.

Centre de Génétique Humaine, IPG, Gosselies, Belgium.

Kabuki syndrome was first described in 1981. The five cardinal features of the syndrome are characteristic face, skeletal anomalies, unusual dermatoglyphic patterns, mild to moderate intellectual deficiency and postnatal growth retardation. In 2010, KMT2D (previously MLL2) mutations were found in 9 patients with clinical diagnosis of Kabuki syndrome. Since the discovery of KMT2D, 9 cohort of patients with Kabuki syndrome were published and a KMT2D mutation was found in 34-76% of patients. In 2012, genic and exonic deletions of KDM6A were found in three patients. A role for KDM6A in Kabuki syndrome was then confirmed by four studies.
Since 2012, we have collected 212 patients with a clinical suspicion of Kabuki syndrome. We found a mutation in KMT2D in 64 of them for a diagnostic yield of 30%, probably closer to a clinical routine. Clinical data were available for 54 patients and confirmed the cardinal features of Kabuki syndrome. Feeding difficulties were present in 75% of infants but BMI study showed that they tend to be overweighed after 8 years old. Palate abnormalities, hearing loss, cardiac malformations and recurrent infections were common. A phenotypic association study showed that congenital malformation (cleft palate and cardiac defect) are often associated and are part of a more severe phenotype.
Including our cohort, 444 mutations in KMT2D were described. Truncating and splice mutations are scattered along the gene and missense mutations occur recurrently in few hotspots in or outside protein functional domains.
Among our cohort, we found 11 mutations in KDM6A (5%). In total, 20 patients were reported with a mutation in KDM6A. Clinically, boys are more severely affected but some girls present with a severe phenotype. Typically, patients with KDM6A mutations present with developmental delay, short stature, microcephaly, feeding difficulties, hypotonia, hyperlaxity, hirsutism and congenital heart defect. The face is less typical and large superior incisors were seen in some patients. Chronic hyperinsulinism was reported in 4 patients. Even though not statistically significant, some features were more frequent in patients with KDM6A mutations, such as growth retardation, microcephaly and hirsutism. On the other hand, cleft palate and uro-genital malformations were more frequent in individuals with KMT2D mutations.

THE DIAGNOSTIC ODYSSEY OF KABUKI SYNDROME: A NEVER ENDING STORY?

J. BRECKPOT[1], T. DE RAVEL[1], H. VAN ESCH[1], J.-P. FRYNS[1] AND K. DEVRIENDT[1]

[1] Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium.

E-mail for correspondence: Jeroen.Breckpot@uzleuven.be

Kabuki syndrome (KS) is diagnosed clinically based on the facial gestalt, featuring long palpebral fissures with ectropion of the lateral third of the lower eyelids, arched eyebrows and a depressed nasal tip, in association with short stature, intellectual disability, brachydactyly and/or visceral abnormalities, including heart and urogenital defects. Since the first reports on Kabuki syndrome by Niikawa and Kuroki in 1981, genetic studies were launched to unravel its etiology, from conventional karyotyping over array CGH to genome-wide sequencing efforts. Two causative genes have been identified so far: *KMT2D* (previously called *MLL2*) and *KDM6A*, encoding a H3K4-specific methyl transferase and a H3K27 demethylase, respectively.
Here, we review on the diagnostic odyssey in 20 patients, who were clinically diagnosed with Kabuki syndrome in our center. The age of clinical diagnosis ranged from 2 weeks to 13 years (median 16 months). Clinical diagnosis of KS is challenging in the first months of life because the phenotype tends to evolve over time and characteristic facial features become more evident during childhood. Pathogenic *KMT2D* mutations (8 frame shift or truncating mutations and 2 *de novo* missense mutations) were found in 10 patients (50%). In addition, one *KMT2D*-negative KS patient with hyperinsulinemic hypoglycemia was found to carry a *de novo* truncating mutation in *KDM6A*. Few clinical differences exist between *KMT2D* positive and negative patients within the cohort, advocating that KS is a genetic heterogeneous disorder with more genes remain to be discovered. Interestingly, we recently detected a *de novo* 264 kb deletion on 9q21.32 in a mutation negative patient with typical features of Kabuki syndrome. Future high throughput sequencing studies in large cohorts of mutation negative KS patients will clarify whether genes within this region are recurrently affected by mutations in Kabuki syndrome patients, and will aid to further untangle the genetic etiology of KS.

GENETIC ARCHITECTURE AND PHENOTYPIC RANGE IN A LARGE JOUBERT SYNDROME COHORT

R. BACHMANN-GAGESCU[1,2], J. DEMPSEY[3], I. PHELPS[3], C. ISABELLA[3], D. O'DAY[3], B. O'ROAK[4], J. SHENDURE[4], I. GLASS[3] AND D. DOHERTY[3]

[1] Institute of Medical Genetics,
[2] Institute for Molecular Life Sciences, University of Zurich, Switzerland;
[3] Dept of Pediatrics,
[4] Dept of Genome Sciences, University of Washington, Seattle, USA

E-mail for correspondence: ruxandra.bachmann@imls.uzh.ch

Background: Joubert syndrome (JS) is a ciliopathy characterized by a distinctive hindbrain malformation (the Molar Tooth Sign), ataxia and cognitive dysfunction. Like most ciliopathies, JS displays prominent genetic heterogeneity and phenotypic variability. The purpose of this work is to provide comprehensive sequencing data for all known JS genes, a description of the phenotypic range and extensive gene-phenotype correlations in a large JS cohort.
Methods: Phenotypic data was analyzed for 532 individuals from the University of Washington JS cohort. All 28 known JS genes were sequenced in 429 individuals (364 families) using the MIPs capture technique and next-generation sequencing.
Results: Core JS diagnostic features (hypotonia, ataxia, cognitive dysfunction, oculo-motor apraxia) are present in >80% of individuals, while abnormal breathing pattern is reported in 60%. Frequently associated features include retinal dystrophy (31.4%), renal disease (20.9%), coloboma (17.7%), polydactyly (15.3%), liver fibrosis (15.2%) and encephalocele (8%). Liver fibrosis and coloboma are strongly associated with each other (Odds Ratio 7.0, 95% Confidence Interval=3.0-13.2), while retinal dystrophy - renal disease (O.R. 2.2, 95% C.I. = 1.7-5.6), encephalocele - polydactyly (O.R. 2.8, 95% C.I. = 1.03-7.8) and liver fibrosis - renal disease (O.R. 3, 95% C.I.=1.6-5.5) are weakly associated. While some associations are consistent with previously described JS sub-types, we observed all possible combinations of features such that no clear-cut distinction between subtypes is observed. Multiple additional clinical features reported by families include other brain abnormalities (n=73), seizures (n=49), cleft palate (n=16), hearing loss (n=14) and psychiatric problems (n=45). The genetic cause can be identified in 62% of families, with 5 genes accounting for the majority of patients (*C5ORF42, CEP290, CC2D2A, AHI1*, *TMEM67)*. We observe statistically significant differences in mutation-patterns between commonly mutated genes: while individuals with causal mutations in *CC2D2A*, *TMEM67* or *INPP5E* harbor a majority of missense mutations, those with mutations in *CEP290* or *CSPP1* harbor mainly truncating mutations. Bi-allelic causal mutations in *B9D2* and *C2CD3* are present in 2 families each, while the new JS gene *KIAA0586/TALPID3* is mutated in 9 families. Bi-allelic mutations in 2 different genes are present in 5 families, without an obvious effect on disease severity, and heterozygous mutations (in addition to the causal mutation) are observed in 62 individuals. The most strongly significant ($p<0.0001$) gene-phenotype correlations observed are *CEP290* with renal disease/retinal dystrophy and *TMEM67* with liver fibrosis/coloboma. In addition, we identified several weaker positive and negative associations.
Conclusion: This work gives a relatively unbiased snapshot of the genetic make-up and phenotypic range of JS, providing essential information to guide medical monitoring and variant interpretation.

A DETAILED CLINICAL ANALYSIS OF THIRTEEN PATIENTS INCLUDING SIX ADULTS WITH AUTS2 SYNDROME FURTHER DELINEATES THE AUTS2 SYNDROME AND UNDERSCORES THE BEHAVIORAL PHENOTYPE

G. BEUNDERS[1], J. VD KAMP[1], P. VASUDEVAN[2], J. MORTON[3], K. SMETS[4], T. KLEEFSTRA[5], S.A. DE MUNNIK[5], J. SCHUURS-HOEIJMAKERS[5], B. CEULEMANS[6], M. ZOLLINO[7], S. HOFFJAN[8], J. SO[9], L. MERCER[9], T. WALKER[9], L. VELSHER[9], M. PARKE[10], A.C MAGEE[11], B. ELFFERS[12], R.F. KOOY[13], H.G. YNTEMA[5], E.J. MEIJERS-HEIJBOER[1] AND E.A. SISTERMANS[1]

[1] Department of Clinical Genetics, VU University Medical Center Amsterdam, the Netherlands.
[2] Department of Clinical Genetics, University Hospitals of Leicester, Leicester, UK.
[3] Department of Clinical Genetics, Birmingham Women's Hospital, Edgbaston, Birmingham, UK.
[4] Department of Neurology, University and University Hospital Antwerp, Antwerp, Belgium.
[5] Department of Human Genetics, Radboud university medical centre, Nijmegen, The Netherlands.
[6] Department of Neurology- Paediatric Neurology, University Hospital Antwerp, Antwerp, Belgium.
[7] Department of Medical genetics, Cattolica del Sacro Cuore University, Policlinico A. Gemelli, Rome, Italy.
[8] Department of Human Genetics, Ruhr University Bochum, Bochum, Germany.
[9] Department of clinical genetics, Thunder Bay District health unit, Thunder Bay, USA.
[10] Department of Clinical Genetics, Sheffield Children's Hospital, Sheffield, UK.
[11] Department of Clinical Genetics, Belfast city hospital trust, Belfast, UK.
[12] Department of Medical care for patients with intellectual disability, AMSTA, Amsterdam, The Netherlands.
[13] Department of Medical Genetics, University and University Hospital Antwerp, Antwerp, Belgium.

E-mail for correspondence: g.beunders@vumc.nl

Background: AUTS2 syndrome is an 'Intellectual Disability syndrome' caused by genomic rearrangements, deletions, intragenic duplications or mutations causing disruption of the *AUTS2* sequence. So far 47 Patients with AUTS2 syndrome where described, but clinical data are limited and almost all cases concern young children. This hampers counseling parents about the prognosis and treatment options of (young) children diagnosed with AUTS2 syndrome.
Methods: Here we present a detailed clinical description of seventeen patients that where systematically evaluated by one clinical geneticist. Thirteen patients (including six adults) with AUTS2 syndrome have a pathogenic mutation or deletion in *AUTS2*. In addition we describe four patients with clinical features consistent with AUTS2 syndrome and a (de novo) variant of unknown significance in *AUTS2*.
Results: All patients have Intellectual disability or developmental delay, ranging from borderline to severe. Microcephaly and feeding difficulties are seen in 80-90%. Congenital malformations are rare, but mild heart defects, contractures and genital malformations do occur. There are no major health issues in the adults, the oldest of which is now 59 years of age. A friendly outgoing character marks the behavior. Specific features of autism are seen frequently, like stereotypic movement and obsessive behavior. A relatively mild clinical phenotype is associated with small in frame 5' deletions, which are often inherited. Deletions and mutations causing haploinsufficiency of the full length AUTS2 transcript give a more severe phenotype and occur all *de novo*.
Conclusion: All together these thirteen AUTS2 syndrome patients confirm a phenotype-genotype correlation whereas in frame 5'deletions cause a less severe and les specific phenotype. Despite individual variations, AUTS2 syndrome emerges as a specific ID syndrome with microcephaly, feeding difficulties, dysmorphic features and a specific behavioural phenotype.

MACROCEPHALY, EPILEPSY, AND SEVERE INTELLECTUAL DISABILITY IN A PATIENT WITH COMPOUND HETEROZYGOUS MUTATIONS IN *SZT2* GENE

B ALBRECHT[1], H-J LÜDECKE[1], T STROM[2], H ENGELS[3] AND DWIECZOREK[1]

[1] *Institut für Humangenetik, Universitätsklinikum Essen, Universität Duisburg Essen, Germany.*
[2] *Institut für Humangenetik, Helmholtz Zentrum Münchren, Germany.*
[3.] *Institut für Humangenetik, Biomedizinisches Zentrum Universitätsklinikum Bonn, Germany.*

We report on a family included in a trio exome sequencing study performed on 250 patients with intellectual disability.
The 15 year old boy is the first and only child of healthy, non-consanguineous German parents, born at term after a pregnancy complicated by uterus myomatosus and gestosis. Birth measurements were normal but green amniotic fluid was noted. The boy walked independently with 2 ½ years and never learned to speak and he is not toilet trained. Seizures started with 4 years of age and could be treated effectively. Agitated behavior and autistic features needed medication. Brain MRI revealed reduced temporal gyri on the left. The patient attends a special school and behaves like a toddler. Body measurements were normal throughout life, but head circumference was above the 97th. The patient has a high and broad forehead, prominent lips and small hands and feet.
Trio exome sequencing revealed a maternally inherited frame-shift mutation (c.841delC, p.(Gly281Ser*fs**33)) and a paternally inherited missense mutation in *SZT2* gene (c.9787G>A, p.(Asp3263Asn)). The possibly damaging missense mutation may retain some residual protein function and cause a milder phenotype resembling the three brothers described by Falcone *et al* (2013). Patients with homozygous or compound heterozygous truncating mutations as described by Basel-Vanagaite *et a*l (2013) show severe infantile encephalopathy with epilepsy. This sixth patient broadens the phenotypic spectrum caused by mutations in *SZT2* gene showing an intermediate clinical course compared to the patients published to date.

ACROMELIC FRONTONASAL DYSOSTOSIS CAUSED BY MUTATION IN ZSWIM6

L. BOMME OUSAGER[1], C.R. FAGERBERG[1], H. HOVE[2], A.O.M. WILKIE[3] AND S.R.F. TWIGG[3]

[1] Department of Clinical Genetics, Odense University Hospital, Odense, Denmark
[2] Department of Clinical Genetics, Rigshospitalet, Copenhagen, Denmark
[3] Clinical Genetics Group, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, United Kingdom

E-mail for correspondence: lilian.bomme.ousager@rsyd.dk

We present 2 unrelated cases of acromelic frontonasal dysostosis (AFND):
Case 1: A boy, aged 6 years, with obvious features of AFND detected prenatally. He was born at GA 32 and had severe symmetric frontonasal dysplasia with median cleft face, carp-shaped mouth, widely spaced nasal alae and severe hypertelorism. His hands were normal, but he had bilateral tibial hemimelia and bifid 1st toe. His neurocognitive and motor development was delayed. MRI of the cerebrum showed an interhemispheric lipoma and partial agenesis of the corpus callosum.
His mother had a similar but much milder phenotype with hypertelorism, bifid nose, and normal intellectual development. This is accordance with autosomal dominant inheritance with significant variability in expression, possibly caused by mosaicism.
Case 2: A female fetus with abnormalities detected at GA 19 +3. Ultrasound examination revealed bilateral club foot and a facial malformation with orbital hypertelorism and a broad glabella. The foetus had an abnormal flat forehead and aplasia/hypoplasia of the nasal bone. The pregnancy was terminated at GA: 20. Postnatally the clinical features of AFND were seen with frontonasal malformation of the face including nasal clefting/bifid nose and hypertelorism. The fetus had bilateral tibial hypoplasia. No polydactyly was seen. No other family members had similar abnormalities.
In 2014 Smith *et al*. performed whole-exome sequencing in 3 unrelated patients with AFND and identified a *de novo* missense mutation in *ZSWIM6* (c. 3487C>T, p.Arg1163Trp) in all three patients. In a fourth patient, with a milder phenotype, a 60:40 ratio of wild-type to mutant allele was seen, suggestive of mosaicism.
We performed mutation analysis of samples from our two probands and found both to be heterozygous for the identical mutation in *ZSWIM6* as reported previously. Sanger sequencing of blood samples from the parents only revealed the wild-type allele in both cases.
As the mother of case 1 had a mild phenotype of AFND we suspected mosaicism. Therefore, we collected additional samples from her (saliva, two buccal swabs, skin biopsy and urine sediment) and performed Sanger sequencing. A suggestion of a low level of mutant allele within the buccal samples prompted us to perform Ion Torrent-based deep sequencing of *ZSWIM6* to explore this further. The results of these analyses will be presented at the meeting.

MED13L, THREE CASES SUPPORTING THE VARIABILITY OF THE PHENOTYPE

C. FAGERBERG[1], L. KROGH[1], M. LARSEN[1], N. ILLUM[2], M. KIBÆK[2], L.W. LAULUND, M. ZOLLINO[3] AND C. BRASCH ANDERSEN[1]

[1] Department of Clinical Genetics, Odense University Hospital, Denmark; [2]Department of Pediatrics, Odense University Hospital, Denmark; [3]Istituto di Genetica Medica, Università Cattolica Sacro Cuore, Roma, Italy.

E-mail for correspondence: christina.fagerberg@rsyd.dk

In the last few years several reports on patients with mutations in MED13L has been published revealing a very broad spectrum of phenotypes including mental retardation, severe language delay, dysmorphic features, heart defects, and skeletal anomalies.
We report three new patients with aberrations in MED13L and review the literature so far.

ROTHMUND-THOMSON SYNDROME IN A PATIENT FORMERLY PUBLISHED WITH A CLINICAL DIAGNOSIS OF COPS SYNDROME

M.C. VAN RIJ[1], K.B.M. HANSSON[1], N.M. APPELMAN-DIJKSTRA[2], M. MERADJI[3], A.P. ORANJE[4] AND S.G. KANT[1]

1 Department of Clinical Genetics, Leiden University Medical Centre
2 Department of Endocrinology, Leiden University Medical Centre
3 Dept of Radiology, Erasmus University Hospital Rotterdam and Sophia Children's Hospital Rotterdam
4 Pediatric dermatologist, Huid.nl, Rotterdam, and Dermicis Skin Hospital Alkmaar, The Netherlands.

E-mail for correspondence: m.c.vanrij@lumc.nl

Rothmund-Thomson syndrome is a dermatogenetic syndrome characterised by poikiloderma, sparse hair, skeletal abnormalities and an increased risk of developing osteosarcoma. We present a patient who was previously reported with the diagnosis COPS syndrome: calcinosis cutis, osteoma cutis, poikiloderma and skeletal abnormalities.
Recently, this 34 year old patient was referred to the clinical genetic department for treatment of osteoporosis. Both the patient, and his brother are now diagnosed with Rothmund-Thomson syndrome. The diagnosis was confirmed by compound heterozygous mutations in the RECQL4 gene. Our case is the first patient with Rothmund-Thomson syndrome presenting with osteoma cutis. Additionally, both our patient and his brother have a mild developmental delay which is only rarely reported in association with Rothmund-Thomson syndrome.

DE BARSY SYNDROME REVISITED

B. FISCHER-ZIRNSAK[1,2,], N. ESCANDE-BEILLARD[3,*], J. GANESH[4], Y.X. TAN[3], M. AL BUGHAILI[1], I.L SAHAI[5], P. BAHENA[6], S. CHADWICK[4], A. LOH[7], G.D. WRIGHT[3], J.LIU[3], E. RAHIKKALA[8], E. PIVNICK[9], U. KRÜGER[1], T. ZEMOJTEL[1,10], C. VAN RAVENSWAAIJ-ARTS[11], R. MOSTAFAVI[9], I. STOLTE-DIJKSTRA[11], S. SYMOENS[12], L. PAJUNEN[8], L.H AL-GAZALI[13], D. MEIERHOFER[14], P.N. ROBINSON[1,2,15], S. MUNDLOS[1,2,15], C.E. VILLARROEL[6], P. BYERS[16], A. MASRI[17], S.P. ROBERTSON[18], U. SCHWARZE[19], B. CALLEWAERT[12,&], B. REVERSADE[3,20,&] AND U. KORNAK[1,2,15,&]*

* These authors contributed equally to this work
& These authors contributed equally to this work

1 Institut fuer Medizinische Genetik und Humangenetik, Charité-Universitaetsmedizin Berlin., Augustenburger Platz 1, 13353 Berlin, Germany.
2 Max-Planck-Institut fuer Molekulare Genetik, FG Development & Disease, Ihnestr. 63-73, 14195 Berlin, Germany.
3. Institute of Medical Biology, A*STAR, Singapore, Singapore.
4 Children's Hospital of Philadelphia, United States.
5 Mass General Hospital for Children, Boston, United States.
6 Departamento de Genética Humana, Instituto Nacional de Pediatría, Mexico City, Mexico.
7 Institute of Molecular and Cellular Biology, A*STAR, Singapore, Singapore.
8 Department of Clinical Genetics, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland.
9. Division of Medical Genetics, Department of Pediatrics, University of Tennessee; Memphis, United States.
10 Labor-Berlin, Berlin, Germany.
11 Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.
12 Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium.
13 United Arab Emirates University, Faculty of Medicine and Health Sciences, Departments of Pediatrics (L.A.), Pathology (B.A.A.) and Radiology (R.L.), Al Ain, United Arab Emirates.
14 Max-Planck-Institut fuer Molekulare Genetik, Mass-Spectrometry facility, Ihnestr. 63-73, 14195 Berlin, Germany.
15 Berlin-Brandenburg Center for Regenerative Therapies, Charité-Universitaetsmedizin Berlin, Germany.
16 Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, Washington, United States.
17 Department of Pediatrics, Faculty of Medicine, University of Jordan, Amman, Jordan.
18 Department of Women's and Children's Health, University of Otago, Dunedin, New Zealand.
19 Department of Pathology, University of Washington, Seattle, Washington, United States.
20 Department of Paediatrics, National University of Singapore, Singapore

E-mail for correspondence: Bert.Callewaert@Ugent.be

In 1968, de Barsy and colleagues described a novel syndrome characterized by 'dwarfism, oligophrenia and degeneration of the elastic tissue in skin and cornea'. Nowadays, progeroid disorders overlapping with De Barsy syndrome (DBS) are collectively denoted as autosomal recessive cutis laxa type 3 (ARCL3). They are caused by biallelic mutations in *ALDH18A1*, encoding pyrroline-5-carboxylate synthase (P5CS), or in *PYCR1* (pyrroline-5-carboxylate reductase 1), respectively, which both operate in the mitochondrial proline cycle.
We report here on eight unrelated individuals born to non-consanguineous families clinically diagnosed with DBS. We found three heterozygous mutations in the *ALDH18A1* gene leading to missense mutations of the same highly conserved residue p.Arg138 in P5CS. A *de novo* origin was confirmed in all six probands for whom parental DNA was available. All patients presented with a typical facial gestalt (triangular face, prominent low-set ears, and cataract or corneal clouding), a thin, translucent skin, postnatal growth retardation and a delayed neuromotor development. Though hypotonia and joint hyperlaxity were universally present in early childhood, some patients developed brisk peripheral reflexes. Interestingly, several patients showed intracerebral arterial tortuosity on MRI.

Further analyses on fibroblasts indicated that the P5CS-R138W protein was stable and able to interact with wild type P5CS. The PC5S mutant complex, however, showed an altered structure or composition as well as a different sub-mitochondrial distribution. Furthermore, enzymatic function was reduced leading to lower proline synthesis rates, which may account for observed alterations in collagen synthesis.

In summary, recurrent *de novo* mutations of the highly conserved p.Arg138 residue of P5CS cause a novel autosomal dominant form of cutis laxa with progeroid features that more closely recapitulated the initial description by de Barsy. Our data provide novel insights into the etiology of cutis laxa diseases and advice to be cautious in counseling these disorders without molecular confirmation of the genetic defects.

RESULTS OF EXTENSIVELY CLINICAL STUDIES ON COGNITION AND HEARING IN NOONAN SYNDROME

I. VAN DER BURGT[1], E. WINGBERMUHLE[2], R.L. ROELOFS[2], J.L. EGGER[2], D.C. VAN TRIER[3], E.A. CROONEN[3], R.J. ADMIRAAL[4] AND J.M. DRAAISMA[3]

1 Department of Human Genetics, Radboudumc, Nijmegen,
2 Vincent van Gogh Institute of Psychiatry, Venray,
3 Department of Paediatrics, Radboudumc, Nijmegen,
4 Department of Othorhinolaryngology, Head and Neck surgery, Radboudumc, Nijmegen, The Netherlands.

E-mail for correspondence: ineke.vanderburgt@radboudumc.nl

Noonan syndrome (NS) is a genetic disorder characterised by short stature, facial dysmorphia and congenital heart defects. Mildly lowered intellectual abilities are reported and also frequently some hearing abnormalities. We present the results of two studies, one on the cognitive functioning in adults with NS, and one on the hearing impairment and external ear anomalies in persons with NS.
We present the first study in which functioning within the major cognitive domains is systematically evaluated in a group of 42 adults with NS and compared with a control group. The age of the included patients ranged from 16 to 61 (mean=30.67, SD = 13.38; 24 females). The education level ranged from 2 (only primary school completed) to 7 (academic degree), according to the Dutch educational system (see Duits & Kessels 2006). With respect to genetic subtypes, 22 patients had a confirmed mutation in the PTPN11 gene, five in SOS1, one in KRAS and one in SHOC2. In seven patients, no known mutation could be found and in six patients, mutation analyses had not been performed or completed. On the domain speed of information processing patients performed worse than controls ($P < 0.05$). Furthermore, none of the other cognitive domains showed between-group differences. On the questionnaires, patients reported substantially more complaints about their own cognitive abilities than controls ($P < 0.05$). A lowered speed of information processing and relatively intact functioning in other cognitive domains characterises the cognitive profile of adult NS patients, in contrast to previous findings in children with NS, who seem to have more generalised cognitive deficits.
The second study is the first cohort in which hearing impairment and external ear anomalies in Noonan Syndrome are described extensively. Retrospective analysis of the otorhinolaryngological and clinical genetic data from 97 Noonan Syndrome (NS) patients are presented. Forty-four NS patients were seen by an otorhinolaryngologist for the analysis of hearing impairment. In our cohort 80 of the 97 patients were genetically tested. In 71 of these mutations were found: in 48 patients a mutation in PTPN11, in 10 patients in SOS1, in 5 patients in SHOC2, in 5 patients in RAF1, in 1 patient in MAP2K2, in 1 patient in KRAS and in 1 patient in A2ML1. External ear anomalies were reported in 75 NS patients (77%). In 69 patients the ears were low-set, 28 patients had posteriorly rotated ears, 14 patients showed protruding ears and 18 had thickened helices. Hearing impairment was detected in 34 NS patients. Nine patients had sensorineural hearing impairment, two a permanent conductive hearing impairment, two other patients had mixed hearing impairment and 20 patients had conductive hearing impairment in the past, caused by otitis media with effusion. Their temporary conductive hearing impairment resolved between the ages of 2 and 18 years. Sensorineural hearing impairment varied between mild high-frequency hearing impairment and profound (uni- and bilateral) hearing impairment and was progressive in three patients. Four NS patients received cochlear implants for their severe sensorineural hearing impairment. The cohort is small for genotype-phenotype correlations, but sensorineural hearing impairment, especially the bilateral severe hearing impairment, was only seen in patients with a PTPN11 mutation.

NOONAN SYNDROME AND RELATED DISORDERS ASSOCIATED WITH COLOBOMA: FIVE CASE REPORTS AND REVIEW OF LITERATURE

H. DRIDI[1], F. GUIMIOT[2, 3], D. HERON[4], M. TILL[5], N. PHILIP[6], H. DOLLFUS[7,8], L. VERA[9], H. CAVÉ[1], A. VERLOES[1,3] AND Y. CAPRI[1]

[1] Department of Genetics, AP-HP, Robert-Debré Hospital, 48 boulevard Sérurier Paris 75019, France.
[2] Service de Biologie du Développement, AP-HP, Hôpital Robert Debré, 48 boulevard Sérurier Paris 75019, France.
[3] Paris VII, Paris Diderot university, INSERM UMR1141, France.
[4] Medical Genetics Unit, AP-HP, Pitié-Salpêtrière University Hospital, 47 boulevard de l'Hôpital, 75013 Paris, France.
[5] Service de Cytogénétique Constitutionnelle, Hospices Civils de Lyon, CBPE, Bron Cedex, France.
[6] Department of Medical Genetics, AP-HM and University of Mediterranee, Timone Children's Hospital, Marseille, France.
[7] Laboratoire de Génétique Médicale EA3949 Inserm Avenir, Université de Strasbourg, Strasbourg, France.
[8] Service de Génétique Médicale, Centre de Référence pour les Affections Rares en Génétique Ophtalmologique (CARGO), Hôpitaux Universitaires de Strasbourg, Strasbourg, France.
[9] Service d'ophtalmologie pédiatrique, AP-HP, Hôpital Robert Debré, 48 Boulevard Sérurier, Paris 75019 France.

E-mail for correspondence: yline.capri@aphp.fr

Noonan syndrome (NS) is a multiple congenital malformation disease whose incidence is evaluated from 1/1000 to 1/2500 living births, quite frequent among the rare diseases. Characteristic features are short stature, facial dysmorphism, heart defects and cryptorchidism. Orthopedic, renal malformations, development delay and intellectual disability are also observed. Eyes complications are less described but very common since 95% of patients with NS displayed at list one or more ophthalmologic findings. Most of those findings are external features belonging to the characteristic facial dysmorphism of NS (hypertelorism, ptosis, down slanting palpebral fissures and epicanthic folds). Strabismus and refractive errors (myopia, hypermetropia and astigmatism) are also frequent. Fundus changes are reported less frequently. Few cases of iris and/or optic disc coloboma in patients with NS or related disorders have been described since 1987. Only one study focused on eye abnormalities in NS had found coloboma in 4%. None of the previously NS cases with coloboma was confirmed by molecular analysis.
We describe 5 new cases of NS (or related disorders) with iris and/or optic disc coloboma and review the 10 previously reporter cases. Elevated incidence of NS could let thought this association would be fortuitous but the 2 familial cases (one family previously reported and one new family) may suggest that coloboma is a rare complication of Rasopathy.

NEUROIMAGING FINDINGS IN MOWAT-WILSON SYNDROME: A STUDY OF 30 PATIENTS

L. GARAVELLI[1], M. POLLAZZON[1], I. IVANOVSKI[1], D. SANTODIROCCO[1], E. ABDALLA[2], M. ADAM[3], S.G. CARAFFI[4], G. COCCHI[5], D.M. CORDELLI[6], G. CUTURILO[7,8], R. EPIFANIO[9], F. FARAVELLI[10], L. GIORDANO[11], M. GRASSO[12], A. IODICE[13], D. LACOMBE[14,15], M. MAGGI[16], B. MALBORA[17], I. MAMMI[18], R. PASCARELLA[16], M.L. POCH OLIVE[19], F. RIVIERI[20], S. SAVASTA[21], A. SELICORNI[22], B. SOPENA[23], G. SORGE[24], L. TARANI[25], A. TRIMOUILLE[14], E. VALERA[26], S. SCHRIER VERGANO[27,28], N. ZANOTTA[9], M. ZOLLINO[29], W.B. DOBYNS[30,31] AND A. PACIORKOWSKI[32,33,34,35]

E-mail for correspondence: livia.garavelli@asmn.re.it

1 Clinical genetics Unit, Department of Obstetrics and Pediatrics, IRCCS S. Maria Nuova Hospital, Reggio Emilia, Italy.
2 Department of Human Genetics Medical Research Institute University of Alexandria Alexandria, Egypt
3 Division of Genetic Medicine, University of Washington School of Medicine, Seattle, Washington, USA.
4 Laboratory of Translational Research, IRCCS S. Maria Nuova Hospital, Reggio Emilia, Italy.
5 Neonatology Unit, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.
6 Child Neurology and Psychiatry Unit, S Orsola Malpighi Hospital, University of Bologna, Italy.
7 Faculty of Medicine, University of Belgrade, Belgrade, Serbia.
8 Department of Medical Genetics, University Children's Hospital, Belgrade, Serbia.
9 Clinical Neurophysiology Unit, IRCCS, E Medea Scientific Institute, Bosisio Parini, Lecco, Italy.
10 Medical Genetics Unit, Galliera Hospital, Genoa, Italy.
11 Neurophychiatric Department, Spedali Civili Brescia, Italy.
12 Laboratory of Human Genetics; Galliera Hospital, Genoa, Italy.
13 Neuropsychiatric Department, IRCCS-ASMN, Reggio Emilia, Italy.
14 Génétique médicale, CHU, Bordeaux, France.
15 Univ. Bordeaux, Maladies Rares: Génétique et Métabolisme (MRGM), Bordeaux, France.
16 Neuroradiology Unit, IRCCS S. Maria Nuova Hospital, Reggio Emilia, Italy.
17 Department of Pediatrics, Gulhane Military Medical Academy, Haydarpasa Training Hospital, Istanbul, Turkey.
18 Medical Genetics Unit, Dolo Hospital, Venice, Italy.
19 Department of Pediatrics, H. San Pedro, La Rioja, Logrono, Spain.
20 Genetics Unit, St Chiara Hospital, Trento, Italy.
21 Department of Pediatrics, IRCCS San Matteo, Pavia, Italy.
22 Department of Pediatrics, Hospital S. Gerardo, University of Milano-Bicocca, Monza, Italy.
23 Thrombosis and Vasculitis Unit, Internal Medicine Service, Complexo Hospitalario Universitario of Vigo (CHUVI), Vigo, Pontevedra, Spain.
24 Department of Pediatrics and Medical sciences, ‘’Vittorio Emanuele" Hospital, University of Catania, Catania, Italy.
25 Department of Pediatrics, University ‘‘La Sapienza,’’ Rome, Italy.
26 Division of Pediatric Oncology, Department of Pediatrics; Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil.
27 Department of Pediatrics, Eastern Virginia Medical School, Norfolk, Virginia.
28 Division of Medical Genetics and Metabolism, Children’s Hospital of The King’s Daughters, Norfolk, Virginia.
29 Institute of Medical Genetics, Catholic University, Rome, Italy.
30 Department of Pediatrics and Department of Neurology, University of Washington, Seattle, USA.
31 Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, USA.
32 Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA.
33 Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA;.
34 Department of Biomedical Genetics, University of Rochester Medical Center, Rochester, NY, USA.
35 Center for Neural Development and Disease, University of Rochester Medical Center, Rochester, NY, USA.

Here, we report the neuroimaging findings and neurological changes in 30 patients with Mowat-Wilson syndrome (MWS, OMIM: #235730). MWS is a genetic disease characterized by distinctive facial features, moderate to severe intellectual disability and congenital malformations including Hirschsprung disease, genital anomalies, eye abnormalities and congenital heart defects. [Mowat *et*

al., 1998, 2003; Cacheux *et al*., 2001; Garavelli *et al*., 2003; Zweier *et al*., 2005; Adam *et al*., 2006; Garavelli and Cerruti-Mainardi 2007]. MWS is caused by heteroxygous mutations or deletions of the *ZEB2* gene, a member of the two-handed zinc-finger/homeodomain transcription factors whose functions in neuro-embryology have been recently clarified during the last years. Its role during development has been confirmed by invalidations in mice, leading to arrest of embryonic development with severe neural plate and somatogenesis defects and migratory failure of neural crest cells [Van de Putte *et al*., 2003], as well as hypocellularity of enteric neurons [Van de Putte *et al*., 2007].
Weng *et al*. (2012) demonstrated in mice models that *ZEB2* acts as a master regulator that coordinates extracellular signaling pathways to promote myelination and a nexus that connects extracellular signaling pathways to intracellular transcriptional programs for myelination in the CNS. *ZEB2* is also a key regulator for the transition from immature to mature myelinating oligodendrocytes.
Neurological involvement is a main feature: moderate to severe intellectual disability is present in all patients; Epilepsy has a prevalence of 70-75% and has an age-dependent electro-clinical pattern [Cordelli *et al*., 2013].
We analyzed the 30 patients with available brain MRI and compared their findings with features identified by a comprehensive review of published cases. Patients were included as part of an ongoing multi-centered study, which is being carried out in several Genetics and Pediatric Neurology Units in order to delineate the neurologic phenotype of MWS. To be eligible for this research, patients had to have: a confirmed molecular diagnosis of MWS and had to have at least performed a brain MRI study. Minimum requirements for MRI study were: a) 3-dimensional sagittal T1-weighted (T1-w) images with coronal and axial reconstructions and sagittal; b) axial and coronal T2-weighted (T2-w) images; c) axial Fluid Attenuation Inversion Recovery (FLAIR) images
White matter abnormalities were commonly observed findings, with reduction of thickness, which was diffused in the whole brain or more evident in one or more lobes. A distinctive feature in more than half of the patients was a commissural defect. Corpus callosum abnormalities were in fact documented in most patients with complete callosal agenesis or hypoplasia, which was localized in the caudal or in the rostral third.
Concurrently, with the development of these findings, ventriculomegaly had developed with widening of the temporal horns or the occipital ones. Bilateral hippocampal abnormalities were noted in almost half of our population, with morphological or position anomalies. Other findings included a high frequency of big basal ganglia.
We also observed some examples of abnormal cortical morphogenesis, including polymicrogyria and cerebellar hypoplasia.
The aim of our study is to compare neuro-radiological features in 6 groups with different types of mutations, delineate MRI phenotypes, genotype-phenotype correlation to better understand the role of *ZEB2* in the development of the human brain.
In conclusion, several degrees of malformations can be detected with brain MRI, usually involving corpus callosum and hippocampus. CNS defects found in MWS appear correlated with the data observed in mice models and confirm in vivo the *ZEB2* properties in regulating, at least, myelination and hippocampus development.

A NEW CASE OF TUBGCP6 MUTATION IN A CHILD WITH A MCPH PHENOTYPE

S. PASSEMARD[1–3], V. EL GHOUZZI[1], P. GRESSENS[1,3], S. DRUNAT[1,2] AND A. VERLOES[1–3]

[1] PROTECT INSERM U1141, Paris, France.
[2] Département de Génétique Clinique, Hôpital Robert Debré, Paris, France.
[3] Université Paris Diderot, Sorbonne Paris Cité, Paris, France.

E-mail for correspondence: sandrine.passemard@rdb.aphp.fr

Primary microcephaly is a rare and heterogeneous group of affections recessive inherited (MCPH) that is characterized by a reduction in brain volume associated with intellectual disability. This entity may be associated with primordial dwarfism (microcephalic primordial dwarfisms, such as Seckel, MOPD2 and Meyer Gorlin syndromes). At least, twenty genes have been identified in both disorders, and genes identified so far encode centrosomal proteins (*MCPH1*, locus MCPH1; *WDR62*, locus MCPH2; *CDK5RAP2*, locus MCPH3; *CASC5*, locus MCPH4; *ASPM*, locus MCPH5; *CENPJ*, locus MCPH6/SCKL4; *STIL*, locus MCPH7; *CEP135*, locus MCPH8; *CEP152*, locus MCPH9/SCKL5; *ZNF335*, locus MCPH10; *PHC1*, locus MCPH11; *CDK6*, locus MCPH12; *CENPE*, locus MCPH13; *ATR*, locus SCKL 1; *RBBP8*, locus SCKL2; *CEP63*, locus SCKL6; *NIN*, locus SCKL 7; *DNA2*, locus SCKL8). Centrosome is composed of a pair of centrioles and a pericentriolar matrix that nucleates and anchors cytoplasmic microtubules necessary for mitotic spindle formation and chromosome segregation. Interestingly, mutations in centriole biogenesis and microtubules organization genes have also been recently identified in autosomal recessive microcephalic dwarfism and retinopathy (*PLK4* and *TUBGCP6* mutations) or in autosomal-recessive microcephaly and chorioretinopathy (*TUBGCP4* mutations).
Here, we report on a child with *TUBGCP6* mutation that was thought to be MCPH.
Intrauterine growth retardation was noticed at the 2nd trimester of pregnancy. She was born prematurely (7th month of pregnancy) with a birth weight of 1400g, length 43cm and OFC 30cm. She was hypotonic within the first 6 months of life, had feeding difficulties. She started walking at the age of 15 months old. She never had seizures. At the age of 5 years old, her weight was 11kg (-3 SD), length 99cm (-1.5 SD) and OFC 43 cm (-7 SD). She still had no language at 5 years old. Ophthalmoscopic examination was normal. Her cranial MRI showed microcephaly with simplification of the gyration.
NGS on the 13 known MCPH genes did not reveal any mutation. Whole exome sequencing identified 2 compound heterozygous mutations in *TUBGCP6* gene.
This case report suggests that MCPH, microcephalic primordial dwarfism and autosomal recessive microcephaly and chorioretinopathy may be a phenotypic continuum, increasing more and more the number of disease-causing mutations in autosomal recessive microcephaly and suggests changing our management of microcephalic patients in including neurosensory examination.

CLOVE SYNDROME: A CASE REPORT

D.P. GERMAIN[1,2], J.-B. RIVIERE[3], I. DABAJ[4], J. BATAILLE[4] , C. JAUNY[2], I.E. JURCA-SIMINA[2], L. FAIVRE[3] AND I. HAEGY[4]

1 University of Versailles, UFR des Sciences de la Santé Simone Veil, Division of Medical Genetics, 78180 Montigny, France.
2 Assistance Publique – Hôpitaux de Paris (AP-HP), Referral Center for Fabry disease and inherited disorders of connective tissue, 92380 Garches, France.
3 Fédération Hospitalo-Universitaire Médecine Translationnelle et Anomalies du Développement (TRANSLAD), Centre Hospitalier Universitaire Dijon, Dijon, France.
4 Assistance Publique – Hôpitaux de Paris (AP-HP), Division of Paediatrics, 92380 Garches, France.

E-mail for correspondence: dominique.p.germain@aphp.fr

Background*:* CLOVE syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, and Epidermal nevi) is a sporadically occurring malformation syndrome caused by somatic mutations of *PIK3CA* gene and characterized by asymmetric somatic hypertrophy and others anomalies.
Case Report*:* A thirteen year-old girl presented was referred to our paediatric intensive care unit followed spine orthopedic surgery for severe scoliosis. In the absence of diagnosis, genetic counseling was requested by the family. Since the age of 3 months, she presented with lipomatous masses in the right posterior thoracic region, the right lombar region, the right gluteal region, and the sole of the right foot. She also had a history of synringomyelia associated with a tethered cord. She had a severe progressive scoliosis since the age of 6 months. Based on those symptoms a diagnosis of Proteus syndrome had been proposed but genotyping of *PTEN* gene (at that time, considered as a potential Proteus syndrome gene) had yielded negative results.
Results*:* Clinical examination (DPG) showed multiple naevocellular nevi, lipomatous masses, a sandal gap, and epidermal naevus in favor of a diagnosis of CLOVE syndrome. Both restrictive and obstructive respiratory syndrome was present. Two skin biopsies were performed in the area of the lipomatous masses and cultured. Genotyping of *PIK3CA* gene was performed on DNA extracted from confluent skin cultures and revealed a missense mutation: p.(Glu542Lys) in exon 10 of the gene. The mutation was considered pathogenic based on previous reports and in silico analysis. The mutation was found in respectively 30% and 39% of the DNA isolated from two different fibroblastic cultures.
Discussion*:* Diagnosis of CLOVE syndrome may be delayed due to its fairly close phenotypic similarity to Proteus syndrome. Nevertheless, the prognosis and complications differ. Our case shows the difficulty of this diagnosis and the diagnostic wandering and odyssey. PIK3CA has been shown to be a critical kinase for cellular growth and metabolism. No malignancy has been registered yet. Increased knowledge of the hypertrophic syndromes related to *PIK3CA*-associated somatic overgrowth disorders should allow an earlier diagnosis of those recently elucidated conditions.

A NOVEL FAMILY WITH KOHLSCHÜTTER-TÖNZ SYNDROME

K. STEINDL[1], L. GOGOLL[1], P. JOSET[1], E.R KELLER[2] AND A. RAUCH[1]

[1] Institute of Medical Genetics, University of Zurich
[2] Kantonsspital Chur, Switzerland

E-mail for correspondence: steindl@medgen.uzh.ch

Kohlschutter-Tonz syndrome (KTS; MIM 22675) is a rare autosomal recessive disorder characterized by intellectual impairment, spasticity, epilepsy, and amelogenesis imperfecta. We describe a novel family with two affected females with complex phenotypes harboring compound heterozygosity for the ROGDI mutations c.532-2A>T and c.531+5G>C, both of which have been described before in a not obviously related Swiss family. Both sisters had abnormal teeth, but only one had epileptic encephalopathy, while the other sister did not yet experience any seizure so far. In addition, both sisters suffered from septic granulomatosis due to a homozygous NCF1 gene mutation.

PATIENTS WITH MUCOLIPIDOSIS IV: WHAT CAN WE LEARN FROM THE PARENTS? A PRELIMINARY STUDY

P. SEGAL[1] AND A. RAAS-ROTHSCHILD[2]

[1] Department of Psychology, Hebrew University, Jerusalem, Israel.
[2] Institute of Rare Diseases & Institute of Medical Genetics, Sheba Medical Center; Tel-Hashomer; 52621, Israel & the Sackler School of Medicine; Tel Aviv University; Ramat Aviv; Israel.

E-mail for correspondence: Annick.rothschild@sheba.health.gov.il

Background*:* Identification of behavioral phenotype is important in anticipatory guidance and counseling for families of children with neurogenetic diseases; Mucolipidosis IV [ML IV] is a rare autosomal recessive disorder which present with non-specific developmental delay;
Objective: Identification of the behavioral characteristics of 12 ML IV patients, aged from 2.5 years to 34 years, collected from their caregivers' observation.
Methods*:* The information was gathered from the patient's parents using an extensive semi-structured interview specially designed for this study. Each interview lasted around three hours. The first part of the questionnaire consisted of open-ended questions covering behavioral and developmental characteristics. The second part of the questionnaire included questions that were rated on a likert-type 4 points scale;
Results*:* Patients were uniformly described as attracted to music; they are friendly and show explicit pleasure from social interactions; their main difficulties are in the field of psychomotor development, and their general health is good. Caregivers were aware of the need for chronic iron supplementation. The patients present deterioration of motor and communication skills over the years. Since the ML IV gene identification, diagnosis is made earlier in life. Episodes of ocular pain, with ipsilateral flushing of the face and tearing were frequently reported as well as shortening of the Achilles tendon.
Conclusion*:* We suggest that ML IV be considered in the differential diagnosis of patients with developmental delay, who present the behavior phenotype reported. More clinical research is needed to confirm these preliminary findings.

FOUR NOVEL PATIENTS WITH TRICHO-HEPATO-ENTERIC SYNDROME: CLINICAL PRESENTATION AND NATURAL HISTORY

O. VANAKKER AND B. CALLEWAERT

Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

E-mail for correspondence: olivier.vanakker@ugent.be

Tricho-hepato-enteric syndrome (THES; OMIM# 222470 & 614602) is a rare autosomal recessive disorder with an estimated incidence of 1/1.000.000 births. The disease is characterized by intractable diarrhea of infancy, usually leading to failure to thrive and requiring parental nutrition. Patients have facial dysmorphism with prominent forehead and cheeks, broad nasal bridge, hypertelorism and have abnormal hair which is described as woolly. Very often, trichorrhexis nodosa is observed. Patients frequently have an immune deficiency, though the literature is not always clear on the precise characteristics. More than half of the children with THE have liver disease, mainly cirrhosis and siderosis as well as (mild) mental retardation which is poorly documented in reported cases. Other signs which have been described include skin features (xerosis, café-au-lait spots), cardiac anomalies and abnormal platelet morphology. More recently, also milder or atypical forms of THES have been reported.

THES is caused by mostly private mutations in the TTC37 (OMIM* 614589) and SKIVL2 (OMIM* 600478) gene, encoding components of the human ski complex. The precise function of the ski complex is unknown and most data come from studies in yeast and fruit flies. In these models, the ski complex is the cofactor of the cytosolic exosome whose function is to decay aberrant mRNAs in the 3'-5' way.

We present 4 novel patients with THE syndrome between 17 months and 10 years of age. Based on their clinical histories, we discuss the phenotypic diversity of THE, with detailed description of the immunological and neurological presentation in our patients, their management and treatment options. The natural history is documented and compared with the data available from previously reported patients.

MACS (RIN2) SYNDROME: THE FIRST CAUCASIAN PATIENT. EVOLUTION OF THE PHENOTYPE OVER TIME

S. ROSATO, I. IVANOVSKI[1], M. POLLAZZON[1], D. SANTODIROCCO[1], M. BELTRAMI[2], L. GARAVELLI[1] AND F.MALFAIT[3]

1 Clinical Genetics Unit, Department of Obstetrics and Pediatrics, IRCCS S. Maria Nuova Hospital, Reggio Emilia, Italy.
2 Department of Internal Medicine, IRCCS S. Maria Nuova Hospital, Reggio Emilia, Italy.
3 Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

E-mail for correspondence: garavelli.livia@asmn.re.it

MACS (RIN2) syndrome (MIM613075) is a rare autosomal recessive disorder with only nine patients in the literature to date. Hallmark features of this condition are normal to enlarged occipitofrontal circumference, sparse hair, soft redundant skin, scoliosis and progressive facial coarsening. It is caused by a homozygous mutation in the RIN2 gene, which encodes a protein involved in the regulation of cell trafficking. All previously reported patients come from several families of North African and Middle East origin. We report the first patient of Caucasian origin, with a mutation already reported in the literature, but with a slightly different clinical appearance.

"WIEDEMANN-STEINER SYNDROME SHOULD BE CLINICALLY RECOGNIZABLE, BUT APPARENTLY IT IS NOT"

F. DUIJKERS[1], A. BROOKS[2], E. SMEETS[3], A. VAN HAERINGEN[4], A. VAN HAGEN[5], P. TERHAL[6] AND J. MAARTEN COBBEN[1]

[1] Clinical Genetics and Pediatrics, AMC, Amsterdam,
[2] Clinical Genetics, Erasmus MC, Rotterdam
[3] Clinical Genetics, MUMC, Maastricht
[4] Clinical Genetics, LUMC, Leiden,
[5] Clinical Genetics, VUMC, Amsterdam
[6] Clinical Genetics, UMCU, Utrecht, the Netherlands.

E-mail for correspondence: f.a.duijkers@amc.nl

We report 10 patients with Wiedemann-Steiner syndrome caused by a pathogenic de novo mutation in the KMT2A gene. All 10 were diagnosed in a genetic centre in The Netherlands, but only 1/10 on clinical suspicion with targeted gene analysis and 9/10 by Whole Exome Sequencing (WES). Initially the Wiedemann-Steiner syndrome was not clinically suspected in 8 of these 9 WES cases. In several patients, other tentative diagnoses were made before the results of the WES appeared. Retrospectively, the Wiedemann-Steiner phenotype fits the clinical picture in all these 10 patients, but not all show specific features, such as the characteristic hairy elbows. A few factors may contribute to the excess of diagnoses of Wiedemann-Steiner by WES instead of targeted sequencing. E.g. the syndrome may be more heterogeneous than previously thought and therefore less recognizable. Also, the syndrome may be under recognized by clinical geneticists due to the lack of knowledge of the phenotype. We will present several Wiedemann-Steiner cases diagnosed in the Netherlands; in the hope of increasing recognisability of this apparently not so rare syndrome.

PTDSS1-RELATED CUTIS LAXA

L. VAN MALDERGEM[1], M. SIMANDLOVA[2], J. LESPINASSE[3], P. STANIER[4] AND S.B. SOUSA[4,5]

1 Centre de génétique humaine, Université de Franche-Comté, Besançon, France.
2 Department of Biology and Medical Genetics, University Hospital of Motol and Second Faculty of Medicine, Prague, Czech Republic.
3 Unité Fonctionnelle de génétique chromosomique, Centre hospitalier de Chambery-Hotel-Dieu, Chambery, France.
4 UCL Institute of Child Health, London, UK
5 Serviço de Genetica Medica, Hospital Pediatrico, Centro Hospitalar e Universitario de Coimbra, Portugal.

Recent studies have demonstrated that the molecular basis of congenital cutis laxa remains not elucidated in a majority of cases, even after sequencing a panel of genes known to be associated with this phenotype. We describe how a very rare skeletal dysplasia (Lenz-Majewski syndrome) reported in less than a dozen patients until now, may present with congenital cutis laxa, facial dysmorphia and delayed closure of the fontanelles. Clinical course of two unreported patients, now aged 10 and 32y indicates a trend towards disappearance of cutis laxa over time, alongside with stunted growth, major brachydactyly and a disharmonious craniofacial growth especially of the mandible. Intellectual deficiency is moderate to profound. A multicentric effort resulted in identification of gain-of function mutations in *PTDSS1*, encoding phosphatidylserine synthase 1. We shall present two new patients, detailing their major growth delay from -4 to -10 SD, their behavioral phenotype, their dysmorphia that includes progressive enlargement of the mandible, macroglossia, macrostomia, telecanthus and broad forehead. These clinical signs and symptoms are thought to occur as a consequence of an excess of phosphatidylserine. One could also speculate on a potential secondary depletion of serine in the pathophysiology of intellectual deficiency. It is a major neuron-glia interactor and its depletion is known to be associated with a severe epileptic encephalopathy with microcephaly in a rare inborn error of metabolism: glycerophosphate dehydrogenase deficiency.

CONFIRMATION OF HAPLOINSUFFICIENCY OF XPO1 AND USP34 AS CAUSAL GENES OF SPECIFIC PHENOTYPE IN 2P15 DELETION SYNDROME

A. GONZALEZ-MENESES LÓPEZ.

Dysmorphology Unit. Hospital Universitario Virgen del Rocío. Sevilla. Spain.

The 2p15-p16 deletion syndrome was described by first time in 2007 by Rajcan-Separovit, in two patients with microcephaly, brain malformations, autistic features and facial dysmorphism. Since then, up to 16 patients have been described with somehow similar clinical presentation. Recently (Fannemel *et al*. 2014), haploinsufficiency of the genes XPO1 and USP34 have been suggested to be related with the main phenotypic features of these patients, in a boy with 230 kb deletion affecting this two genes. We present a boy with a 152Kb deletion also affecting XP01 and USP34 genes with overlapping features with those described by Fannemel *et al*. in 2014, confirming that the haploinsufficiency of these genes can have a specific dysmorphic pattern and increasing the knowledge of its biological function.

He is the second son from healthy non consanguineous parents without mental retardation or congenital anomalies family history. Craneosinostosis was detected in the first year of life and surgery was performed. He also had a testicular torsion with 2y.o. His development was retarded from the beginning without brain malformations detected by MRI. The face was dysmorphic with flat occipital bone and large nose, ptosis with downslanted palpebral fissures, and flat chest with wide separation of mamiles. Micrognathia with crowded teeth is also a feature. He presented with an impossibility to flexion both thumbs in interphalangical joints as well as metacarpophalangical ones without any other malformations in hands or feet. He has microcephaly (-3,07SD), short stature (-2,54SD) and weight of P7 (-1,45SD). G-banding karyotype, FGFR 3 muenke mutation and TWIST gene mutations were normal.

Array CGH (Agilent platform 60K) detected a de novo 2p15 deletion of 152 Kb affecting only to USP34; SNORA70B and XPO1 gene. A 699Kb deletion in 8p23.1 was also detected but is considered to be a benign CNV. This patient has a very striking resemblance with that described by Fannemel *et al*. with haploinsufficiency of this two genes.

XPO1 is highly conserved in evolution in 96.7% of its amino acid identity and plays an important role in mucleocytoplasmatic transport receptor mediating nuclear export of proteins and RNAs, coordination of nuclear events such as mitosis and transcriptional activation, and may be involved in maintenance of higher order chromosome structure.

USP34 encodes a deubiquitinating enzyme that it is expressed in brain at low level but also interacts positively with Wingless-type signaling pathway (WNT) that plays an important role in developmental processes such us cell fat specification, cell migration and proliferation.

This patient confirms the importance of the haploinsufficiency of this genes in human pathology and also contributes to confirm the clinical phenotype.

COPY NUMBER VARIATONS IN INTELLECTUALLY DISABLED ADULTS WITH CATATONIA

A. VOGELS, E. WEYTS, G. VAN BUGGENHOUT, R. CAEYENBERGHS, N. BRISON, L. LEEMPOELS AND G. D'HAENENS

Centre of Human Genetics, University Hospitals Leuven, Department of Human Genetics, KULeuven,, Belgium
Psychiatric Hospital Sint-Camillus, Bierbeek, Belgium.

E-mail for correspondence: Annick.Vogels@uzleuven.be

Introduction
The term "developmental disorder" is used to refer to a range of conditions characterised by cognitive, mental and/or neurological manifestations occurring during the development of the nervous system. The various clinical entities such as intellectual disability, autism, schizophrenia or epilepsy show considerable comorbidity. Data from recent studies show that copy number variations are found at an increased frequency in these neurodevelopmental disorders. Almost all CNV regions that have been shown to be associated with intellectual disability are also associated with one of the neuropsychiatric disorders indicating clinical heterogeneity.
Methods
We examined a cohort of 210 adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders. Out of these group, 13 intellectually disabled adults were diagnosed with catatonia, a unique clinical syndrome that has been rediscovered over the last two decades. Analysis of copy number variations was performed in all adults and compared with data from the literature.
Results
CNV (deletions and duplications) were found in three adults with catatonia
Conclusion
Catatonia was diagnosed in 6 percent of a population of adults with a dual diagnosis of intellectual disability and psychiatric disorders. Until now little is known about the pathophysiology and/or underlying aetiology of catatonia. The results of this study may provide more insight in the genetic causes of this severe psychiatric disorder.

GENOTYPE-PHENOTYPE CORRELATIONS IN ATYPICAL 22q11.2 DELETIONS: THE ROLE OF TBX1

J. ROOSENBOOM[1], G. HENS[1], L. LAGAE[2], P. CLAES[3], W. DEMAEREL[4], A. SWILLEN[4], E. VERGAELEN[4], J.BRECKPOT[4], H. PEETERS[4], P. HAMMOND[5] AND K. DEVRIENDT[4]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, KU Leuven & UZ Leuven, Belgium.
[2]. Department of Pediatrics, KU Leuven & UZ Leuven, Belgium.
[3]. KU Leuven, ESAT/PSI – UZ Leuven, MIRC – iMinds, Medical IT Dept, Leuven, Belgium.
[4] Center for Human Genetics, KU Leuven & UZ Leuven, Belgium.
[5] Molecular Medicine Unit, UCL Institute of Child Health, London, UK.

The recurrent del22q11.2 causes a recognizable but highly variable phenotype. It is thought that the *TBX1*-gene is the key gene responsible for the core physical features, i.e. facial dysmorphism, conotruncal heart malformations, malformations of the palate (velopharyngeal insufficiency (VPI) or, rarely cleft palate), and hypoplasia of the thymus and parathyroid glands. This is based on the location of *TBX1* in the commonly deleted region, the phenotype of *tbx1* -/- mice and the phenotype of rare cases with intragenic *TBX1* mutations.
We report three cases with a unique deletion located in the critical A-D region.
We previously reported a large family with autosomal dominant nonsyndromic velopharyngeal insufficiency, (Vantrappen *et al*., Clin Genet. 2002 Jan;61(1):74-6). A small atypical 22q11.2 deletion was detected by microarray-CGH, involving *C22orf29*, *GNB1L* and the last 5 exons of *TBX1.* Assessment of speech and velopharyngeal function showed that VPI was correlated to the deletion. None of the other characteristics of the del22q11.2 was seen and facial features were unremarkable. 3D morphometric analysis of the facial features of 2 affected children did not show resemblance to age-matched del22q11.2 patients. The adult cohort of del22q11.2 patients is being extended to allow comparison of adults in this family.
A second, sporadic individual presented with a cleft palate and oligodontia. She has a university degree and normal facial features. Microarray analysis revealed the presence of a de novo 721 kb deletion (chr22:19,171,528-19,892,620 – Hg19) encompassing 14 genes, including *TBX1*.
This suggests that *TBX1* haploinsufficiency might be responsible for the palate anomalies, but is not sufficient for the facial features.
We also observed a boy age 10 years, with a 22q11.2 deletion with breakpoints in LCR B-D, (chr22:20,719,137-21,441,944 Hg19), not containing the *TBX1* gene. He was referred for drug-resistant absence epilepsy and has a moderate intellectual disability. He is the second child in the family. His mother, deceased, had a normal intelligence, father had epilepsy until age 18 years and was not available for testing. Biometry was normal. He had a distinct facial phenotype with narrow palpebral fissures and hooding of the upper eye lids, hypertelorism and broad nasal bridge and special ears. An objective analysis by means of 3D facial imaging revealed that his facial features fall within the spectrum of those associated with a classical del22q11.2.
These data strongly suggest that the facial features in individuals with a classical del22q11.2 are not solely explained by haplo-insufficiency of the *TBX1* gene. *CRKL* is an alternative candidate gene for this phenotype.

A DE NOVO INTRAGENIC DELETION IN *HIRA* (*TUPLE1*) IN A PATIENT WITH A 22q11.2 MICRODELETION PHENOTYPE

M. JEANNE, S. VONWILL, D. HAYE, N. CHELLOUG AND A. TOUTAIN

Service de Génétique, Centre Hospitalo-Universitaire, Tours, France.

E-mail for correspondence: mederic.jeanne@gmail.com

The 22q11.2 microdeletion syndrome is associated with a wide phenotypic spectrum. Candidate genes located in the 3 Mb deleted region or DGCR1 (DiGeorge syndrome critical region) have been proposed to explain part of the features, such as *TBX1* for the heart defects, but to date none of them explains the entire phenotype and the cause of the neurodevelopmental problems remains speculative. Here we report an intragenic deletion in the *HIRA* (*Tuple1*) gene, which is located in the DGCR1 region, in a 5-year-old female patient with features highly suggestive of the 22q11.2 deletion syndrome.

She had severe psychomotor retardation, growth retardation, velopharyngeal insufficiency and dysmorphic traits similar to those found in the microdeletion 22q11.2. FISH analysis with the Tuple1 commercial probe (Cytocell®) did not show any deletion. Array-CGH detected a de novo 28kb deletion in the *HIRA* gene. PCR analysis and sequencing showed a deletion of exons 2 to 13 of the HIRA transcript. No normal transcript was observed suggesting the absence of transcription of the non-deleted allele.

To our knowledge this is the first description of an intragenic deletion of the *HIRA* gene. The similarity between the phenotype of the present case and the classical 22q11.2 deletion syndrome strongly suggests that this gene could be a candidate for the neurodevelopmental phenotype and the dysmorphic traits of the 22q11.2 deletion syndrome.

COARCTATION OF AORTA WITH DYSMORPHIC FEATURES IN A PATIENT WITH TRIPLICATION OF 15q26.1-q26.3: CLINICAL AND MOLECULAR ANALYSIS

B. ALEKSIŪNIENĖ[1,2], R. MATULEVIČIŪTĖ[3], Ž. ČIULADAITĖ[1,2], A. MATULEVIČIENĖ[1,2], A. UTKUS[1,2] AND V. KUČINSKAS[1,2]

[1] Centre for Medical Genetics at Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania.
[2] Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
[3] Faculty of Medicine, Vilnius University, Vilnius, Lithuania.

E-mail for correspondence: beata.aleksiuniene@santa.lt

We present an interstitial triplication of 15q in a patient with distinctive facial features, coarctation of aorta and other organ anomalies and, development delay.
Our patient is a 5-year-old second-born female child of non-consanguineous parents with uncomplicated family history. The patient was vaginally delivered at 37 weeks' gestation. At birth, she weighed 4100 g (above 97th percentile), with the length of 54 cm (above 97th percentile), occipitofrontal circumference of 36 cm (above 97th percentile), and chest circumference of 35 cm. Apgar scores were 6 and 8, at 1st and 5th minutes, respectively. Muscular hypotonia, floppiness from the birth and coarctation of aorta complicated patient's postnatal condition. Dolichocephaly, broad forehead, widely spaced eyes with expressed epicanthus, anteverted nares, deep long philtrum, everted lower lip, micrognathia, low set ears with ridges within the left concha, short neck, small hypothenar eminence, camptodactyly of the 4th finger, widely spaced nipples with chest wall deformity were observed during phenotypical evaluation. Orthopaedist diagnosed left hip dysplasia. Heart ultrasound revealed coarctation of aorta with aortic arch hypoplasia. The patient underwent surgical intervention required for this pathology in the first weeks after birth. CT scan showed congenital hydrocephaly and bilateral frontal lobe atrophy. Hypothyrosis, immunodeficiency, severe hypermetropia with strabismus, sensorineural hearing loss were detected at the time.
Chromosome analysis of peripheral blood lymphocytes revealed derivated chromosome 15. Array Comparative Genome Hybridization plus Single Nucleotide Polymorphism (array CGH+SNP) was used to specify the findings and showed 9,6 Mb triplication of 15q26.1-q26.3.
We assume that the interstitial triplication of 15q26.1-q26.3 could result in the described phenotype. Development delay, dysmorphic features, malformations of heart and great vessels, strabismus have been associated with duplication of 15q26 region in previously described cases. Based on gene function, expression profile and information of the phenotypic consequences of gene mutations in humans and gene knockouts in model organisms (mouse and zebrafish) we prioritize *IGF1R*, *BLM*, *MEF2A, VPS33B, NR2F2, SYNM* as candidate genes for these clinical findings.

A NOVEL DE NOVO DUP (4) (q28.2-qter) & DEL (8) (pter-p23.1) DUE TO UNBALANCED TRANSLOCATION IN A GIRL: CLINICAL AND MOLECULAR ANALYSIS

A. MATULEVIČIENĖ[1,2], B. ALEKSIŪNIENĖ[1,2], L. TAMULIENĖ[3], A. LIUBŠYS[3,4], Ž. ČIULADAITĖ[1,2], A. UTKUS[1,2] AND V. KUČINSKAS[1,2]

1 Centre for Medical Genetics at Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania.
2 Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
3 Centre of Neonatology, Children's Hospital, Affiliate of Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania.
4 Centre of Neonatology, Clinics of Children's Diseases, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.

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

We present a partial trisomy 4q28.2-qter with partial monosomy 8pter-p23.1 in a patient with distinctive facial features, multiple organ anomalies and development delay. Such complex chromosomal aberration to our knowledge has not been previously reported.

Our patient is a 3-month-old first-born female child of non-consanguineous parents with complicated family history (3 previous pregnancies resulting in miscarriages). The patient was delivered at 34 weeks' gestation via Caesarean section. At birth, she weighed 1840 g (10-25th percentile), with the length of 43 cm (10-25th percentile), and occipitofrontal circumference of 31 cm (25-50th percentile), and chest circumference of 27 cm. Apgar scores were 4 and 5, at 1st and 5th minutes, respectively. Preterm delivery, respiratory distress and microcirculatory dysfunction complicated patient's condition. Dolichocephaly with scalp defect of 6 cm in length and 1 cm in width, triangular face, widely spaced eyes with short asymmetric palpebral fissures, prominent nasal bridge, micrognathia, pointed chin, low set posterior angulated ears with overfolded helix, decreased palmar creases, widely spaced gap between the great and the second toe were observed during phenotypical evaluation. Orthopaedist diagnosed bilateral hip contractures. Heart ultrasound revealed patent ductus arteriosus (PDA) and secondary atrial septal defect. Due to ventricular volume overload surgical correction of PDA at the age of two months. Upon MRI examination membranous choanal atresia and suspected basal encephalocele could be observed. Instrumental testing of other organs systems did not reveal any abnormalities at the time.

46,XX, der(8) add (8)(p21) was detected by chromosome analysis of peripheral blood lymphocytes. Array Comparative Genome Hybridization plus Single Nucleotide Polymorphism (array CGH+SNP) analysis showed a duplication of the region 4q28.2–qter and a deletion in the region 8p23.1-pter of ~60 Mb and ~11 Mb, respectively. *De novo* origin of the rearrangement was confirmed by parental karyotype analysis.

The combined effect of deleted and duplicated chromosome segments may produce such combination of phenotype. In previously described cases, dup (4)(q28.2-qter) had been associated with severe development delay, dysmorphic features and congenital heart anomalies as also observed in our patient, whereas the deletion observed in our patient involves genes, which have been linked to embryonic development, including *ARHGEF10, MYOM2, SOX7*. Moreover, 306,5 kb upstream the breakpoint at chromosome 8 is *GATA4* which is a strong candidate gene for heart anomalies, therefore, disruption of *GATA4* expression due to position effect or interruption of the gene regulatory elements should not be excluded.

A CASE REPORT OF A PRENATAL DIAGNOSIS OF A COMPLEX CHROMOSOMAL REARRANGEMENT: WHAT COULD BE THE PHENOTYPE?

M. DE RADEMAEKER[1], A. VAN DEN BOGAERT[1], M. LEYDER[2], A. VORSSELMANS [2] AND K. KEYMOLEN[1]

[1] Centre for Medical Genetics, Reproduction and Genetics, Reproduction Genetics and Regenerative Medicine, Vrije Universiteit Brussel (VUB), UZ Brussel, Laarbeeklaan 101, 1090 Brussel, Belgium.
[2] Centre for Prenatal diagnosis, Gynaecology and Obstetrics, Vrije Universiteit Brussel (VUB), UZ Brussel, Laarbeeklaan 101, 1090 Brussel, Belgium.

E-mail for correspondence: Marjan.derademaeker@uzbrussel.be

We report on a case of a complex chromosomal rearrangement: an inverted duplication 2p25.3 with concomitant deletion and a partial trisomy 6q 25. The phenotypic effects of both aberrations are discussed.
In a twin pregnancy, established after assisted reproduction with frozen embryo transfer, a fetal ultrasound at 23 weeks of gestation demonstrated a suspicion of tetralogy of Fallot. The patient initially declined prenatal diagnosis. Follow up ultrasound showed a bilateral postaxial polydactyly, intra uterine growth retardation and urogenital anomalies. During the last trimester a severe polyhydramnios was diagnosed for which an evacuating puncture was needed. Array comparative genomic hybridization (aCGH) analysis was performed with the 44 K Agilent array and showed a complex chromosomal aberration with a 4.4 MB inverted duplication of 2p25 3 involving SOX11 gene with a 2.3 MB terminal deletion 2p25.3p25.1 involving SNTG2 and MYT1L genes and a 16.5 MB duplication 6q25 2 q27 overlapping more than 50 OMIM genes. Parental karyotyping and array CGH was normal. At birth the tetralogy of Fallot was confirmed and he showed dysmorphism (flat nasal bridge, hypertelorism, micrognathia), a postaxial polydactyly, a hypospadias and a distal arthrogryposis. Brain imaging was normal. At the age of 4 months he is still fed by naso-gastric tube feeding and the psychomotor development is very poor.
Inverted duplications adjacent to terminal deletions have been described in an increasing number of chromosomes as on chromosome 2p. Some of the earlier described pure trisomy 2p cases with classical cytogenetic methods could be inverted duplications/ deletions .The characteristics of the recurrent inverted duplication / deletion of 2p25.1-25.3 cases are very similar to the earlier described pure partial trisomy 2p with distinctive facial dysmorphic features as high forehead, depressed nasal bridge , hypertelorism and micrognathia , intellectual disability and congenital heart malformations as also observed in our patient. Phenotype is often described rather consistent despite the presence of a second chromosome involved in the rearrangement. In our patient the presence partial trisomy 6q is mainly contributing to the phenotype. Partial trisomy 6q is a rare but recognizable phenotype with facial dysmorphism (downslanting palpebral fissures, hypertelorism falt nasal bridge, carp- shaped mouth), flexion contractures, cardiac anomalies and profound intellectual disability. The presence of arthrogryposis and very poor development at this stage is due to the partial trisomy 6q. Also the heart defect could be explained by the partial trisomy 6q. In prenatal diagnosis microarray analysis can detect chromosomal anomalies which are clearly associated with postnatal phenotypes. The detection of complex chromosomal rearrangement and the lacking of genotype phenotype of the same combinations is an issue in predicting a well-defined phenotype.

EVIDENCE FROM ADULTS WITH INTELLECTUAL DISABILITY TO CNV IN PRENATAL PERIOD: HOW TO BUILD PENETRANCE VALIDATION AND APPROPRIATE GENETIC COUNSELLING? AN EXAMPLE WITH 10q11.22 DUPLICATION

Y. SZNAJER[1], C. BANDELIER[1], M. RAVOET[1], J. VERMEESCH, K. JANSSENS, K. VAN DEN BOGAERT, F. KOOY, A. VAN DEN BOGAERT, J. DÉSIR, A. DHEEDENE, J. MUYS, C. STAESSEN, C. VILAIN, K. KEYMOLEN, J.-S. GATOT, B. MENTEN, B. GRISARD, S. ROMBOUT, O. VANAKKER; B. BLAUMEISER, M. DE RADEMAEKER, G. SMITS, A. DE LEENER, B. PICHON, A. DESTREE; T. DE RAVEL DE L'ARGENTIÈRE, S. GAILLEZ, J.H. CABERG, N. REVENCU, S. JANSSENS, S. BULK, C. MELOTTE AND K. DEVRIENDT

[1] Center for Human Genetics, Cliniques Universitaires St Luc, U.C.L, Brussels; Belgium
Each author is a member of the 'BEMAPRE'*

E-mail for correspondence: yves.sznajer@uclouvain.be

Introduction

The discovery of Copy Number Variation in our genome has led to a better understanding for genomic architecture and the occurrence of disorders related to gene dosage effect. While interpretation of large deletions containing dosage sensitive genes might be relatively straightforward, identification of interstitial tandem duplications always invariably raises the question on the precise relationship to phenotype. Size, 'de novo' vs inheritance, dosage sensitive genes involved as position may reinforce appropriate interpretation. Nevertheless, in a prenatal setting, interpretation is hindered by the absence of a clear phenotype, precluding e.g. the possibility to predict penetrance for intellectual disability. To illustrate this, we report on a specific CNV identified in a sporadic patient and in a prenatal setting and hope to share our attitude for better Genetic Counselling (GC) and improve our practice.

Patient report

We present a 50 year-old Caucasian man who developed moderate intellectual disability, behaviour problems (anxiety disorder, onychotrichotillomania, inability to live by himself for daily life needs). He did not have any congenital anomaly nor brain anatomic malformation although the delivery was reported to be complicated (no data on APGAR score but he was not admitted to neonatal intensive care and brain CT scan was reported to be normal). He developed seizures at the age of 12. At age 50, his height, weight and head circumference were in the normal range.

Method

Work-up included SNP-arrays screening for genomic architecture imbalance (Affymetrix human mapping 250k-Nsp1) and identified a 5.5 Mb duplication on 10q: arr [hg19] 10q11.22q11.23(46,593,290-51,817,653)x3. 2 other duplications of <350 kbs and without coding genes,… were considered as benign. Parental DNA was not available. Very recently, an almost identical 5.52Mb duplication (arr [g 19] 10q11.22q11.23 (46,263,946-51,780,901x3) was identified in a prenatal setting. In this case, duplication was confirmed to be maternally inherited, but phenotypic information to the mother was lacking. Indication for microarray investigation was intrauterine growth retardation. This last was presented on the national consortium interface for advise (refers to Vanakker *et al*. 2014)

Discussion

To date, 7 patients with a duplication in the 10q11.22 have been reported in the Decipher database. In a large cohort of patients (30.000 children) with intellectual disability (Coe 2014), 10 patients have been identified with a similar duplication. In this cohort, the duplication was considered to be a 'recurrent CNV', but authors did not comment on involvement related to size, gene content, position, expression or possible gender effect to account for variability. Stankiewicz *et al*. reported 17 patients with a 10q11.22 duplication ID and autistic behaviour (17/17), atrial septal defect (2/17), brain MRI anomalies (3/17), hypotonia (1/17), seizures (3/17) and T cell lymphopenia (1/17). Information on dysmorphic features was lacking. Non Allelic Homologous Recombination mechanism as the cause for the occurrence of duplication cannot be sustained since in 9 patients, chromosomal region was not directly oriented with Low Copy Repeat. A possible 'two hit' mechanism may be considered in patients with additional CNVs but this needs to be investigated (Stankiewicz 2012).

While Xu *et al*. elaborated a complicated path to calculate and possibly obtain a more precise estimate (Xu 2011), Rosenfeld *et al*. draw lines of evidence for significant recurrent CNVs (Rosenfeld 2013).

Conclusion: it remains at present very difficult to assess ID penetrance based on CNV detection in the prenatal setting...

** BEMAPRE stands for The 'BElgian consortium on MicroArray in PREnatal cases'*

References

1)Vanakker O. et al Eur J Med Gene 2014(57):151–156
(2) Coe B. et al. Nat Genet 2014;46(10):1063-1071
(3) Stankiewicz P, et al. Hum Mutat 2012;33:165–79
(4) Xu et al. BMC Bioinformatics 2011;12:331-341
(5)Rosenfeld J. et al. Genet Med 2013;15(6) :478-481

FETOPLACENTAL DISCORDANCE FOR AN UNBALANCED SUBTELOMERIC TRANSLOCATION DETECTED BY POSTNATAL CNV ANALYSIS ON EXOME DATA

C. FAUTH[1], B.KRABICHLER[1], J. ZSCHOCKE[1] AND R. PFUNDT[2]

[1] Division of Human Genetics, Medical University Innsbruck, Austria
[2] Radboud University Nijmegen Medical Centre, Department of Human Genetics, Division of Genome Diagnostics, Nijmegen, the Netherlands.

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

Prenatal cytogenetic analysis on chorionic villi routinely includes combined analysis of both, short and long term culture. This combined approach has been shown to have a very low rate of false negative results (Grati *et al.*, 2014). These data apply to numerical and gross structural abnormalities. However, the incidence of false negative results for pathogenic cryptic imbalances has not yet been assessed which is of particular importance for prenatal molecular karyotyping which is now increasingly being used in prenatal diagnosis.

Here we describe an extraordinary case of fetoplacental discordance for an unbalanced subtelomeric aberration which was not present in chorionic villi. The index patient is a little baby girl who was born as the first child of non-consanguineous Austrian parents. She had facial dysmorphism and multiple congenital anomalies including heart defect, brain malformation, multicystic dysplastic kidneys, and sensorineural deafness. First trimester screening during pregnancy had shown an increased neck translucency (4.2 mm) which prompted chorionic villus sampling. In both, short and long term culture a normal female karyotype was found. Prenatal molecular karyotyping on DNA extracted from long term culture confirmed this result at a higher level of resolution (Illumina Human CytoSNP-12 v2.1 BeadChip, contamination by maternal DNA was excluded).

As no diagnosis could be established exome analysis on DNA from blood was performed after birth. Apart from a *de novo* nonsense variant of unclear clinical significance in *MIB1* no pathogenic mutation was detected. However, subsequent CNV analysis on the exome data led to the detection of two imbalances: a small subtelomeric deletion 9q34.3 (~1.5-2 Mb) and a small subtelomeric duplication 17p13.3 (~2 Mb). This double segment imbalance was due to an unbalanced translocation der(9)t(9;17)(q34.3;p13.3) and could be confirmed by FISH on metaphases from blood lymphocytes and skin fibroblasts of the child but *not* on metaphases from the chorionic villus sample. FISH analysis on chromosomes of both parents showed normal results. Remarkably, analysis of fetal and parental SNPs in chromosome band 9q34.3 revealed a small stretch of maternal isodisomy in chorionic villus DNA which had nearly the same size as the deletion 9q34.3 that was found in the blood sample of the child.

Based on these data we hypothesize that the rearrangement probably started in the early zygote with a terminal deletion of 9qter on the paternal chromosome 9 which subsequently was “corrected” in two different ways: (1) By using the maternal chromosome 9 as template in chorionic cells resulting in segmental isodisomy 9q34.3 in the placenta and (2) by using chromosome 17 as template in fetal cells resulting in an unbalanced translocation der(9)t(9;17)(q34.3;p13.3) in the child.

This puzzling case of a false negative result for molecular karyotyping on chorionic villus DNA indicates that a repeated postnatal CNV analysis may sometimes lead to the right diagnosis.

MUTATIONS IN *KCNH1* AND *ATP6V1B2* CAUSE ZIMMERMANN-LABAND SYNDROME

F. KORTÜM[1,21], V. CAPUTO[2,21], C.K. BAUER[3,21], L. STELLA[4], A. CIOLFI[5], M. ALAWI[6,7,8], G. BOCCHINFUSO[4], E. FLEX[5], S. PAOLACCI[2,5], M.L. DENTICI[9], P. GRAMMATICO[10], G.C. KORENKE[11], V. LEUZZI[12], D. MOWAT[13,14], L.D. V. NAIR[15], T.T.M. NGUYEN[16], P. THIERRY[17], S. M. WHITE[18,19], B. DALLAPICCOLA[9], A. PIZZUTI[2], P.M. CAMPEAU[20], M. TARTAGLIA[5,9,22] AND K. KUTSCHE[1,22]

1 Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
2 Dipartimento di Medicina Sperimentale, Università La Sapienza, Rome, Italy.
3 Department of Cellular and Integrative Physiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
4 Dipartimento di Scienze e Tecnologie Chimiche, Università "Tor Vergata", Rome, Italy.
5 Dipartimento di Ematologia, Oncologia e Medicina Molecolare, Istituto Superiore di Sanità, Rome, Italy.
6 University Medical Center Hamburg-Eppendorf, Bioinformatics Service Facility, Hamburg, Germany.
7 Center for Bioinformatics, University of Hamburg, Hamburg, Germany.
8 Heinrich-Pette-Institute, Leibniz-Institute for Experimental Virology, Virus Genomics, Hamburg, Germany.
9 Ospedale Pediatrico Bambino Gesù-Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy.
10 Dipartimento di Medicina Molecolare, Università La Sapienza, Ospedale San Camillo-Forlanini, Rome, Italy.
11 Zentrum für Kinder- und Jugendmedizin, Neuropädiatrie, Klinikum Oldenburg gGmbH, Oldenburg, Germany.
12 Dipartimento di Pediatria e Neuropsichiatria Infantile, Università La Sapienza, Rome, Italy.
13 Department of Medical Genetics, Sydney Children's Hospital, Sydney, Australia.
14 School of Women's and Children's Health, UNSW Medicine, University of New South Wales, Sydney, Australia.
15 Department of Pediatrics, Saveetha Medical College and Hospital, Saveetha University, Chennai, Tamil Nadu, India.
16 Sainte-Justine Hospital Research Center, University of Montreal, Montreal, QC, Canada.
17 Service de Pédiatrie, CHI Haute-Saône, Vesoul, France.
18 Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia.
19 Department of Paediatrics, University of Melbourne, Australia.
20 Department of Pediatrics, Sainte-Justine Hospital, University of Montreal, Montreal, QC, Canada.
21 These authors contributed equally to this project.
22 These authors jointly directed this project.

E-mail for correspondence: kkutsche@uke.de

Zimmermann-Laband syndrome (ZLS) is a developmental disorder characterized by facial dysmorphism with gingival enlargement, intellectual disability, hypo/aplasia of nails and terminal phalanges and hypertrichosis. We report that heterozygous missense mutations in *KCNH1* account for a significant proportion of ZLS. *KCNH1* encodes the voltage-gated K^+ channel Eag1/Kv10.1. Patch-clamp recordings revealed strong negative shifts in voltage-dependent activation for all but one KCNH1 channel mutant (Gly469Arg). Co-expression of Gly469Arg with wild-type KCNH1 resulted in heterotetrameric channels with reduced conductance at positive potentials but pronounced conductance at negative potentials. These data support a gain-of-function effect of all ZLS-associated KCNH1 mutants. We also identified a recurrent *de novo* missense change in *ATP6V1B2*, encoding the B2 subunit of the multimeric vacuolar H^+-ATPase, in two individuals with ZLS. Structural analysis indicated a perturbing effect of the mutation on complex assembly. Our findings demonstrate that *KCNH1* mutations cause ZLS, and document genetic heterogeneity for this disorder.

INTELLECTUAL DISABILITY ASSOCIATED WITH SPASTIC PARAPLEGIA AND GLAUCOMA IN AN ALGERIAN FAMILY IS CAUSED BY A HOMOZYGOUS MUTATION IN *GRID1*, A GENE ENCODING A SUBUNIT OF GLUTAMATE RECEPTOR CHANNELS

A. TOUTAIN[1,2], Y. HUMEAU[3], D. UNG[2], M.-P. MOIZARD[1,2], N. LEBRUN[4], J. CHELLY[4,5], G. STEVANIN[6] AND F. LAUMONNIER[1,2]

1 Service de Génétique, CHU de Tours, France.
2 Unité INSERM U930, Faculté de Médecine, Université François Rabelais, Tours, France.
3 Team Synapse in Cognition, Institut Interdisciplinaire de NeuroScience, CNRS UMR5297, Université de Bordeaux, Bordeaux, France.
4 Institut Cochin, INSERM U1016, Université Paris-Descartes, Paris, France.
5 IGBMC, Strasbourg, France.
6 Laboratoire EPHE de Neurogénétique, Institut du Cerveau et de la Moelle épinière, Paris, France.

E-mail for correspondence: annick.toutain@univ-tours.fr

Intellectual disability (ID) and spastic paraplegia (SPG) are disorders with marked clinical and genetic heterogeneity. In both groups, non-specific and syndromic forms have been described. The association of ID and SPG is frequent with more than 80 entries in the OMIM database, but the association of ID, SPG and glaucoma has been reported only twice in the literature: in 4 patients of both sexes in two sibships of a large inbred Swedish pedigree, and in three male Canadian siblings born to first-cousin parents. We had the opportunity to examine three brothers, born of Algerian consanguineous parents, with the same condition. The three patients had mild/moderate ID with normal OFC, associated with none or slowly progressive SPG diagnosed in infancy and no other neurological signs, and juvenile open angle glaucoma responsible for a severe visual impairment. Brain MRI, metabolic investigations, chromosome analysis and *MECP2* sequencing were normal. A contiguous gene syndrome was excluded by array-CGH analysis (Agilent CGH 1M) which did not detect any CNV. Consanguinity in all three pedigrees and affected females in one of them support autosomal recessive transmission (OMIM 270850).
By homozygosity mapping in our family we have defined a region of localization of 30.6 Mb containing around 250 genes and MiRNAs at 10q23.1-q25.2 with a maximum Lod Score of 2.53. No gene responsible for ID and/or SPG and/or glaucoma was known in this region. By exome sequencing we have identified a homozygous missense mutation in *GRID1*, a gene located in the previously defined interval. The mutation segregated with the disease. No *GRID1* mutation could however be identified in a cohort of more than 200 patients affected with SPG, isolated or associated with ID. This mutation was also not found in ExAC dataset.
To assess the pathogenicity of the mutation, functional studies were performed on mouse primary hippocampal mature neuronal cultures transfected with either a wild-type or mutated GRID1 construct. While neurons overexpressing the wild-type GRID1 protein displayed an increased frequency of mEPSC currents, the mutated form led to a decreased mEPSC frequency when compared to untransfected neurons. These findings suggest a loss-of-function impact of the mutation. Confocal microscopy analyses also showed a decreased number of dendritic spines in neurons expressing the mutation.
In conclusion, we report the first pathogenic homozygous mutation in *GRID1*. This gene encodes a subunit of glutamate receptor channels. These channels mediate most of the fast excitatory synaptic transmission in the central nervous system and play key roles in synaptic plasticity. This further supports that *GRID1* is the gene responsible for the condition observed in our family.

ABLEPHARON-MACROSTOMIA & BARBER-SAY SYNDROMES AND THE SPECTRUM OF "TWISTOPATHIES"

M. ZENKER[1], D. SCHANZE[1], C.A. STEVENS[2], F. BRANCATI[3], A.T. VULTO-VAN SILFHOUT[4], A. KARIMINEJAD[5], V. FERRAZ[6], N. ROCHE[7], O. BARTSCH[8], P. FARNDON[9], E. BERMEJO-SANCHEZ[10], L. MAZZANTI[11], S. MARCHEGIANI[12], T. DAVIS[12], M.C.V. MALICDAN[12], C. F. BOERKOEL[12], B.B.A. DE VRIES[4] AND M. VAN HAELST[13]

1 Institute of Human Genetics, University Hospital Magdeburg, Germany.
2 Department of Medical Genetics, T.C. Thompson Children's Hospital, Chattanooga, USA.
3 Department of Medical, Oral, and Biotechnological Sciences, University of G. d' Annunzio Chieti and Pescara, Chieti, Italy.
4 Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands.
5 Kariminejad-Najmabadi Pathology and Genetics Center, Tehran, Iran;
6 Departamento de Genetica, Faculdade de Medicina de Ribeirao Preto, Universidade de Sao Paulo, Brazil.
7 Department of Plastic and Reconstructive Surgery, University Hospital of Ghent, Belgium.
8 Institute of Human Genetics, Johannes Gutenberg University, Mainz, Germany.
9 Clinical Genetics Unit, Birmingham Women's Healthcare Trust, Birmingham, UK.
10 ECEMC (Spanish Collaborative Study of Congenital Malformations), CIAC, Instituto de Investigación de Enfermedades Raras (IIER), Instituto de Salud Carlos III, Madrid, Spain.
11 Department of Pediatrics, S. Orsola-Malpighi Hospital University of Bologna, Italy.
12 NIH Undiagnosed Diseases Program, Common Fund, Office of the Director, NIH and National Human Genome Research Institute, NIH, Bethesda, USA.
13 Department of Medical Genetics, University Medical Center Utrecht, the Netherlands.

E-mail for correspondence: martin.zenker@med.ovgu.de

Ablepharon macrostomia syndrome (AMS) and Barber-Say syndrome (BSS) are very rare congenital malformation syndromes. They are characterized by overlapping clinical features including abnormalities of eyelids and nose, large mouth, malformed ears, wrinkled skin, abnormal hair, and genital malformations. Recently, a large international consortium established recurrent heterozygous TWIST2 mutations as the genetic basis of these distinct syndromes (Marchegiani *et al*.: Am J Hum Genet 2015). Recessive TWIST2 mutations were previously found to cause Setleis syndrome, a focal facial dermal dysplasia syndrome that shares some similarities with AMS and BSS (Tukel *et al*.: Am J Hum Genet 2010). The gene TWIST1, that encodes a protein with strong sequence homology, is long known to be mutated in craniosynostosis disorders belonging to the phenotypic spectrum of Saethre-Chotzen syndrome (SCS).
TWIST proteins are bHLH transcription factors that exhibit highly overlapping expression profiles during development and have the ability to either form homo- or heterodimers. They are known to directly interact with a large set of transcription factors and may behave either as transcription repressors or activators, depending on the cellular context.
Herein, we delineate mutation spectrum, genotype phenotype correlations, and molecular pathogenesis of AMS and BSS. We review the clinical spectrum of disorders caused by TWIST mutations to depict the phenotypic link between TWIST1- and TWIST2-associated diseases.

KDM1A MUTATIONS IN INTELLECTUAL DISABILITY

A. RAUCH AND E. BOLTSHAUSER

Institute of Medical Genetics and Neuropediatrics, University of Zurich, Zurich, Switzerland.

E-mail for correspondence: anita.rauch@medgen.uzh.ch

KDM1A is a histone demethylase that play diverse roles in regulating gene expression during development. Kdm1a is involved in repression of neuronal genes in non-neuronal cells, and during the perinatal period, alternative splicing of KDM1A results in expression of two neuron-specific isoforms that regulate neurite maturation.
We report the phenotype of an 8 years old boy with severe intellectual disability who was found to harbor a de novo variant of unknown significance in KDM1A within our previously published exome sequencing study (Rauch *et al*. Lancet 2012). Further observations suggests now that KDM1A de novo variants indeed cause intellectual disability and distinct facial features such as prominent forehead, slightly arched eyebrows, elongated palpebral fissures, a wide nasal bridge, thick lips, and abnormal teeth.

A FIRST GENE INVOLVED IN GOLDENHAR SYNDROME

D. LACOMBE[1,4], E. LOPEZ[1], M. BERENGUER[1], S. MARLIN[2], A. TINGAUD-SEQUEIRA[1], S. CHARRON[1], H. DE BELVALET, G.MATTHIEU[1], FECLAD[3], P. BABIN[1], B. ARVEILER[1,4] AND C. ROORYCK[1,4]

1 Laboratoire MRGM, EA4576, Université de Bordeaux, Bordeaux, France.
2 Centre de Référence des Surdités Génétiques, Département de Génétique, Hôpital Necker, Paris, France.
3 Fédération des Centres de Référence Anomalies du Développement et syndromes malformatifs, 8 centres, France.
4 Service de Génétique Médicale et Centre de Référence Anomalies du Développement et Syndromes Malformatifs, CHU de Bordeaux, Bordeaux, France.

The oculoauriculovertebral spectrum (OAVS, OMIM 164210) or Goldenhar syndrome is a developmental anomaly involving the first and second branchial arches. This syndrome represents one of the most common congenital craniofacial disorder, with a prevalence around 1/26,000 births. Main features include facial asymmetry resulting from maxillary and/or mandibular hypoplasia, hemifacial microsomia, unilateral or bilateral ear anomalies, ocular defects, and vertebral malformations. To date, although various chromosome abnormalities have been associated with OAVS and several candidate genes have been screened, the genetic etiology of this pathology remains largely unknown. For the present study, a project with national recruitment established a cohort of 156 patients with OAV spectrum. In order to determine the molecular basis of Goldenhar syndrome, we performed exome sequencing in trios including selected patients with Goldenhar syndrome and their healthy parents. We identified a *de novo* nonsense mutation in GOLD1 gene, a poorly characterized transcription factor known to be involved in ear development. Screening of the cohort identified a missense mutation in a second patient. Interestingly, GOLD1 belongs to a genetic environment within a paralogon that was already involved in another Copy Number Variant associated with OAVS. Functional studies by transient knockdown in zebrafish model evidenced gold1 as craniofacial cartilages architecture key factor. In conclusion, we report GOLD1 as the first gene involved in Goldenhar syndrome. Future identification of other genes should allow a better understanding of molecular processes leading to OAVS.

HETEROZYGOUS LOSS-OF-FUNCTION MUTATIONS IN A NEW GENE FOR ADAMS-OLIVER SYNDROME

J.A.N. MEESTER[1], L. SOUTHGATE[2], A.-B. STITTRICH[3], H. VENSELAAR[4], S.J.A. BEEKMANS[5], N. DEN HOLLANDER[6], E.K. BIJLSMA[6], A. HELDERMAN-VAN DEN ENDEN[6], J.B.G.M. VERHEIJ[7], G. GLUSMAN[8], J.C. ROACH[3], A. LEHMAN[8], M.S. PATEL[8], B.B.A. DE VRIES[9], C. RUIVENKAMP[6], P. ITIN[10], K. PRESCOTT[11], S. CLARKE[11], R. TREMBATH[12], M. ZENKER[13], M. SUKALO[13], L. VAN LAER[1], B. LOEYS[1] AND W. WUYTS[1]

[1] Center of Medical Genetics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium.
[2] Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
[3] Institute for Systems Biology, Seattle, Washington, USA.
[4] Centre of Molecular and Biomolecular Informatics, Radboudumc, Nijmegen, the Netherlands.
[5] Department of Plastic and Reconstructive Surgery, VU Medical Center Amsterdam, the Netherlands.
[6] Department of Clinical Genetics, Leiden University Medical Center, the Netherlands.
[7] Department of Medical Genetics, University Medical Centre Groningen, the Netherlands.
[8] Department of Medical Genetics and Child and Family Research Institute, University of British Columbia, Vancouver, Canada.
[9] Department of Human Genetics and Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, the Netherlands.
[10] University Hospital, Dermatology, Basel, Switzerland.
[11] Department of Clinical Genetics and 12: Dermatology, Chapel Allerton Hospital, Leeds, UK.
[13] Institute of Human Genetics, Otto-von-Guericke-Universität Magdeburg, University Hospital Magdeburg, Germany.

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

Adams-Oliver syndrome (AOS) is a rare developmental disorder typically characterized by the presence of both congenital cutis aplasia (ACC) of the scalp vertex and terminal limb defects. In addition, cardiovascular anomalies are also frequently observed. Five causal genes for AOS have been identified so far. Mutations in EOGT and DOCK6 cause the autosomal recessive form of AOS, while mutations in ARHGAP31, RBPJ and NOTCH1 lead to autosomal dominant AOS.
Because of the cardiovascular features in AOS patients and as RBPJ, NOTCH1 and EOGT are all members of the Notch signaling pathway, we hypothesized that mutations in other genes involved in this pathway could lead to AOS as well. Targeted sequencing of NOTCH pathway members in 113 families showed nine heterozygous mutations in the gene for a NOTCH1 ligand, including nonsense and missense mutations, identifying an additional cause of autosomal dominant AOS or isolated ACC. Affected mutation positive individuals present with variable clinical expression with no emerging genotype-phenotype correlations.

TRANSMISSION OF THE P250R MUTATION OF THE FGFR3 GENE IN FOUR GENERATIONS WITH HIGHLY VARIABLE PHENOTYPE

H. BUCIEK HOVE[1], M. DUNØ[1], J. DAUGAARD-JENSEN[2] AND SVEN KREIBORG[1,2,3]

[1] Department of Clinical Genetics, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.
[2] Resource Centre for Rare Oral Diseases, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark and
[3] Department of Paediatric Dentistry and Clinical Genetics, School of Dentistry, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

E-mail for correspondence: Hanne.buciek.hove@regionh.dk

Background & Purpose: The P250R mutation of the FGFR3 gene is the most common mutation known to be associated with craniosynostosis in humans. A few studies have, however, documented affected family members without craniosynostosis. This report documents a family where the P250A mutation was discovered by chance in two brothers examined for a mutation in the FGFR3 gene known to cause hypochondroplasia. The boys and their mother had short stature, but no signs of craniosynostosis.
Methods: After discovery of the P250R mutation in the two brothers, DNA analysis of the FGFR3 gene was carried out in their mother and the mother's aunt and grandmother. All individuals were examined clinically and some by roentgencephalometry.
Results: All examined family members (four generations) had the P250R mutation of the FGFR3 gene. However, only two of these family members had, previously undiagnosed but evident, craniosynostosis, namely the mother's aunt (bicoronal synostosis) and grandmother (unicoronal synostosis). All examined family members had short stature and short fingers and toes.
Conclusions: The P250R mutation of the FGFR3 gene was identified by chance in two brothers without craniosynostosis. The mutation was subsequently found to be present in a total of five family members in four generations, and only two of these individuals, one in generation I and one in generation II, had craniosynostosis; and to a variable degree. It is concluded that the P250R mutation of the FGFR3 gene is probably quite often not associated with craniosynostosis.
Main Objectives of Presentation: To present a family where the P250R mutation of the FGFR3 gene was identified by chance in two brothers with short stature and examined for a mutation in the FGFR3 gene known to cause hypochondroplasia. Subsequently, two family members with previously undiagnosed craniosynostosis and the P250R mutation were identified.

A BALANCED RECIPROCAL TRANSLOCATION t(10;15)(q22.3;q26.1) INTERRUPTING ACAN GENE IN A FAMILY WITH IDIOPATHIC SHORT STATURE: FURTHER DELINEATION OF THE AGGRECAN-ASSOCIATED PHENOTYPES

M. T. BONATI[1], M. CRIPPA[2], S. GIANGIOBBE[1], C. SCACCABAROZZI[2], L. FATTI[3], F. BELLINI[1], L. LARIZZA[2], L. PERSANI[3, 4, 5] AND F. PALMA[2, 6]

1 Clinic of Medical Genetics, San Luca Hospital, IRCCS Istituto Auxologico Italiano, Milano, Italy.
2 Laboratory of Medical Cytogenetic and Molecular Genetics, IRCCS Istituto Auxologico Italiano, Milano, Italy.
3 Division of Endocrinology and Metabolic Diseases, San Luca Hospital, IRCCS Istituto Auxologico, Milano, Italy.
4 Laboratory of Endocrine and Metabolic Research, IRCCS Istituto Auxologico Italiano, Milano, Italy.
5 Department of Clinic Sciences and Community Health, University of Milan, Milano, Italy.
6 Department of Medical Biotechnology and Translational Medicine, University of Milan, Milano, Italy.

E-mail for correspondence: mt.bonati@auxologico.it

Stature is genetically determined, as evidenced by a height heritability value of 80%. A complex genetic model has been hypothesized in most cases showing idiopathic short stature (ISS). However, in a subset of subjects ISS may also be caused by mutations in single genes. Among those involved in skeletal development, the aggrecan (ACAN) has recently been added to a short list as a result of the identification, by mean of whole exome sequencing (Nilsson *et al*., 2014) or target gene screening (Quintos *et al*., 2015), of four different point mutations in four families with ISS. Aggrecan is a chondroitin sulfated proteoglycan, which is a major component of cartilage extracellular matrix, both in articular and growth plate cartilage, and is essential not only for cartilage development, but also for its integrity.
Similarly to the SHOX gene, heterozygous ACAN mutations are responsible for a final height whose range goes from -2 to -4 SDS and they may be associated either with ISS (Nilsson *et al*., 2014; Quintos *et al*., 2015) or skeletal dysplasias, i.e. SEDK (Gleghorn *et al*., 2005) or OD (Stattin *et al*., 2010). On the other hand, homozygous mutations are the cause of the severe short-limb type short stature SEMD (Tompson *et al*., 2009), with a final height range from -14 to -15 SDS. And as happens in SHOX gene mutations, even within aggrecan heterozygous mutated families classified as ISS, very mild sign of skeletal dysplasias (flat nasal bridge, midface hypolpasia, osteochondritis dissecans at knees) may be recognized.
We report on a four-generation family from Southern Italy with 9 members affected by proportional short stature, all found to be carriers of a balanced reciprocal translocation t(10;15)(q22.3;q26.1). Fluorescence in situ hybridization finely mapped the chromosome 15 translocation breakpoint (bkp) within IVS1 of the ACAN gene, whereas the chromosome 10 bkp was found to lie close to the *ANXA11* gene (annexin A11). Moreover, through high-resolution array CGH analysis the presence of rare CNVs spanning the translocation bkp or localized elsewhere in the genome were ruled out in the translocation's carriers.
As the bpk interrupts the gene before its ATG starting codon, which is located in exon 2, it causes haplo-insufficiency. It may therefore be compared to the point mutations identified in family 1 and 2 reported by Nilsson *et al*. (2014) as well as to the family described by Quintos *et al*. (2015), in which haplo-insufficiency could be only predicted. However, differently from the families reported by Nilsson and Quintos, where ISS were associated with advanced bone age, which was the cause of early growth cessation, in our family the bone age of the two girls in the fourth generation followed-up for growth hormone (GH) therapy corresponded with their chronological age. GH deficiency was excluded in both patients and GH treatment did not improve the growth rate.
In addition, a few minor radiological peculiarities have been revealed at skeletal assessments: thin ribs, an extension of the tibial epiphysis beyond the femoral epiphysis on the lateral side, bilateral femoral valgus, stocky femoral necks and ovoid femoral heads. Family members of the second generation were included in this evaluation as well.
This represents further evidence in support of the involvement of aggrecan in ISS. The absence of advanced bone age in particular seems to expand the aggrecan-associated phenotypes. In addition, growth rate does not seem to be improved by GH treatment.

Key-words: SEDK, spondyloephiphyseal dysplasia, Kimberley type; OD, Osteochondritis dissecans; SEMD, spondyloepimeaphyseal dysplasia, aggrecan type

PROGRESSION OF CLINICAL AND MORPHOLOGICAL FEATURES IN MAN WITH HAJDU-CHENEY SYNDROME DURING 23 YEARS OF OBSERVATION

A.T.MIDRO[1], K. KOZŁOWSKI [2] E. HUBERT[3], J. BORYS[3], E. HASMANN-POZNAŃSKA[4], [E]. TARASÓW[5], J. SKOWRONSKI[6], M. RYDZANICZ[7], A. POLLAK[8], P. STAWIŃSKi[8], B. STASIEWICZ-JAROCKA[1] AND R.PLOSKI[7]

1 Department of Clinical Genetics, Medical University, Bialystok, Poland.
2. Royal Alexandra Hospital for Children, Sydney, Australia.
3. Maxillo-Facial Surgery of Clinic, Medical University, Bialystok, Poland.
4. Paediatric Otolaryngology of Clinic, Medical University, Bialystok, Poland.
5. Radiology Clinic, Medical University, Bialystok, Poland.
6. Orthopedic Clinics, Medical University, Bialystok, Poland.
7. Department of Medical Genetics, Warsaw Medical University, Warsaw, Poland.
8. World Hearing Center, Institute of Physiology and Pathology of Hearing, Warsaw, Poland.

E-mail for correspondence: alinamidro@gmail.com; midro@umb.edu.pl

We present a natural history of 32 year-old man with Hajdu-Cheney syndrome (HJCYS) (102500#OMIM) due to a *de novo* truncating mutation in the exon 34 of *NOTCH2* (c.6424-6427delTCTG, p.Ser2142ArgfsX4).The small stature, acro-osteolysis of terminal phalanges and distinctive craniofacial features including dental anomalies were basis of clinical diagnosis. Additionally, many clinical (hearing loss, vocal scale limited to lower tones, delayed fontanels closure, delayed dental eruption, open bite, depressed sternum) and radiological findings (Wormian bones, acro-osteolysis, generalized osteoporosis) have been observed. As a main diagnostic tool for quantitative evaluation a protocol of 800 well defined and systematised traits (by Stengel-Rutkowski with own modifications) was used. Analysis of his morphological and clinical phenotype has been performed at the age of 9, 12 and 32 years. The progression of clinical changes in the form of skeletal dysplasia which affects skull, spine, fingers of hands and foot as well as abnormalities affecting vision, hearing, speaking and dentition have been observed. Fortunately, the intellectual development was perfect.

A PATIENT WITH GELEOPHYSIC DYSPLASIA-PLUS PHENOTYPE DUE TO NOVEL MUTATIONS IN *ADAMTSL2*

L. MACKENROTH[1], P. LORENZ[2], N. DI DONATO[1], A. RUMP[1] AND A. TZSCHACH[1]

[1] Faculty of Medicine Carl Gustav Carus, Institute for Clinical Genetics, Fetscherstr. 74, 01307 Dresden, Germany.
[2] Mitteldeutscher Praxisverbund Humangenetik, Praxis Meerane, Marienstr. 18, 08393 Meerane, Germany.

E-mail for correspondence: Luisa.mackenroth@uniklinikum-dresden.de

Geleophysic dysplasia (GD) type 1 (OMIM #231050) is a rare autosomal recessive disorder affecting primarily bones and connective tissue. Skeletal abnormalities include severe short stature, brachydactyly and shortened long tubular bones, joint contractures, delayed bone age and cone-shaped epiphyses. The facial gestalt is considered to be characteristic leading to a fairly “happy” face. Life-limiting complications can occur due to progressive cardiac valvular thickening and respiratory insufficiency. Lysosomal inclusions have been reported in some patients leading to hepato- and cardiomegaly. Intelligence is supposed to be normal. Until today, less than 100 patients have been reported [Garcia-Ortiz *et al*. 2015].
Mutations in two genes have been identified as the molecular cause of GD: Biallelic mutations in *ADAMTSL2* cause the autosomal recessive inherited GD type 1. However, few reports have been published on families with a dominant transmission of *ADAMTSL2* mutations causing GD [Garcia-Ortiz *et al*. 2015]. In addition, monoallelic mutations in *FBN1* [Le Goff *et al*. 2011] cause an autosomal dominant form of GD (type 2). Each gene accounts for approximately 50% of the molecular bases of GD.
We report on a male child who was referred for genetic counseling because of recurrent respiratory infections, progressive short stature and minor anomalies. Skeletal survey revealed severe brachydactyly with shortening of all short tubular bones including metacarpalia and all phalanges. In addition, he showed poor diaphyseal modelling of the phalanges but there was no sign of the typical proximal tapering of metacarpal bones. Typical cone-shaped epiphyses were not seen as the bone age was severely delayed at the age of one year an three months and as no epiphyses were detectable. Long tubular bones showed mild shortening of femur, humerus (which had already been seen in prenatal ultrasound) and ulna. He had mild pulmonary stenosis and facial dysmorphism including thin lip vermilion, long philtrum and broad nasal tip as well as bilateral ptosis. Furthermore, he showed delayed speech and motor development.
Molecular genetic investigation revealed two novel mutations in *ADAMTSL2*: NM_001145320.1(*ADAMTSL2*):c.2533G>T, p.(Glu845*) and NM_001145320.1(*ADAMTSL2*):c.799G>A, p.(Gly267Ser). Parental testing confirmed biallelic distribution of the mutations. The missense mutation has been found twice in a heterozygous state whereas the nonsense mutation has never been found in the ExAC cohort. CADD score for the missense mutation was 33 with four bioinformatic tools (MutationTaster, Polyphen2, PREOVEAN, SIFT) predicting pathogenicity.
Biallelic mutations in ADAMTSL2 correlate with the most of the clinical features and explain progressive short stature and severe brachydactyly. However, specific facial anomalies present in the child as well as developmental delay have not been associated with GD before. Our case report may expand the clinical spectrum of GD type 1, although we cannot rule out a “double trouble” – the presence of a second undiagnosed condition responsible for the specific facial anomalies and developmental delay.

CAMURATI-ENGELMANN DISEASE WITH TORUS PALATINUS: COINCIDENCE OR CLINICAL OVERLAP WITH WORTH HYPEROSTOSIS?

D. HAYE[1-3], C. COLLET[2] AND A. TOUTAIN[3-4]

1 Département de Génétique, APHP Robert Debré, Paris, France.
2 Service de Biochimie et Biologie Moléculaire, Hôpital Lariboisière, Paris, France.
3 Service de Génétique, CHU de Tours, France.
4 UMR_INSERM U930, Faculté de Médecine François Rabelais, Tours, France.

Camurati-Engelmann disease (CED), also known as progressive diaphyseal dysplasia, is a rare autosomal dominant condition with 300 cases described until now. It is characterized by hyperostosis of the long bones and the skull, joint limitations, proximal muscle weakness, wadding gait and chronic bone pain. CED is caused by mutations in the *TGFB1* gene.
We report here a 39 year old Vietnamese woman with no family history. She was referred for limb pains and hyperostosis of the long bones and the skull, consisting of periosteal involvement with uneven cortical thickening and endosteal bone sclerosis. Physical examination showed a torus palatinus (TP). Radiological findings and TP raised the question of benign cortical hyperostosis (Worth type), but no mutation was found in the *LRP5* gene. Direct sequencing of the *TGFB1* gene identified a heterozygous mutation thus confirming the diagnosis of CED.
Torus palatinus is an exostosis formed of cortical bone, usually located along the median line where palatine shelves merge. TP is more common in certain ethnic groups and countries but its frequency seems to be low in the Vietnamese group (0.9%). Pathogenesis of TP is not solved but it has been proposed to be genetically determined. TP is usually associated with Worth endosteal hyperostosis but is not usually part of CED. To our knowledge, CED with TP was only reported in 2011 by Whyte *et al.* in a Caucasian male patient and his mother. Camurati-Engelmann disease should therefore be considered in case of radiological hyperostosis of the long bones and the skull associated with torus palatinus.

DETECTION OF FACIAL DYSMORPHISM IN CENTRAL AFRICAN PATIENTS

A. LUMAKA[1,2,3,4], N. COSMANS[1], A. LULEBO MAMPASI[5], H.PEETERS[1], M. HOLVOET[1], T.PR. LUKUSA[1,2,3,4] AND K. DEVRIENDT[1]

1 Center for Human Genetics, University Hospitals Leuven, Katholieke Universiteit Leuven, Leuven Belgium.
2 Center for Human Genetics, Faculty of Medicine, University of Kinshasa, Democratic Republic of the Congo.
3 Department of Paediatrics, Faculty of Medicine, University of Kinshasa, Democratic Republic of the Congo.
4 Institut National de Recherche Biomedical, Democratic Republic of the Congo.
5 Kinshasa School of Public Health, Faculty of Medicine, University of Kinshasa, Kinshasa, DR, Congo.

Introduction and Methods

Recent advances in morphometric analysis have explored the possibility to perform an objective evaluation of the facial gestalt from 2D or 3D facial images and find a reliable syndrome match. This requires matching the face of a patient with similar patients in a database of individuals with known syndromes. Such tools hold great promise of reaching a rapid diagnosis for common genetic syndromes. Especially in low resource countries, where access to laboratory testing is limited, the potential of such user-friendly tools is great.

Studying dysmorphism in Central Africa is challenging, because the facial morphology in normal individuals presents obvious differences between African and other populations. In addition, the craniofacial presentation of some syndromes in a patient of African origin may differ from a Caucasian with the same syndrome as showed for the del22q11, Fragile X and fetal alcohol syndromes.

We aimed to assess the performance of the tool Face2Gene, at the current stage of its development, to recognize Down syndrome in Congolese versus Caucasian patients. The study is part of an etiological diagnostic study in 127 patients with intellectual disability, recruited in 6 specialized clinics and schools in Kinshasa in the DR Congo. We uploaded to Face2Gene the facial photographs of 17 DS patients from Congo and 20 DS patients from Flanders in Belgium. Patients from the 2 groups were sex and age matched.

Results

Face2Gene reported DS match within the first 10 matches in 16/20 (80 %) Belgian patients but only in 6/17 (35.29 %) Congolese patients. In Congolese patients, Down syndrome was the first suggested match in 2, ranked within the first 5 matches in 5 and within the first 10 in 6 of them. Conversely, Down syndrome was the first suggested match in 8, ranked within the first 5 matches in 13 and within the first 10 in 17 of them in the 20 Flemish cases. The mean rank in the Congolese patients was 8.29, which is significantly lower than the mean 4.65 recorded from Europeans ($p = 0.004446 \pm 0.000674$). Altogether, Face2Gene showed an Accuracy of 0.35 in Congolese against 0.8 in Belgians and a Precision of 1 in both groups.

Discussion

Our data indicate that the system has a high precision in both groups. However, the accuracy in the Caucasian cohort was much higher compared to the African cohort. This is interesting, since it confirms that there are differences in facial appearance of Caucasian versus African Down syndrome patients. The most likely explanation why Face2gene is underperforming in Congolese Down syndrome is that the tool is trained mostly with Caucasian cases. We therefore anticipate that the performance will improve when the system is trained with more Down syndrome cases from Central Africa. A collaborative effort to test this hypothesis is ongoing.

FETAL WARFARIN SYNDROME AND HYPERINSULINISM: A POSSIBLE PHENOTYPIC EXPANSION?

Á. MARTÍN-RODRÍGUEZ[1], E.J. GARCÍA[1], L. CASTAÑO[2], A. AGUAYO[2] AND A. GONZÁLEZ-MENESES[1]

[1] Pediatrics Department. Children's Hospital. Hospital Universitario Virgen del Rocío. Sevilla, Spain.
[2] Biocruces Health Research Institute. Hospital Universitario Cruces, Barakaldo, Spain.

E-mail for correspondence: alvaromartin.md@gmail.com

Fetal warfarin syndrome is a rare condition first described by DiSaia in 1966. Warfarin is an oral anticoagulant drug used for the treatment and prophylaxis of thromboembolic disease and systemic embolism associated with valvular heart disease and prosthetic heart valves. Due to its teratogenic effects, it should be avoided during pregnancy. The effects of warfarin in exposed fetuses are diverse and range from spontaneous abortion to a spectrum of congenital anomalies.
We present the case of a male infant, whose mother was under treatment with acenocoumarol (a warfarin analogue) because she carried a prosthetic aortic valve, due to a tetralogy of Fallot.
The diagnosis of fetal warfarin syndrome was established based on the facial and body findings and the consumption of a warfarin analogue by his mother until the fifth month of gestation.
Clinically, the infant had a marked nasal hypoplasia with a broad and depressed nasal bridge, and epicanthal folds. His fingers were short and wide. He also presented global hypotonia.
During his first month of life he was admitted twice to the hospital because of upper airway obstruction, feeding difficulties, and a failure to thrive.
At five months of age he developed relevant hypoglycaemias, and was diagnosed of hyperinsulinism, so oral diazoxide and hydrochlorothiazide was started.
Both genetics studies (chromosomal abnormalities and hyperinsulinism susceptibility genes) were normal.
To our knowledge, this is the first reported case of fetal warfarin syndrome associated with hyperinsulinism. The mechanisms underlying this association are still unclear, so further studies should be done.
This case may reinforce the importance of avoiding teratogens during pregnancy and aware about hyperinsulinism in infants affected by fetal warfarin syndrome.

WHEN A COMMON SYNDROME PRESENTS IN A LESS COMMON WAY…

K. KEYMOLEN[1], M. DERADEMAEKER[1], D. HASAERTS[2] AND S. SENECA[1]

[1] Centre for Medical Genetics, Reproduction and Genetics, Reproduction Genetics and Regenerative Medicine, Vrije Universiteit Brussel (VUB), UZ Brussel, Laarbeeklaan 101, 1090 Brussel
[2] Department of Paediatric Neurology, Vrije Universiteit Brussel (VUB), UZ Brussel, Laarbeeklaan 101, 1090 Brussel

E-mail for correspondence: Kathelijn.Keymolen@uzbrussel.be

Two patients will be presented to illustrate that the diagnosis may be delayed when the reason of referral is "an occasional abnormality" of the underlying syndrome.
The first child was referred at 7 months because of facial dysmorphism and skeletal anomalies. He had a round face, epicanthic folds, narrow thorax and kyphosis in sitting position.
Metabolic, chromosomal and skeletal investigations were performed but did not allow to make the diagnosis...
Familial history finally led to the diagnosis.
The second patient was seen at the genetics department at the age of 13 months because of cleft palate. No other major congenital anomalies were present. Chromosomal investigation was normal. Clinical follow-up allowed to make the diagnosis.

Both patients have the same underlying diagnosis, confirmed by molecular testing of the index and family members.
With the presentation of these two unrelated cases, we want to draw the attention to a possible diagnostic pitfall.

SYSID: A SYSTEMATIC APPROACH TO THE GENETIC AND CLINICAL HETEROGENEITY OF INTELLECTUAL DISABILITY DISORDERS

C. ZWEIER[1], K. KOCHINKE[2], B. NIJHOF[2], M. FENCKOVA[2], P. CIZEK[3], F. HONTI[4], S. KEERTHIKUMAR[3], M.A.W. OORTVELD[2], T. KLEEFSTRA[2], J.M. KRAMER[2], C. WEBBER[4], M.A. HUYNEN[3] AND A. SCHENCK[2]

1 Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.
2 Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical centre, Nijmegen, The Netherlands.
3 CMBI, Radboud Institute for Molecular Life Sciences, Radboud university medical centre, Nijmegen, The Netherlands.
4 MRC Functional Genomics Unit, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK.

E-mail for correspondence: christiane.zweier@uk-erlangen.de

Intellectual disability (ID) disorders are clinically and genetically extremely heterogeneous and thus represent a major challenge in clinical genetics and diagnostics. Though recent studies on specific subsets of ID and co-morbid autism spectrum disorders have indicated that convergent molecular pathways underlie common phenotypic aspects, a comprehensive and systematic understanding of ID disorders and their underlying biology is still limited.
To provide an inventory on monogenic causes of ID and to systematically unravel common molecular themes, we established a database that currently contains more than 700 reliable known ID genes and additionally more than 300 ID candidate genes. Further gene-related information, various functional datasets and information on associated disorders were implemented. We also classified all reliable ID genes according to their ID manifestation (syndromic with or without structural malformations, non-syndromic,) and severity and according to 27 associated core clinical features such as organic or neurological anomalies. Currently, mutations in 62% of 706 ID genes follow autosomal recessive inheritance, mutations in 25% are autosomal dominant (mainly de novo), and 15% are X-linked. This database will be accessible after publication and can be exploited for various queries and clinical, diagnostic and research purposes.
Using this integrated resource we show that nearly half of all ID proteins physically interact with other ID proteins and that they are significantly co-expressed, particularly in the hippocampus. 86% of ID genes fall into 32 common biological, Gene Ontology based processes: metabolism and nervous system development among the largest, and hedgehog and glutamate signalling among the most enriched groups.
By combining functional and phenotype information we found that certain phenotypic subgroups can predict novel gene functions, and that vice versa, certain functional themes correlate with specific phenotypic features. The latter revealed characteristic, process defined phenoprofiles in terms of IDopathies, including chromatinopathies or DNArepairopathies. We also could show that the biological coherence among ID genes is sufficient to predict ID genes and that utilization of phenotypic information adds even more predictive power.
We provide a widely usable database containing ID genes, their associated disorders, phenotypes and biological functions. Using this resource, our study provides systematic insight into the molecular and clinical landscape of ID disorders and proves the utility of systematic phenomic analyses in highly heterogeneous genetic disorders.

UNRAVELING UNUSUAL PRESENTATIONS OF CLASSICAL SYNDROMES BY EXOME SEQUENCING: THE CASE OF PRIMARY MICROCEPHALY

A. VERLOES[1], S. PASSEMARD[1], S. DRUNAT[1], C. DUPONT[1], M. OUACHEE[2], E. CUADRO[3] AND R. KOM[3]

[1] Department of Genetics and INSERM UMR1141
[2] Department of Hematology, Robert DEBRE University Hospital
[3] Department of Pediatrics, Cayenne General Hospital, French Guyana, France.

Whole exome sequencing (WES) has entered clinical practice, at least with a research background, allowing unbiased molecular evaluation of patients with genetic disorders without the need to select a panel of candidate genes based on cornerstone features. In our search of genetic etiology for unexplained congenital microcephalies, we undertook exome WES of two patients. The first case is a 10 years-old girl of Caribbean ancestry, with IUGR, severe congenital microcephaly, major feeding problems and susceptibility to infections detected at age 7. She had large café-au-lait spots but no photosensitivity. Many investigations were carried out in infancy, including search for induced chromosome break. WES identified biallelic mutations in BLM syndrome. The diagnosis was confirmed by SCE study. Bloom syndrome was overlooked because the typical photosensitive lupus-like rash was not present. Patient 2 is a 4 year-old girl with deep developmental delay and spasticity, born to unrelated Guyanese parents. She never had any epileptic manifestations. Her brother, who was similarly affected, died at age 4 months from infectious diarrhea with dehydratation. He never had objective seizures. MRI showed in both children small but normally formed brain. Extensive genetic and metabolic screen were negative (including aminoacid chromatogram), but CSF fluid was not investigated. WES demonstrated biallelic mutation in 3-phosphoglycerate dehydrogenase (PHGDH) coding the enzyme that converts 3-P-glycerate to 3-P-OH-pyruvate. Very low seine level in CSF confirmed the diagnosis. Congenital microcephaly and spastic tetraparesis are well known manifestations of PHGDH, but early onset, often intractable seizures are the hallmark of this type of encephalopathy. Those two cases illustrate how a “simple” diagnosis may be missed when the triggering features are missing. Not surprisingly, a widening of the clinical spectrum of many inherited disorders should be a side effect of generalizing WES, as our current practices tend to limit costing single gene screenings to patients who have typical Gestalt

EXOME AND GENOME ANALYSIS IN NEONATAL AND PAEDIATRIC INTENSIVE CARE UNITS – THE HAMBURG EXPERIENCE

M. HEMPEL[1], T. DIEHL[2], M. BLOOM[2], P. DEINDL[2], E. MAHLER[1], T.B. HAACK[3,4], C. KUBISCH[1], T.M. STROM[3,4] AND D. LESSEL[1]

1 Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
2 Department of Pediatrics, University Medical Center Eppendorf, Hamburg, Germany.
3 Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany.
4 Institute of Human Genetics, Technische Universität München, Munich, Germany.

Corresponding author: m.hempel@uke.de

Next-generation sequencing (NGS) technologies are powerful tools to dissect the genetic basis of monogenic diseases. During the last years, this fast and comprehensive genome-wide analysis highly accelerated the identification of disease-causing mutations. Moreover, NGS is currently being widely implemented in medical practice either through targeted resequencing of “Gene panels” or through “Clinical whole-exome sequencing”. NGS is mainly offered to patients for differential diagnosis of putative monogenic disease, mostly after lots of time consuming, expensive and in particular, invasive routine tests had been performed. It is currently estimated that one third of Neonatal and Paediatric Intensive Care Unit (NICU and PICU) patients have an underlying monogenic disease and the knowledge of the right genetic diagnosis could influence therapy and/or management. Notably, the precise prevalence remains largely unknown because of low ascertainment rates and early-deaths. Here we report on our experience with exome and genome analysis in a NICU and PICU setting. We have analyzed 12 severely ill patients with suspected monogenic disease. The procedure of patient enrollment, previous clinical and routine diagnostics, NGS procedures, results and its impact of patient’s management will be presented. Briefly, mutation in an OMIM disease gene was identified in only a single patient. In three patients no causative gene variation could be detected. In the remaining patients, we discovered variations in candidate genes which pathogenicity should be confirmed by further analyses. Based on our experience and supporting data from the literature, genome wide sequencing in a trio setting implemented in a diagnostic work up in NICU and PICU, accelerates the molecular diagnosis and may have an impact on treatment and management. Hence, the analysis should be performed rapidly, within one ore 2 weeks, to be relevant for decision-making. However, currently the diagnostic yield is poor if only OMIM disease gens are considered. Thus, this may change in the near future through higher awareness and ascertainment rates and consecutive identification of novel genetic causes of this very heterogeneous group of diseases.

THE GENOME ERA: A CLINICAL PERSPECTIVE

C. STUMPEL and many colleagues in Maastricht and Nijmegen

Department of Clinical Genetics and School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, 6202 AZ Maastricht, the Netherlands

E-mail for correspondence: c.stumpel@mumc.nl

The clinical genetic work poses challenges as long as we know. Making a diagnosis in an individual with congenital anomalies and or developmental delay/intellectual disability has a benefit in many aspects.
The amazingly increased lab-technical possibilities make the genetic practice exciting but the input of the medical expert is and remains very valuable.
In this presentation a number of examples will be presented to underline the relevance of a good interaction between the clinician and the lab expert. For example: a normal gene analysis result but still a clinical diagnosis.
On the other hand, our clinical experience is disappointing and we can be surprised by the results of the exome sequencing. Examples are given. Diagnosis at an adult age is no exception in these cases.
Finally, we have patients with a mutation in a ‘new’ gene, where we need additional cases to define the situation.
In conclusion, the presentation will show many individuals with a surprising finding from a clinical - or from a genomic point of view.

REVERSE PHENOTYPING OF A PATIENT WITH CRIPT GENE MUTATION AND FURTHER DELINEATION OF THE ASSOCIATED PHENOTYPE

B. DEMEER[1,2], A. DADBAN[3], P. VABRES [4,5], G. MORIN[1] , B. ARAL[4,6], A. VARENTERGHEM[7], J. THEVENON[4,8], D. BREMOND-GIGNAC[9], J. ST-ONGE[10,6], J. RIVIÈRE[4,6], J. COURCET[4], C. THAUVIN[4,8] AND L. FAIVRE[4,8];

1 Genetics Department, CHU Amiens-Picardie, Amiens, France.
2 EA 4666, Université de Picardie Jules Verne, Amiens, France.
3 Dermatology Department, CHU Amiens-Picardie, Amiens, France.
4 Equipe d'Accueil 4271 Génétique des Anomalies du Développement, Fédération Hospitalo-Universitaire, Université de Bourgogne, Dijon, France.
5 Service de Dermatologie, CHU Le Bocage, Dijon, France.
6 Laboratoire de Génétique moléculaire, FHU-TRANSLAD, Plateau technique de Biologie, CHU, Dijon, France.
7 Pediatric gastroenterology department, CHU Amiens-Picardie, Amiens, France.
8 Centre de Référence Maladies Rares "Anomalies du Développement et Syndromes Malformatifs" de l'Est, Centre de Génétique et Pédiatrie 1, Hôpital d'Enfants, Dijon, France.
9 Ophtalmology department, CHU Amiens-Picardie, Amiens, France.
10 Equipe d'Accueil 4271 Génétique des Anomalies du Développement, Fédération Hospitalo-Universitaire, Université de Bourgogne, Dijon, France.

Corresponding author: demeerbenedicte@chu-amiens.fr

We report on a 3 ½ year old boy, with prenatal onset growth deficiency (height:-4SD), microcephaly (OFC:-3.5 SD), transient neonatal pancytopenia, facial dysmorphism, feeding difficulties, developmental and speech delay, global hyperlaxity, significant sleep disturbance, and genital, ocular and extremities anomalies. He also presents with generalized pigmentation anomalies, and signs of ectodermal dysplasia. Array CGH (Agilent 60k), cytogenetic diagnosis of chromosomal breakage syndrome and metabolic screening are negative. The whole exome sequencing performed revealed a homozygous frame-shift mutation of the CRIPT gene, recently described as a novel primordial dwarfism gene (Shaheen *et al*, 2014). The mutation (c.132delA), described as probably pathogenic, was confirmed in the homozygous state by Sanger sequencing. Both healthy consanguineous parents were proven to be carrier in the heterozygous state. Few available clinical data of the 2 described patients show very similar clinical appearance with strikingly facial dysmorphism, growth deficiency, microcephaly, psychomotor delay, and ocular and extremities anomalies. Mottled hypopigmentation is also described in the older patient. This report is an example of “reverse phenotyping”. The first description of the CRIPT gene by Shaheen *et al* helped us to reach a diagnosis in our patient. Nevertheless the term of primordial dwarfism and its broad definition used by the authors can be confusing; and can prevent some clinicians from suggesting this diagnosis. Cutaneous signs seem also to be very specific, and need to be precisely looked at in additional patients presenting with this unique syndrome.

A NOVEL MUTATION IN *WDR45* IN A GIRL WITH DEVELOPMENTAL DELAY, LOSS OF SPEECH AND MOTOR SKILLS

J. KOHLHASE[1], T. NEUMANN[1,2], M. BRAUNER[1] AND M. FEDORCAK[3]

[1] Center for Human Genetics, Freiburg, Germany.
[2] Praxis für Humangenetik, Halle, Germany.
[3] Kinderklinik, St. Elisabethen-Krankenhaus, Lörrach, Germany.

E-mail for correspondence: jkohlhase@humangenetik-freiburg.de

Mutations in *WDR45* have been shown to cause an X-linked dominant form of neurodegeneration with brain iron accumulation (NBIA) designated as the “beta-propeller protein associated neurodegeneration”. More recently, *WDR45* mutations were also identified as the cause of “static encephalopathy of childhood with neurodegeneration in adulthood (SENDA)". Here we present a girl, who was born after a mostly uneventful pregnancy at 34 weeks. The initial motor and speech development was mildly delayed, but in the second year of live she rapidly lost most of her motor and language skills. Testing for Angelman, Rett and Pitt-Hopkins syndromes were normal, as were karyotype and array CGH. After the development of febrile seizures at 2 years of age, *SCN1A* and *PCDH19* were also tested with normal results. Due to the severe phenotype and the wish of the family to have more children, we decided to perform NGS testing by means of the TrueSightOne Panel (Illumina) and evaluate the data for mutations in genes related to the phenotype. We found a novel intronic variant predicted to result in disturbed splicing. Sanger sequencing in the child and her parents confirmed the variant and showed the *de novo* occurrence. Although initial MRI investigations only showed delayed myelinisation, a new investigation at 7 years confirmed iron accumulation in the globus pallidus and the substantia nigra. We present the case and a review of the literature.

FETAL WHOLE EXOME SEQUENCING IDENTIFIES MUTATIONS IN THE *ERCC2(XPD)* GENE ASSOCIATED WITH SEVERE CONGENITAL ICHTHYOSIS AND DYSMORPHIC FEATURES

M. MIGUET[1], J. THEVENON[2,3], V.t LAUGEL[4,5], A. BOURCHANY[2], J.-B. RIVIERE[3,6], E. SCHAEFER[1], M.-C. ANTAL[7], R. ABIDA[8], M. LEFEBVRE[2], A.-S. WEINGERTNER[9], V. KREMER[10], C. THAUVIN-ROBINET[2,3], P. VABRES[11,3], F. MORICE-PICARD[12], M. GONZALES[13], D. LIPSKER[14], S. FRAITAG[15], J.L. MANDEL[16], H. DOLLFUS[1,5], L. FAIVRE[2,3], N. CALMELS[16] AND S. EL CHEHADEH[1].

1 Service de génétique médicale, Institut de génétique médicale d'Alsace (IGMA), Centre de Référence Maladies Rares «Anomalies du développement et syndromes malformatifs» de l'Est, Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre, Strasbourg, France.
2 FHU TRANSLAD, Centre de Référence Maladies Rares «Anomalies du développement et syndromes malformatifs» de l'Est, Centre de Génétique, CHU de Dijon, France.
3 GAD: EA 4271, «Génétique et Anomalies du Développement» (GAD), Université de Bourgogne, Dijon, France.
4 Service de neuropédiatrie, Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre, Strasbourg, France.
5 U1112 Laboratoire de génétique médicale, Faculté de médecine, Université de Strasbourg, Strasbourg, France.
6 Laboratoire de biologie moléculaire, Plateau technique de biologie, CHU de Dijon, France.
7 Faculté de Médecine, Institut d'Histologie, Strasbourg, France.
8 Centre de Ressources Biologiques, Hôpitaux Universitaires de Strasbourg, Strasbourg, France.
9 Service de gynécologie-Obstétrique, Centre médico-chirurgical et obstétrical, Schiltigheim, France.
10 Service de cytogénétique, Hôpitaux universitaires de Strasbourg, Hôpital de Hautepierre, Strasbourg, France.
11 Service de dermatologie, CHU de Dijon, Dijon, France.
12 Service de génétique médicale, CHU de Bordeaux, Hôpital Pellegrin, Bordeaux, France.
13 Département de génétique médicale, CHU Paris Est, Hôpital Armand Trousseau, APHP et UPMC, Paris, France.
14 Service de dermatologie, Hôpitaux universitaires de Strasbourg, Hôpital civil, Strasbourg, France.
15 Département de pathologie, Hôpital Necker-Enfants Malades, APHP, Paris, France.
16 Laboratoire de diagnostic génétique, Hôpitaux Universitaires de Strasbourg, Hôpital civil, Strasbourg, France.

Correspondence to:
Salima El Chehadeh, MD
Service de génétique médicale, Institut de génétique médicale d'Alsace (IGMA), Centre de Référence Maladies Rares «Anomalies du développement et syndromes malformatifs» de l'Est, Hôpitaux Universitaires de Strasbourg, Hôpital de Hautepierre, Strasbourg, France
tel: + 33 3 88 12 81 20 ; fax: + 33 3 88 12 81 25

Mutations in *ERCC2(XPD)* cause rare autosomal recessive NER (Nucleotide Excision Repair)- related diseases including xeroderma pigmentosum (XP), trichothiodystrophy (TTD), cerebrooculofacioskeletal syndrome (COFS), XP/Cockayne syndrome, and XP/TTD. To date, while pregnancy and neonatal complications have been previously reported in patients with *ERCC2(XPD)* mutations, there have been few reports describing fetal cases. We describe a male fetus, the second child of healthy unrelated parents, who died in utero at 28 weeks of pregnancy. The autopsy revealed severe harmonious intrauterine growth retardation, delayed bone maturation, congenital ichthyosis, facial dysmorphism, retracted tapering fingers with hypoplastic nails. Placenta was abnormal. Whole exome sequencing revealed a novel nonsense mutation and a previously described missense mutation (p.Gln698* and p.Arg722Trp, respectively) in *ERCC2(XPD)*, that were consistent with the clinical features, suggesting a severe form of trichothiodystrophy, and transmitted from each parent. Functional studies revealed defect of the NER pathways and a prenatal diagnosis could be done for the next pregnancy. This case confirms the power of exome sequencing in the rapid identification of rare clinically non-recognisable diseases. This is particularly valuable in the absence of clinical clues suggesting a diagnosis, as in severe congenital ichthyosis, a condition that includes several distinct subtypes with significant genetic heterogeneity.

NEUROCOGNITIVE PROFILE IN ATYPICAL MECP2 RELATED RETT SYNDROME

J. HENDRIKSEN[1], E. SMEETS[2] AND H. VLES[1,2]

[1] Center for Neurological Learning Disabilities, Epilepsycenter Kempenhaeghe, Heeze, the Netherlands.
[2] Rett Expertise Center Maastricht University Medical Center, Maastricht, the Netherlands.

E-mail for correspondence: eric.smeets@mumc.nl

Rett's syndrome is nowadays a well-known but still unique neurodevelopmental disorder related to an X-dominant mutation in the MECP2-gene, MECP2 related phenotypes in females and males are very heterogeneous.
The classical and atypical MECP2 related phenotypes are diagnosed, according to clinical diagnostic consensus criteria, almost only in females. Good clinical alertness and coincidental finding in whole exome sequencing leads to a growing number of MECP2 related disorder diagnosed in adolescent females with more preserved cognitive and motor abilities.
We present five molecularly confirmed cases of atypical Rett syndrome. Their neurocognitive and behavioural profile and the experience of the neuropsychological approach will be discussed.

HMSN TYPE IIC AND SCOLIOSIS IN PATIENTS WITH A TRPV4-GENE MUTATION

L. SPRUIJT[1], A. VERRIPS[2], E.-J. KAMSTEEG[3] AND C. MARCELIS[1]

1 Department of Genetics, Radboud University Medical Centre Nijmegen, the Netherlands.
2 Department of Neurology, Canisius Wilhelmina Hospital Nijmegen, the Netherlands.
3 Department of Genome diagnostics, Radboud University Medical Centre Nijmegen, the Netherlands.

E-mail for correspondence: Liesbeth.spruijt@radboudumc.nl

Mutations in the TRPV-4 gene are associated with autosomal dominant skeletal dysplasias and peripheral nervous system syndromes (PNSS). Whole exome sequencing was carried out in a patient with coarse features of the face, and also coarse hands and feet, without brachydactyly. She had a normal height, a scoliosis without vertebral malformations and a neuropathy. Clinically, this patient shows a progressive scoliosis and impaired walking ability. She has a sister that is wheelchair bound and a son with a ptosis. All have a normal length.
In the patient a previously unreported mutation in the TRPV4-gene was found. Comparing the phenotype of our patient with others in our department we found similar features with “coarse” hands, without brachydactyly, neuropathy consistent with HMSN type IIc and normal height and in their childhood, especially in the elbows and fingers, but also so in the hips, knees and feet.
We discuss phenotypical presentation in a small group of patients with a TRPV4-mutation, not immediately suggestive for a skeletal dysplasia, expanding the clinical phenotype.

Participants 26th European Dysmorphology Meeting 2015

Name	First name	E-mail address
ALBRECHT	Beate	beate.albrecht@uni-due.de
ALEKSIŪNIENĖ	Beata	beata.aleksiuniene@santa.lt
BACHMANN-GAGESCU	Ruxandra	Ruxandra.bachmann@imls.uzh.ch
BAYAT	Allan	allan.bayat@regionh.dk
BEUNDERS	Gea	g.beunders@umcg.nl
BIJLSMA	Emilia	E.K.Bijlsma@lumc.nl
BOMME OUSAGER	Lilian	Lilian.Bomme.Ousager@rsyd.dk
BONATI	Maria Teresa	mt.bonati@auxologico.it
BRECKPOT	Jeroen	jeroen.breckpot@uzleuven.be
CALLEWAERT	Bert	Bert.Callewaert@Ugent.be
CAPRI	Yline	yline.capri@rdb.aphp.fr
DE RADEMAEKER	Marjan	Marjan.DeRademaeker@uzbrussel.be
DEVRIENDT	Koen	Koen.Devriendt@med.kuleuven.be
DUIJKERS	Floor	f.a.duijkers@amc.nl
EL-CHEHADEH	Salima	salima.elchehadeh@chru-strasbourg.fr
FAGERBERG	Christina	christina.fagerberg@rsyd.dk
FAUTH	Christine	Christine.Fauth@i-med.ac.at
FRYNS	Jean-Pierre	Jean-Pierre.Fryns@med.kuleuven.be
GARAVELLI	Livia	livia.garavelli@asmn.re.it
GERMAIN	Dominique P.	dominique.p.germain@aphp.fr
GONZALES	Marie	marie.gonzales@trs.aphp.fr
GONZALEZ-MENENSES LOPEZ	Antonio	meneses@arrakis.es
HAYE	Damien	damien.haye@aphp.fr
HEMPEL	Maja	m.hempel@uke.de
HOVE	Hanne	hanne.buciek.hove@regionh.dk
IVANOVSKI	Ivan	ivan.ivanovski@asmn.re.it
JEANNE	Médéric	mederic.jeanne@gmail.com
JOURNEL	Hubert	hubert.journel@ch-bretagne-atlantique.fr
KEYMOLEN	Kathelijn	Kathelijn.Keymolen@uzbrussel.be
KOHLHASE	Jürgen	jkohlhase@humangenetik-freiburg.de
KUTSCHE	Kerstin	kkutsche@uke.de
LACOMBE	Didier	didier.lacombe@chu-bordeaux.fr
LEDERER	Damien	damien.lederer@ipg.be
LUKUSA TSHILOBO	Tshilobo	p.lukusat@gmail.com
LUMAKA ZOLA	Aimé	aime.lumaka@uzleuven.be
MACKENROTH	Luisa	Luisa.Mackenroth@uniklinikum-dresden.de
MARTIN-RODRIGUEZ	Álvaro	alvaromartin.md@gmail.com
MATULEVICIENE	Ausra	ausra.matuleviciene@mf.vu.lt
MIDRO	Alina	alinamidro@gmail.com
MUBUNGU LUMBONO	Gerrye	gmubungu@gmail.com
PASSEMARD	Sandrine	sandrine.passemard@rdb.aphp.fr

Name	First name	E-mail address
PEREZ-AYTES	Antonio	aperezaytes@gmail.es
RAAS-ROTSCHILD	Annick	annick.rotschild@sheba.health.gov.il
RAUCH	Anita	anita.rauch@medgen.uzh.ch
SMEETS	Eric	eric.smeets@mumc.nl
SPRUIJT	Liesbeth	liesbeth.spruijt@radboudumc.nl
STEINDL	Katharina	steindl@medgen.uzh.ch
STOLL	Claude	cstoll@unistra.fr
STUMPEL	Connie	c.stumpel@mumc.nl
SZNAJER	Yves	yves.sznajer@uclouvain.be
TOUTAIN	Annick	annick.toutain@univ-tours.fr
VAN DER BURGT	Ineke	Ineke.vanderburgt@radboudumc.nl
VAN MALDERGEM	Lionel	vmald@hotmail.com
VAN RIJ	Maartje	m.c.vanrij@lumc.nl
VANAKKER	Olivier	Olivier.vanakker@ugent.be
VERLOES	Alain	alain.verloes@gmail.com
VOGELS	Annick	Annick.Vogels@uzleuven.be
ZENKER	Martin	martin.zenker@med.ovgu.de
ZWEIER	Christiane	Christiane.Zweier@uk-erlangen.de