TWENTY-THIRD EUROPEAN MEETING ON DYSMORPHOLOGY

6 - 7 SEPTEMBER 2012
LE BISCHENBERG

23rd EUROPEAN MEETING ON DYSMORPHOLOGY

GENERAL PROGRAM

WEDNESDAY 5th 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	

THURSDAY 6th SEPTEMBER

8.25 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 6.00 p.m.			First session
	7.30 p.m.	Dinner	
9.00 p.m. to 11.00 p.m.			Unknown

FRIDAY 7th SEPTEMBER

9.00 a.m. to 1.00 p.m.			First and second sessions
	1.00 p.m.	Lunch	
2.30 p.m. to 6.00 p.m.			Third session
	7.30 p.m.	Dinner	

SATURDAY 8th SEPTEMBER

Breakfast - Departure

SCIENTIFIC PROGRAM

Note: This program is tentative and may be modified.

THURSDAY 6th SEPTEMBER

08.25	Opening address: FRYNS J.P.
08.30-11.00	FIRST SESSION: MCA/ID Chair: STOLL C.
08.30	F. PETIT, B. DEMEER, J. ANDRIEUX , L.M. COLLET, H. COPIN , F. ESCANDE, S. MANOUVRIER-HANU AND M. MATHIEU-DRAMARD Split hand/foot malformation with long bone deficiency and BHLHA9 duplication : two new reports and expansion of the phenotype to radial agenesis.
08.45	C. STOLL, B. DOTT, Y. ALEMBIK AND M-P. ROTH Associated malformations among infants with radial ray deficiency.
09.00	J.C. CZESCHIK, C. VOIGT, Y. ALANAY, B. ALBRECHT, D. FITZPATRICK, A.J. HOOGEBOOM, H. KAYSERILI, A. AVCI, O.S. KIPER, A. KUECHLER, M. MARTIN, S. RAHMANN, M. SPLITT, B. WOLLNIK, M. ZESCHNIGK, H.-J. LÜDECKE AND D. WIECZOREK Clinical and molecular data in ten patients with Nager syndrome.
09.15	Y. CAPRI, D. GRAS, C. BAUMANN, E. BOURRAT, S. DORGERET, D MARTINELL, O. BOESPFLUG-TANGUY AND A. VERLOES Arterial tortuosity and cerebral calcifications in de Barsy syndrome.
09.30	B. ALBRECHT, A. DELLA MARINA, G. UYANIK, B. ZIRN AND W. DOBYNS A mutation in PIK3CA gene causes a megalencephaly syndrome in a patient with features of the megalencephaly-capillary malformation syndrome.
09.45	K. DEVRIENDT, G. NAULAERS, E. LEGIUS, J.P. FRYNS, J. BRECKPOT, J. VERMEESCH, G. HENS AND M. RAYYAN Chromosome 22q11.2 microdeletion : confirmation of the MN1-gene as a candidate gene for cleft palate.
10.00	N. DI DONATO, E. SCHROCK, G. GILLESSEN-KAESBACH, M.A. DEARDORFF AND F.J. KAISER Atypical Cornelia de Lange syndrome due to HDAC8 mutations, a new type of cohesinopathy.
10.15	N. DIKOW, M. KREISS-NACHTSHEIM, H. GASPAR, B. MAAS, A. JAUCH, K. HINDERHOFER, H. JANSSEN, H. ENGELS AND U. MOOG The phenotypic spectrum of 5q35.3 microduplication encompassing NSD1: two familial cases with the reversed Sotos syndrome phenotype.

10.30 H.E. VEENSTRA-KNOL, L.K. LEEGTE, D.A. SIVAL, T.J. WIERSMA, H.Y KROES AND C.M.A. VAN RAVENSWAAIJ
The combination of Sotos-like syndrome and episodic drop attacks due to a 1.4 Mb deletion of 19p13.2p13.13 including the NFIX gene and CACNA1A gene.

10.45 D. SCHANZE, D. NEUBAUER, V. CORMIER-DAIRE, R.C. HENNEKAM, M.A. DELRUE, T. HASEGAWA, R. KOENIG, G. KRUEGER, F. PETIT, I. SCHANZE, E. SEEMANOVA, T.M. STROM, P. MEINECKE, A. REIS AND M. ZENKER
A recurrent ALU repeat-mediated deletion within the NFIX gene accounts for a missing part in Marshall-Smith syndrome.

11.00-11.30 *Coffee Break*

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

11.30 C A. KUECHLER K. KONRAD, D. WIECZOREK, M. TARTAGLIA AND M. ZENKER
Noonan-like syndrome with loose anagen hair is caused by different mutations in SHOC2.

11.45 V. LÓPEZ-GONZÁLEZ, J.A. PIÑERO-FERNÁNDEZ, M.J. BALLESTA-MARTÍNEZ AND E. GUILLÉN-NAVARRO
Familial osteopathia striata with cranial sclerosis due to an Xq11.1 deletion.

12.00 A. MÉGARBANÉ, A. PANGRAZIO, A. VILLA, E. CHOUERY, J. MAARAWI, S. SABBAGH, G. LEFRANC AND C. SOBACCHI
Identification of a stop mutation in the SNX10 gene in an Iraqi family with osteopetrosis and corpus callosum hypoplasia.

12.15 T.M. NEUHANN, F. BAUMEISTER, J. KOHLHASE, S. BALG, E. HOLINSKI-FEDER, A. ABICHT AND B. ERTL-WAGNER
COL4A1 mutations in patients with asymmetric gyration anomalies and cerebral malformations.

AFTERNOON

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

14.30 M. NIELSEN, C.L. VERMONT, E. ATEN, C.A.L. RUIVENKAMP, F. VAN HERREWEGEN, G.W.E SANTEN AND M.H., BREUNING
Deletion of the 3q26 region including the EVI1 and MDS1 genes in a neonate with congenital thrombocytopenia and subsequent aplastic anaemia.

14.45 D. LACOMBE, MA DELRUE, H. CAVÉ, A. VERLOES, M. SALAVERT, C. FRANCANNET, P. FERGELOT AND B. ARVEILER
A new RASopathy.

15.00 I. SCHANZE, M. HARAKALOVA, E. CUPPEN AND M. ZENKER
Intellectual disability and macrocephaly in two half-brothers caused by a novel mutation in BRWD3.

15.15 Y. CASPERS, D.A SCHOTT, W.J.M. GERVER, C. RUSU, K. DEVRIENDT AND C.T.R.M. SCHRANDER-STUMPEL
Growth in individuals with Kabuki Syndrome.

15.30 A. MIDRO, P. IWANOWSKI, B. PANASIUK, G. VAN BUGGENHOUT, M. MURDOLO , R. SMIGIEL ,J. PILCH, E. BOCIAN, M. SĄSIADEK, ,J.-P. FRYNS AND M. ZOLLINO
Quantitative syndrome definition for translocation forms of monosomy 4p16.1-pter together with trisomy 8p23.1-pter.

15.45 K. STEINDL, P. JOSET, A. BAUMER, B. ONEDA AND A. RAUCH
Premature craniosynostosis in primordial dwarfism: A diagnostic challenge.

16.00-16.30 *Coffee Break*

16.30-18.00 FIRST SESSION (Continued)
Chair: SCHRANDER-STUMPEL C.- KOHLHASE J.

16.30 Y. SZNAJER, S. JORIOT, C. BANDELIER, J. ANDRIEUX, O. BOUTÉ AND M. VIKKULA
De novo tandem interstitial 19q13.2 microduplication in two unrelated children with macrocephaly, mental retardation, distinct face. Review of literature before and at the time of SNP-array technology.

16.45 A. TZSCHACH, C. DUFKE, C. BAUER, M. KEHRER, U. GRASSHOFF, A. RIESS, M. STURM, C. SCHRÖDER, A. DUFKE, O. RIESS AND P. BAUER
X-exome analysis detects mutations in syndromic and non-syndromic forms of X-linked intellectual disability.

17.00 J.J. VAN DEN ENDE, N. VAN DER AA AND T. BOIY
The variable spectrum of smad4 mutations.

17.15 L VAN MALDERGEM, J PIARD, J JAEKEN AND U KORNAK
Congenital cutis laxa : an updated differential diagnosis.

17.30 A. VERLOES, O.A. ABDUL-RAHMAN, J. ALLANSON, J.F. ATKIN, M. BARAITSER, H. BRUNNER, N. CHASSAING, K. DEVRIENDT, V. DROUIN, A. FRY, J.P. FRYNS, F. GIULIANO, K.W. GRIPP, D. LACOMBE, A. LIN, G. MANCINI, M. MARBLE, M. NEZARATI, M. NOWACZYK, S. OSIMANI, M. ROSSI, C. RUSU, Y SZNAJER, C. VAN RAVENSWAAAIJ, J. MALIAH, J.B. RIVIÈRE, B.W.M. VAN BON, A. HOISCHEN, W. DOBYNS AND D. PILZ
Baraitser-Winter syndrome: delineation of the phenotypic spectrum in a large series of molecularly defined cases.

17.45 C. ZWEIER, D. WOLFF, S. ENDELE, S. AZZARELLO-BURRI, J. HOYER, M. ZWEIER, I. SCHANZE, B. SCHMITT, A. RAUCH AND A. REIS
Three patients with Nicolaides-Baraitser syndrome caused by in frame deletion and missense mutations of the c-terminal helicase domain of SMARCA2.

21.00-23.00 UNKNOWN
Chair: FRYNS J.P.

FRIDAY 7th SEPTEMBER

09.00-11.00 FIRST SESSION (Continued)
Chair: ALBRECHT B. - VERLOES A.

09.00 E.K. BIJLSMA, S.K. KANT, M. VAN BELZEN, A.C.J. GIJSBERS, D. LUGTENBERG, B. VAN BON AND C.A.L. RUIVENKAMP
Small deletions detected by SNP array: genes do (not) tell more.

09.15 N. VAN DER AA, C. HELSMOORTEL, D. KOOLEN, L.RAYMOND AND F. KOOY
Diagnosing known and unknown MCA/ID syndromes by exome sequencing.

09.30 L. GARAVELLI, A. WISCHMEIJER, S. ROSATO, C. GELMINI, S. TORELLI, R. PICCIATI AND M. TARTAGLIA
Myhre syndrome: description of a case due to a mutation in the SMAD4 gene and evolution of the phenotype over time.

09.45 A. LUMAKA, P. LUKUSA, H. PEETERS AND K. DEVRIENDT
A genetic-etiological study of intellectual disability in the Democratic Republic of Congo. Initial results.

10.00 A. BOTTANI
Not "Ten Years After", but fifteen: would you still recognize now the (in the meantime proven) syndrome which was suspected and presented at this meeting in 1997 ?

10.15 H. PEETERS, V. DE WOLF, S. DE RUBEIS, C. BAGNI AND K. DEVRIENDT
The deletion 15q11.2 and intellectual disability / autism.

10.30 E. COTTEREAU, M.-A. PAPON, S. MAROUILLAT, C. ANTAR, J. CHELLY, H. VAN BOKHOVEN, H. VAN ESCH, M. RAYNAUD, H.-H. ROPERS, C. ANDRES, F. LAUMONNIER AND A. TOUTAIN
Report of a family affected with autism and non syndromic intellectual disability caused by a mutation in PTCHD1, an X-linked gene coding for a transmembrane protein expressed in postsynaptic dendritic spines.

10.45 C. FAUTH, B. KRABICHLER, D. KARALL, F. ROTTENSTEINER, A. HIRST-STADLMANN AND J. ZSCHOCKE
De novo microdeletion 2p14-p15 involving the MEIS1 gene in a boy with developmental delay, facial dysmorphisms, sensorineural hearing loss and inner ear dysplasia.

11.00-11.30 *Coffee Break*

11.30-12.30 SECOND SESSION: FETAL PATHOLOGY
Chair: THAM E. - BIJLSMA E.

11.30 G. GRIGELIONIENE, S. GEIBERGER, A. NORDGREN AND P CONNER
Fetal case: twins with achondrogenesis type Ia.

11.45 J. KOHLHASE, K. SCHONER, W. BOROZDIN, A.M. MÜLLER, T. SCHRAMM, M. PLASSMANN, P. WIEACKER AND H. REHDER
Hydrocephaly, callosal defect and cleft lip/ palate representing frequent associations in fetuses with Peters' plus syndrome and B3GALTL mutations.

12.00 P. MARIN REINA, F. MARTINEZ, R. SEGOVIA AND A. PEREZ-AYTES

Paternal uniparental disomy 14: an entity to include in omphalocele differential diagnosis.

12.15 P. RUMP, J.B. VERHEIJ AND T. DIJKHUIZEN
Maternal and paternal uniparental disomy of chromosome 14.

AFTERNOON

14.30-16.00 SECOND SESSION (Continued)
Chair: RAUCH A. - MÉGARBANÉ A.

14.30 M. GONZALES, A. LAQUERRIERE, Y.SAILLOUR, N. JOYE, C. QUELIN, L. BIDAT, M. DOMMERGUES, S. VUILLAUMIER-BARROT, J. CHELLY, F.ENCHA-RAZAVI AND K. POIRIER
Early fetal akinesia: an unusual presentation of tubulinopathy.

14.45 THIRD SESSION: CARDIAC SHUNTS MALFORMATIONS

14.45 J. BRECKPOT; B. THIENPONT; M. BAUTERS; L.-C. TRANCHEVENT; M. GEWILLIG; K. ALLEGAERT; J.R. VERMEESCH; Y. MOREAU AND K. DEVRIENDT
Congenital heart defects in a novel recurrent 22q11.2 deletion harboring the genes CRKL and MAPK1.

15.00 C. EVERS, J. MORGENTHALER, J.W.G. JANSSEN, A. JAUCH, B. MAAS, K. HINDERHOFER AND U. MOOG
Male with mosaicism for a supernumerary derivative X chromosome lacking the Xist gene and phenotypic features of craniofrontonasal syndrome.

15.15 M. ISRIE, B. SUYS, M. DOCKX AND H. VAN ESCH
Feeding difficulties, heart defect and characteristic facial features as part of the 16p11.2-12.2 microdeletion syndrome.

15.30 K. KEYMOLEN AND A. VAN DEN BOGAERT
West syndrome in half-sibs: a microdeletion explains it all !!

15.45 K. HOFMANN, M. ZWEIER, H. STICHT, C. ZWEIER, W. WITTMANN, J. HOYER, S. UEBE, A. VAN HAERINGEN, C. THIEL, A.B. EKICI, A. REIS AND A. RAUCH
Biallelic SEMA3A defects cause a novel type of syndromic short stature.

16.00-16.30 *Coffee Break*

16.30-18.00 THIRD SESSION (Continued) and UNKNOWN (Continued)
Chair: FRYNS J.P.

16.30 C. OTTE, B. ONEDA, A. KLEIN AND A. RAUCH
Clinical variability in partial Jacobsen Syndrome: report of a sporadic case and three affected family members.

16.45 E. SMEETS AND J.P. FRIJNS
An unknown case: Dysrmorphy, Skeletal anomaly, Eye anomalies, Dextrocardia Asd II, Dental anomalies, Hypotonia/hypermobility, Normal intelligence.

17.00 E. THAM AND G. GRIGELIONIENE
Unknown diagnosis.

17.15 S. BULK, E.H. BRILSTRA, H. VAN WIERINGEN AND T.G.W. LETTEBOER
Unknown syndrome in two sibs and their mother.

Split hand/foot malformation with long bone deficiency and BHLHA9 duplication : two nex reports and expansion of the phenotype to radial agenesis

Petit F[a], Demeer B[c], Andrieux J[b] , Collet L.M[d], Copin H[e] , Escande F[f], Manouvrier-Hanu S[g], Mathieu-Dramard M[b,e]

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[e] laboratoire de cytogénétique et biologie de la reproduction-chu-amiens

[f]Laboratoire de Génétique Médicale, Hôpital Jeanne de Flandre, CHRU Lille, France

[g] service de gynécologie obstétrique-centre multidisciplinaire de diagnostic prénatal-chu-amiens

Split hand/foot malformation (SHFM) with long bone deficiency (SHFLD, MIM#119100) is a rare condition characterized by SHFM associated with long-bone malformation usually involving the tibia. Several families with SHFLD have been reported, and recently, 17p13.3 duplications encompassing the *BHLHA9* gene have been considered to be the most common aetiology of SHFLD.

Here we report two new patients affected with SHFLD, both harboring a 17p13.3 duplication detected by array-CGH, including the *BHLHA9* gene and inherited from an unaffected parent. One of the patients presents a complete radial agenesis, expanding the phenotype of SHFLD3.

ASSOCIATED MALFORMATIONS AMONG INFANTS WITH RADIAL RAY DEFICIENCY

C. STOLL, B. DOTT, Y. ALEMBIK, and M-P. ROTH

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Infants with radial ray deficiencies very often have other associated congenital anomalies. The reported frequency and types of associated malformations vary between different studies. The purpose of this investigation was to assess the frequency and types of associated malformations among infants with radial ray deficiencies in a geographically well defined population from 1979 to 2004 of 346,831 consecutive births. Of the 73 infants with radial ray deficiencies born during this period (prevalence at birth of 2.1 per 10,000), 75 % had associated malformations. Infants with associated malformation were divided into recognizable conditions (16 (22%) infants with chromosomal and 20 (27%) with non chromosomal conditions), and non recognizable conditions (19 (26%) infants with multiple malformations). Trisomies 18 and autosomal deletions were the most frequent chromosomal abnormalities. VACTERL association, thrombocytopenia absent radii syndrome, Fanconi anemia and Holt-Oram syndrome were most often present in recognizable non chromosomal conditions. Malformations in the musculoskeletal, cardiovascular and urogenital systems were the most common other anomalies in infants with multiple malformations and non recognizable conditions. The frequency of associated malformations in infants with radial ray deficiencies emphasizes the need for a thorough investigation of these infants. Routine screening for other malformations especially musculoskeletal, cardiac and urogenital systems anomalies may need to be considered in infants with radial ray deficiencies, and referral of these infants for genetic evaluation and counseling seems warranted.

CLINICAL AND MOLECULAR DATA IN TEN PATIENTS WITH NAGER SYNDROME

J.C. CZESCHIK[1], C. VOIGT[1], Y. ALANAY[2], B. ALBRECHT[1], D. FITZPATRICK[3], A.J. HOOGEBOOM[4], H. KAYSERILI[5], A. AVCI[5], O.S. KIPER[5], A. KUECHLER[1], M. MARTIN[7], S. RAHMANN[8], M. SPLITT[9], B. WOLLNIK[10], M. ZESCHNIGK[1], H.-J. LÜDECKE[1], D. WIECZOREK[1]

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[4]Department of Clinical Genetics, Erasmus Medical Center Rotterdam, The Netherlands
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[10]Institut für Humangenetik, Universität zu Köln, Köln, Germany

Nager syndrome (MIM #154400) is the best known subgroup of preaxial acrofacial dysostosis (AFD) first described by Nager and de Reynier (Nager and de Reynier, 1948). About 100 patients have been described in the literature. The main clinical features are 1.) craniofacial abnormalities, such as downslanting palpebral fissures, malar hypoplasia, micrognathia, atresia of the external auditory canal and other ear defects, and cleft palate, and 2.) preaxial limb defects, such as radial and thumb hypoplasia or aplasia, duplication of thumbs or proximal radioulnar synostosis. Involvement of the lower extremities has been described, but is an uncommon feature of Nager syndrome.

Neurological and psychosocial development is usually normal to mildly delayed, with the latter possibly being induced or aggravated by the common clinical sign of hearing loss. In older case reports, a considerable number of affected patients did not survive the newborn period, mainly because of airway complications.

The molecular basis of Nager syndrome has recently been determined by Bernier and colleagues (AJHG, 2012) using exome sequencing. They identified haploinsufficiency of *SF3B4* (MIM *605593), that encodes SAP49, a component of the pre-mRNA spliceosomal complex, as the underlying cause of the condition. Fifty-seven % (20/35) of familial and 54% (15/28) of sporadic cases in this study had pathogenic aberrations in *SF3B4*. There was no clinical difference identified in mutation positive and mutation negative patients. This suggests genetic heterogeneity of Nager syndrome with a considerable proportion of patients whose underlying genetic aberration is still unknown.

Here, we present ten previously unreported patients, including one familial case, with the tentative diagnosis of Nager syndrome. In the first four patients, exome sequencing and/or Sanger sequencing was performed and identified heterozygous *SF3B4* mutations in three of them. The c.2T>C transition impairs the translation start codon, and must be regarded as a nonsense mutation like the c.574G>T transversion (p.Glu192X) in exon 3. The single base deletion c.1147delC in exon 6, a recurrent mutation (Bernier et al., 2012), results in a shift of the open reading frame (p.His383Met*fs*X75) that changes and non-synonymously elongates the C-terminus of the protein. Sequence analysis in the remaining seven patients is currently under way. We will discuss the clinical findings in respect of the wide phenotypic variability and will present the mutational spectrum.

ARTERIAL TORTUOSITY AND CEREBRAL CALCIFICATIONS IN DE BARSY SYNDROME

Y. CAPRI[1], D. GRAS[2], C. BAUMANN[1], E. BOURRAT[3], S. DORGERET[4], D MARTINELL[5], O. BOESPFLUG-TANGUY[2] and A. VERLOES[1]

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[2]Department of Neurology, APHP – Robert Debré University Hospital, 75019 Paris, France
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De Barsy syndrome (MIM 219150) is a rare autosomal recessive disease characterized by intrauterine and postnatal growth retardation, progeroid appearance, corneal clouding, hypermobility of joints, osteopenia, athetoid movements and mental retardation. Dysmorphic aspect of the face and the skin includes microcephaly, frontal bossing, large dysplastic ears, thin lips, cutis laxa, wrinkled atrophic skin and reduced subcutaneous fat. This disorder belongs to the subgroup of autosomal recessive cutis laxa that are often associated with a progeroid aspect. To our knowledge, only two cases of De Barsy syndrome associated with blood vessels tortuosity have been described.

In spite of this specific features' association, De Barsy syndrome is genetically heterogeneous since 2 genes have recently been identified: *ALDH18A1* encoding delta1-pyrroline-5-carboxylate synthase (P5CS) and the gene encoding pyrroline-5-carboxylate reductase 1(PYCR1). Both genes are involved in proline biosynthesis pathway but pathological mechanisms leading to the syndrome are still misunderstood.

We report the case of a boy displaying all the features of De Barsy syndrome associated with arterial tortuosity and cerebral calcifications. This baby was referred to the university hospital for intrauterine growth retardation with postnatal failure to thrive and microcephaly, hypotonia, abnormal movements, microcalcifications on the basal nuclei and adductus thumbs. His dysmorphic face, progeroid aspect and cutis laxa lead to suspect De Barsy syndrome. Interestingly, brain MRI showed arterial tortuosity of the Willis' polygon, the internal carotid and the superficial femoral arteries. This case strengthens the fact that arterial tortuosity could be a new specific feature of De Barsy syndrome but this is the first case displaying cerebral calcifications.

A MUTATION IN *PIK3CA* GENE CAUSES A MEGALENCEPHALY SYNDROME IN A PATIENT WITH FEATURES OF THE MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME

B. ALBRECHT[1], A. DELLA MARINA[2], G. UYANIK[3], B. ZIRN[4], W. DOBYNS[5]

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2 Neuropädiatrie, Kinderklinik I, Universitätsklinikum, Essen, Germany
3 Institut für Humangenetik, UKE, Hamburg, Germany
4 Zentrum für Kinder- und Jugendmedizin, Pädiatrie II, Göttingen, Germany
5 Devision of Genetic Medicine, Department of Pediatrics, University of Washington, Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, Washington, USA

Megalencephaly-capillary malformation syndrome (MCAP) and megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH) are closely related syndromes caused by mutations in the three core components of the phosphatidylinositol 3-kinase (PI3K)-AKT pathway.
We report on a patient, who is the second child of a healthy, non-consanguineous German couple. Pregnancy was complicated by polyhydramnios. High body measurements and postaxial polydactyly were diagnosed by ultrasound. He was born preterm at 34 weeks of gestation by cesarean section with high birth measurements (weight 4160g (+4.3SD), length 54cm (+2.7SD), OFC 40cm (+4.6SD)). In addition to postaxial polydactyly partial syndactyly of the right second and third finger and capillary hemangioma of the face and the neck were seen. The patient developed epilepsy and severe hydrocephaly because of aqueduct stenosis, needing several surgical interventions. The detection of megalencephaly, polymicrogyria and Arnold Chiari malformation led to the diagnosis of MCAP/MPPH syndrome. Exome sequencing revealed a postzygotic heterozygous mutation in the *PIK3CA* gene (c.3104C>T, p.Ala1035Val). We will present the patient as an example of related megalencephaly syndromes.

Reference:
De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes
Riviere J. et al., Nat Genet. 2012 Jun 24 [Epub ahead of print]

CHROMOSOME 22Q11.2 MICRODELETION : CONFIRMATION OF THE MN1-GENE AS A CANDIDATE GENE FOR CLEFT PALATE.

Koen Devriendt 1, Gunnar Naulaers 2, Eric Legius1, Jean-Pierre Fryns1, Jeroen Breckpot2, Joris vermeesch1, Greet Hens3, Maissa Rayyan2.
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We report two patients with a submicroscopic deletion involving chromosome 22q11.2, who present, amongst other features a palatal malformation.

The first patient was the third child of healthy, unrelated parents. Family history is negative with regard to malformations or mental handicap. She was born at term pregnancy with birth weight 4kg, length 52cm and head circumference 35.5 cm. She had feeding problems, with nasal regurgitation. A mild pulmonary valve stenosis and peripheral pulmonary stenosis was observed, which did not require any intervention. She had a cleft uvula. She walked at the age of 18 months, but especially language development was delayed. . At the age of 3 years, she had surgery for strabismus. But had developed amblyopia, with residual vision of 1/10 at the left eye. She had a high myopia of -5 and – 8 D. Clinical examination at the age of 4 yrs 8 months showed a normal growth (weight 16.7 kg (p25), length 104cm (p25), and head circumference 52.5 cm (p90). Facial features were not very remarkable, with mild hypertelorism. Smooth philtrum. She had long fingers and toes, with shorter 5th toes. The uvula was bifid. Speech was hypernasal due to a velopharyngeal insufficiency, for which at age 5 years a pharyngoplasty was performed. Development was delayed. At age 4 yrs 9 months intelligence on a Wechsler scales was TIQ 83, VIQ 85 and PIQ 84. She followed special education for children with mild learning difficulties. In addition, she was followed by a children's psychiatrist because of hyperactivity. A tentative diagnosis of a del22q11 could not be confirmed. When reexamined at age 14 years, she experienced no medical problems. Biometry was normal.. By means of array-CGH, a de novo microdeletion was detected in chromosome 22q12.2. Since the NF2-gene was implicated in the deletion, brain MRI was performed, which revealed the presence of bilateral acoustic schwannomata.

Patient 2 is the first child of healthy, unrelated parents. He was born after an uneventful pregnancy at term with weight 3,83 kg, length 52 cm and head circumference 36,5 cm. He had a cleft palate, with a hypoplastic soft palate and retrognathia. There was hypoplasia of the terminal phalanges of several toes, hypertelorism and widely spaced nipples. He experienced feeding problems, requiring tube feeding. He was hypotonic, with uncontrolled, irregular movements. Brain MRI revealed the presence of hypoplasia of the corpus callosum. Eye exam was normal, and not other organ malformations were noted. Array-CGH revealed the presence of a 4.3 Mb de novo deletion in 22q11-q12, with the distal breakpoint in the NF2-gene.

In the literature and Decipher, 4 other patients are recorded with a 22q12 deletion and cleft palate, involving the MN1-gene. These observations, together with the mouse expression data and the finding of craniofacial malformations including cleft palate in a Mn1-knockout mouse suggest that this gene is a candidate gene for cleft palate in humans.

ATYPICAL CORNELIA DE LANGE SYNDROME DUE TO *HDAC8* MUTATIONS, A NEW TYPE OF COHESINOPATHY

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Mutations in genes coding for cohesins (*SMC1A*, *SMC3*, *RAD21*) or the functionally associated *NIPBL* result in the broad spectrum of Cornelia de Lange phenotypes (CdL), recently summarized as cohesinopathies. Whereas mutations in *NIPBL* cause the classical clinical presentation of CdL syndrome (CdLS) characterized by typical facial anomalies and limb malformations, the phenotypes of patients with mutations in the other genes appear rather broad and are often difficult to recognize.

Here we present a female patient carrying a nonsense mutation in the *HDAC8* gene, which was recently reported as new gene involved in CdLS.

The patient, a six year old girl presented with intellectual disability, in particular with severe speech delay, short stature, kidney dysplasia, asymmetric skull, minor facial anomalies (arched eyebrows, synophrys, broad nasal bridge, thin lips, and low set ears), clinodactyly of the fifth digits, as well as limb length discrepancy. Sequencing analysis could reveal a *de novo* nonsense mutation c.490C>T, p.R164X in the *HDAC8* gene which results in a premature stop and protein truncation. Further molecular analysis demonstrated a severe skewing of the X inactivation.

Five other patients with missense mutations of *HDAC8* have been described so far (two males and three females). All these patients show overlapping clinical features consistent with CdLS and additional symptoms, which will be discussed.

THE PHENOTYPIC SPECTRUM OF 5q35.3 MICRODUPLICATION ENCOMPASSING *NSD1*: TWO FAMILIAL CASES WITH THE REVERSED SOTOS SYNDROME PHENOTYPE

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Background

Loss-of-function mutations in *NSD1* and 5q35 microdeletions encompassing *NSD1* are a major cause of Sotos syndrome which is characterized by overgrowth, macrocephaly, characteristic facies and variable mental deficiency. Five patients with confirmed microduplication of the 5q35.3 region including *NSD1* have been described. They show a 'reversed phenotype' of Sotos syndrome. Here we report on four patients from two families with interstitial duplication 5q35, widening the phenotypic spectrum.

Clinical report

Both siblings from family 1 had microcephaly, behavioral problems and a distinctive facial phenotype with thin upper lip, flat philtrum, small mouth, short palpebral fissures and epicanthic folds. The 13-year-old girl showed mild to moderate intellectual disability (ID), short stature and cataracts. Her 15-year-old brother had learning problems with an IQ of 78. His length was within the lower normal range. The biological parents were neither available for clinical examination nor for testing.
The 9-year-old patient from family 2 presented with short stature, microcephaly, MR with an IQ of 58 and behavioural problems. He had a flat philtrum and a small mouth. The mother's length corresponded to the 3rd centile (153 cm). She had no facial dysmorphism and reported on learning problems at school.

Molecular findings

Molecular karyotyping (Microarray analysis, Affymetrix® Cytogenetics Whole-Genome 2.7M) in the sister of family 1 revealed a 1.6 Mb interstitial duplication of 5q35.2-q35.3. The duplication was confirmed in both siblings by FISH analysis (using a specific probe for *NSD1*). SNP-array analysis with HumanOmni1-Quad Array revealed a 1.5 Mb interstitial duplication of 5q35.2-q35.3 in the patient of family 2, the duplication was confirmed with MLPA analysis in the boy and his mother. The duplications in both families contained 40 RefSeq genes including *NSD1*.

Discussion

The patients with microduplication 5q35.3 show a reversed phenotype of Sotos syndrome with microcephaly, short stature and intellectual impairment, suggesting that the gene dosage effect of the NSD1 gene is the likely cause of the phenotype. Both families illustrate intra-familial variability of the reversed Sotos syndrome phenotype with IQ-levels ranging from ID to mild learning problems.
Patients with microduplications including *NSD1* appear to have a recognizable phenotype, the symptoms of our patients overlap with those described so far. To further delineate the specific phenotype, more data are needed and we call for patients with microduplication 5q35.3.

The combination of Sotos-like syndrome and episodic drop attacks due to a 1.4 Mb deletion of 19p13.2p13.13 including the *NFIX* gene and *CACNA1A* gene

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Introduction: Sotos syndrome is an autosomal dominant disorder characterised by typical craniofacial features, overgrowth, macrocephaly, advanced skeletal age and learning disability. In the majority of patients, Sotos syndrome is caused by mutations in or deletions of the *NSD1* gene located at chromosome 5q35. Since 2010, mutations and deletions of the *NFIX* gene have been reported in 3 and 7 patients, respectively, presenting with a Sotos-like phenotype [1-3]. We describe a patient with a Sotos phenotype in combination with episodic drop attacks caused by a 19p13.13 microdeletion, including the *NFIX* and *CACN1A* gene.

Case description: The boy was the 2nd child of healthy non-consanguineous parents. He was born at a gestational age of 38 weeks with a birth weight of 3660 grams (+0.9SD) and a length of 51 cm (+0.8 SD) At the age of 4 years he started walking. His growth was above average with an advanced bone age, a macrocephaly and typical facial features. Sotos syndrome was suspected but could not be confirmed by NSD1 analysis. At the age of 13 years he developed unexplained drop attacks, induced by emotional stress. At that time his height was +0,25SD and his head circumference +2SD.

Methods and Results: Array CGH was performed using the 180k oligo array of Agilent. A 1.4 Mb microdeletion of 19p13.13 was found, extending from 12.1Mb to 13.5Mb and containing 43Refseq genes including the *NFIX* gene and the *CACNA1A* gene.

Discussion: The *NFIX* gene is the most likely gene that explains the Sotos-like phenotype of our patient. Frame shift and splice site mutations in *NFIX* are known to result in Marshall-Smith syndrome, another syndrome with accelerated skeletal maturation but different typical facial features. In contrast, in Sotos-like patients partial deletions, nonsense mutations and missense mutations in an important functional domain of *NFIX* are found, indicating a phenotype-genotype relationship [1-3]. Our patient has a larger deletion than the seven previously described patients who carried a partial *NFIX* deletion (n=2) or a complete *NFIX* deletion (n=5) but with a more proximally located distal breakpoint between 12.4 and 12.8 Mb. The proximal region between 13.1 and 13.5 Mb is shared by only two previously published patients [1, 5] and harbours the *CACNA1A* gene. This gene is involved in autosomal dominant episodic ataxia type 2 that is characterised by recurrent attacks of imbalance and ataxia, and can be provoked by physical exertion or emotional stress. In the spell-free intervals, patients present with downbeat nystagmus [4].

Conclusion: We present a patient with a contiguous gene syndrome combining Sotos-like syndrome with episodic ataxia type 2 due to a 19p13.13 deletion containing both *NFIX* and *CACNA1A*.

A recurrent ALU repeat-mediated deletion within the NFIX gene accounts for a missing part in Marshall-Smith syndrome

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Marshall-Smith syndrome (MSS) is a recognizable entity characterized by moderate to severe developmental delay, skeletal abnormalities, upper airway obstruction, and characteristic facial features. Distinct NFIX mutations that escape nonsense-mediated mRNA decay and probably cause dominant-negative effects have been found in MSS patients (Malan et al.: Am J Hum Genet 2010; 87:189-98). NFIX encodes the nuclear factor I/X, a member of a family of transcription factors, which is expressed during human brain and skeletal development. In the original work by Malan et al., NFIX mutations were identified in 9 MSS subjects examined. We have previously reported at this Meeting that in our own cohort 2 out of 6 patients with an unambiguous diagnosis of MSS had normal results on NFIX sequencing, suggesting possible genetic heterogeneity of MSS. Here we report the molecular genetic findings of 14 unrelated patients with MSS, including 3 unreported NFIX mutation-negative cases belonging to the previously published cohort (Malan et al. 2010). We identified 7 novel and one previously described NFIX frameshift and splice-site mutations by direct sequencing. For further evaluation, we set up an MLPA-based screening for exon deletions or duplications. Five of the 6 patients with negative NFIX sequencing results, including the 3 cases from the previously published cohort, were found to carry a heterozygous deletion of exons 6 and 7 of the NFIX gene. One patient had a partial deletion of exon and intron 6 that was also captured by MLPA. Breakpoint sequencing revealed the recurrent exon 6+7 deletion to be mediated by a recombination event between ALU-Y repeats located in introns 5 and 7. Further studies on the mRNA level indicated that the transcript lacking exons 6 and 7 escapes nonsense-mediated mRNA decay, thus suggesting that the deletion leads to the expression of a mutant protein rather than haploinsufficiency of NFIX. We conclude that the recurrent NFIX deletion is specific for MSS, because it mimics the effects of other MSS-associated mutations that are thought to generate mutant proteins able to exert a dominant-negative effect over the wild-type allele. Intronic ALU repeats create predetermined breakpoints facilitating *de novo* occurrence of this deletion, a mechanism that accounts for about one quarter of MSS cases in our joint cohort. Our data thus do no longer support genetic heterogeneity of MSS and rather indicate a unique molecular pathophysiology for this distinct disorder.

Noonan-like syndrome with loose anagen hair is caused by different mutations in *SHOC2*

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Noonan-like syndrome with loose anagen hair (NS/LAH; MIM #607721) is a clinically distinct entity within the spectrum of neuro-cardio-facial-cutaneous disorders, mainly characterized by typical facial features, growth deficiency (frequently with growth hormone deficiency), easy pluckable, sparse, slow-growing hair, darkly pigmented skin and developmental delay. In 2009, Cordeddu et al. identified a germline mutation in *SHOC2* (c.4A>G, p.Ser2Gly) present in all patients published so far. Because of its particular functional mechanism (creation of a recognition site for N-terminal myristoylation), this has been supposed to be the only causative *SHOC2* mutation.

We report on a 4 ½ year-old girl, born to healthy non-consanguineous German parents after an uneventful pregnancy at 37+3 weeks of gestation with normal birth measurements [3300g weight (75th perc.), 50cm length (50th perc.) and 33cm OFC (25th perc.)]. Her psychomotor development was mildly delayed. Hand X-rays at age 15 months and 25 months showed a significantly delayed bone age of 6 and 9 months, respectively. At age 2 $^{7}/_{12}$ years, she was first admitted to our genetics clinic because of short stature with relative macrocephaly, delayed closure of large fontanel, short, sparse, brittle blond hair and a greyish complexion. Measurements were 82.3cm length (3cm <3rd perc.), 11.1kg weight (10th perc.) and 49cm OFC (50th perc.). Endocrinological evaluation revealed a neuro-endocrine dysfunction and growth hormone therapy was started at age 3 $^{8}/_{12}$ years. Re-evaluation at age 4 $^{7}/_{12}$ years showed a length of 97.7cm (almost 3rd percentile), a weight of 15.8kg (25th-50th percentile), and an OFC of 52cm (90th percentile). Echocardiography, hair microscopy, copper and coeruloplasmin levels, array analysis and c7orf11 sequencing were all normal. The DYSCERNE experts suggested *SHOC2* mutation analysis. The typical mutation c.4A>G was excluded, but a novel previously undescribed mutation in exon 2 (c.517A>G, p.M173V) of initially unknown significance was identified and confirmed in a second tissue (saliva sample). Analysis of both parents indicated *de novo* occurrence.

The *de novo* occurrence of this *SHOC2* mutation combined with the typical clinical phenotype strongly suggested the mutation to be pathogenic –thus being the first mutation different from the single mutation described in all earlier published patients. The functional consequences of this novel mutation are currently under further investigation.

Based on this observation, we recommend that extended sequence analysis should be performed in absence of the c.4A>G mutation in patients with typical NS/LAH phenotype.

FAMILIAL OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS DUE TO AN Xq11.1 DELETION

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Osteopathia striata with cranial sclerosis (OSCS; OMIM#300373) is an X-linked dominant skeletal dysplasia owing to *WTX* gene defect (FAM123B, AMER1, locus Xq11.1). Cranial sclerosis and linear striations of the long bones and pelvis, because of increased osteoblast activity, represent disease main features. Other common clinical findings include craniofacial dysmorphism, hearing loss and palate anomalies. Cardiac malformations and developmental delay have also been reported. Age at diagnosis and clinical presentation is highly variable, ranging from asymptomatic to neonatal lethal cases. About hundred cases have been reported to date, the majority of them due to point mutations, whereas approximately 23% are caused by a deletion. 13 females with a gene deletion have been reported to date. 3/13 present intellectual disability and harbor a larger deletion involving contiguous genes (*ARHGEF9* and/or *MTMR8* and/or *ZC4H2*). The *WTX* gene is also mutated in different types of cancer, although there appears not to be an increased risk of it in OSCS patients. We present a case of OSCS with a maternal to daughter transmission, due to a heterozygous Xq11.1 deletion (arr Xq11.1 (63,296,713-63,346,340)x1, 50 Kb, hg18). We will review clinical, radiological and genetic features of the disease.

The girl is the first child of non-consanguineous parents, born at 37 weeks' gestation after an uncomplicated pregnancy. APGAR scores 5/9. Birth length: 47 cm (30th centile), weight: 3230 g (80th centile) and OFC: 33 cm (40th centile). At birth, cleft palate was detected and repaired. Auditory screening showed hearing impairment. Cardiac evaluation revealed ventral septal defect that closed. She developed failure to thrive, hypotonia and mild-to-moderate psychomotor delay. Her ophthalmological evaluation was normal. Her physical examination by the age of 3 years revealed short stature (<3rd centile), relative macrocephaly (75th centile), frontal bossing, hypertelorism, epicanthic folds, broad nasal bridge, low-set ears, short neck and clinodactyly of 5th fingers. In the additional investigations, brain MRI, high resolution karyotype and subtelomeric MLPA were normal. Array-CGH (400K) revealed a 50 Kb deletion in Xq11.1 involving *WTX* gene. Skeletal survey showed typical cranial sclerosis and linear striations of long bones.
Her mother presents with a similar but milder facial phenotype, with recent detection of hearing loss and normal intelligence. By the age of 30 she was diagnosed with a breast cancer. The same Xq11.1 deletion was identified. X-chromosome inactivation in mother and daughter and array-CGH in the maternal grandparents is pending.

CONCLUSIONS: 1) OSCS should be taken into account in females with short stature, macrocephaly, hypertelorism and hearing loss. 2) Skeletal survey is still a key tool for the diagnosis. 3) Array-CGH is an important diagnostic technology but, since most cases are due to point mutations, the awareness of this entity is needed for its correct diagnosis. 4) Although our patient's deletion doesn't include other neighbouring genes, the index patient presents with developmental delay.

Identification of a stop mutation in the *SNX10* gene in an Iraqi family with osteopetrosis and corpus callosum hypoplasia

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Recently a mutation in the *SNX10* gene that belongs to the sorting nexin family was identified as a cause of a new subset of human autosomal recessive osteopetrosis. Here, we identified a novel homozygous mutation (c.46C>T, p.Arg16X) in *SNX10*, in an Iraqi patient from a consanguineous family with a history of infantile osteopetrosis. The proband exhibited macrocephaly, prominent forehead, proptosis of the eyes, strabismus, splenomegaly and joint hyperlaxity. Bone X-rays showed increased bone density, metaphyseal under-modeling, transverse alternating bands of greater and lesser density in tubular bones, anteriorly notched vertebral bodies and bone-in-bone appearance. Brain atrophy, external hydrocephalus and thin corpus callosum were noted at the CT scan. Blood test results revealed the presence of anemia and leukopenia. Our findings confirm the role of *SNX10* in autosomal recessive osteopetrosis and help to better define the core set of manifestations associated with this new pathological entity.

COL4A1 MUTATIONS IN PATIENTS WITH ASYMMETRIC GYRATION ANOMALIES AND CEREBRAL MALFORMATIONS

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Mutations in *COL4A1* are associated with autosomal-dominant type 1 porencephaly; brain small-vessel disease; and hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome. Recently, mutations in COL4A1 have also been identified in patients with presumed Walker-Warburg syndrome. Schizencephaly and abnormal gyration (such as polymicrogyria) have not been described as primary features. We identified two girls with complex brain phenotypes caused by a mutation in *COL4A1*.

Patient 1 is a girl with a de novo mutation in *COL4A1*. She was presented at the age of 4 months with complex brain and eye (congenital cataract, microphthalmia) abnormalities. Her development was markedly delayed. In the further course, she developed West syndrome. The first MRI report stated the presence of schizencephaly, pachygyria / polymicrogyria, hypoplastic corpus callosum, ventriculomegaly, and unclear partially cystic lesion. Reassessing the MRI/CT scans that had been performed since birth, multifocal bleeding episodes at different stages of development and organization as well as porencephalic changes were detected in the early brain imaging studies.

Patient 2 also is a girl, that was first presented at the age of 6 months with developmental delay, heart defect (VSD, ASDII), and impaired vision due to a retinal bleeding after birth. Additionally the MRI, performed at the age of 12 months, showed an asymmetric cerebellum with a very hypoplastic right hemisphere, reduced white matter, hypoplastic corpus callosum, enlarged ventricles, periventricular leukomalacia, and gyral abnormalities. The father of the girl had a cataract diagnosed in childhood. At the age of 21 years he had a suspected transient ischemic attack but fully recovered and is otherwise healthy. These cases highlight, that the brain phenotype in patients *COL4A1* mutations can be very variable and may change over time in patients. Additionally, these complex malformations may mask the primary defects expected in the patients.

Deletion of the 3q26 region including the EVI1 and MDS1 genes in a neonate with congenital thrombocytopenia and subsequent aplastic anaemia

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Gene-targeting studies in mice have revealed a key role for EVI1 protein in the maintenance of haematopoiesis, and argue in favour of a gene dosage requirement for EVI1 in the regulation of haematopoietic stem cells. Furthermore, a fusion transcript of *MDS1* and *EVI1* has been shown to play a critical role in maintaining long-term haematopoietic stem cell function. Inappropriate activation of EVI1, usually due to a translocation, is a well-known and unfavourable change in several myeloid malignancies. We report for the first time a constitutional deletion encompassing the *EVI1* and *MDS1* genes in a human, and argue that the deletion causes congenital bone marrow failure in this patient.

A NEW RASOPATHY

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The RAS/MAPK pathway is essential in human development via the regulation of the cell cycle, differentiation, growth and senescence. The RASopathies include Noonan, LEOPARD, CFC, Costello, Legius syndromes and NF1. They are caused by germline mutations in different genes of the RAS/MAPK pathway. LEOPARD syndrome is mostly linked to *PTPN11* gene mutations, Noonan syndrome with loose anagen hair to *SHOC2* gene mutations, and Costello syndrome is defined at a molecular level by *H-RAS* gene activating mutations, mostly concerning the codon 12.

We report the case of a 18-year-old male patient presenting a new MCA/MR phenotype. Family history was negative. He underwent surgery for craniostenosis at age 4 years. He associated growth retardation, moderate intellectual disability, and facial dysmorphism with hypertelorism. Dermatological features included numerous lentigines/hyperpigmented macules since the age of 11 years, erysipela, severe eczema, acanthosis nigricans, papillomas, verruceous lesions, partial alopecia, and onychonychia of the first toes. He added unexplained leg lymphedema in his evolution. He had hallux valgus and pes cavus. Puberty was delayed. Cardiac examination showed long QT with normal echocardiography. Eye examination noted nystagmus, strabismus, and optic atrophy. Routine blood investigations (blood count, cholesterol, triglycerides, glycemia, insulinemia, renal and immune functions) abdominal ultrasound examination, lower legs electromyography, brain and medullar MRI were normal. Total IgE were elevated (3277UI/L). Molecular analysis of the *H-RAS* gene identified a *de novo* 21 bp duplication of codons 63 to 69 in exon 3 (c.187_207dup21/p.Glu63_Asp69dup). RNA analysis from skin fibroblasts showed that both the normal and mutated alleles were expressed. Complementary functional studies are in process. Sequencing of other RAS/MAPK pathway genes (*PTPN11*, *SHOC2*) was normal. FGFR3 gene study was negative.

We report a new distinct phenotype with a mixed phenotype, especially regarding dermatological features, including characteristics of LEOPARD syndrome, of Noonan-like syndrome and of Costello syndrome, and due to a unique *H-RAS* gene mutation.

INTELLECTUAL DISABILITY AND MACROCEPHALY IN TWO HALF-BROTHERS CAUSED BY A NOVEL MUTATION IN BRWD3

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Mutations in the BRWD3 gene were previously described in three families and two sporadic cases with X-linked intellectual disability. Additional features that were observed in the majority of affected individuals and therefore considered as characteristic of this entity included macrocephaly, tall stature, speech delay, and muscular hypotonia. Carrier females show skewing of X-inactivation with preferential inactivation of the chromosome carrying the BRWD3 mutation. The protein encoded by BRWD3 is thought to have a chromatin-modifying function, and may thus play a role in the regulation of transcription.

We describe two half-brothers with moderate intellectual disability, speech delay, macrocephaly, and tall stature. Both had abnormal EEGs but no clinically apparent seizures were described. The older brother had normal findings on brain imaging whereas the younger brother showed mildly enlarged ventricles. The younger brother was treated because of undescended testes. Both were otherwise in good health. No internal malformations were known, and no specific dysmorphic features were present.

High resolution GTG-banding showed normal karyotypes, molecular testing regarding Fragile-X-syndrome and molecular karyotyping (array-CGH) were unremarkable. The X-inactivation was found to be highly skewed (98%) in the patients' mother. Because of the strong evidence for a X-linked form of intellectual disability, but the non-specific findings in the brothers the coding sequence of the X chromosome (X-chromosomal exome) was investigated using NGS-technology.

We could identify and confirm by Sanger sequencing a novel missense mutation of the BRWD3 gene in both affected half-brothers. The mutation is predicted to be disease causing using several prediction programs. Further segregation analysis in the family showed that the mother of the two boys carried the BRWD3 mutation, as did the maternal grandmother.

We speculate that BRWD3 mutations may be more common than it is suggested by the few previous reports. These patients are likely to be considered having Fragile X or even Sotos syndrome. X-exome sequencing is a useful tool to decipher the genetic defect in families with a pedigree suggesting X-linked inheritance.

Growth in Individuals with Kabuki Syndrome

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Kabuki syndrome is a multiple congenital anomaly/mental retardation syndrome with a presumed incidence of 1 in 32.000. Key clinical features include characteristic facial dysmorphology, developmental delay and postnatal growth retardation.
Kabuki syndrome is caused by mutations in the MLL2 gene in about 75% of cases.
One of the key features in individuals with Kabuki syndrome is postnatal growth restriction. However, information on the specific growth pattern of children with Kabuki syndrome is scarce. Only one Japanese report summarizes data in a growth chart (Niikawa et al., 1988).
Here we present a first report on growth data in 28 individuals with a genetically confirmed diagnosis of Kabuki syndrome. Growth data of these persons are compared to reference data of healthy children from the Netherlands.
Results: birth weight and length were found to be within the normal range, compared to the reference data. Height SDS at the last measurement in individuals aged 12 months or over however, ranged from -0.31 to -5.25 SDS in all individuals. 18/28 individuals fulfilled the definition of short stature (a height more than -2 SD below the population mean). We will show graphics of the data and compare them to the reference data and the data as reported by Niikawa et al. (1988).
The cause of the postnatal growth retardation in individuals with Kabuki syndrome is unknown. A limited number of children with Kabuki syndrome has been or is being treated with growth hormone. Data on these children are provided by Pfizer in the KIGS Database. Additional reports of growth hormone therapy in children with Kabuki syndrome are available in the literature. These children had a documented GH deficiency and growth hormone treatment was shown to be beneficial.
From clinical experience, we suspect that individuals with Kabuki syndrome have an altered body composition similar as in individuals with Prader-Willi syndrome. The children are hypotonic, need tube feeding in the first period of life and may have a similar altered body composition.
We hypothesize that children with Kabuki syndrome may benefit from growth hormone therapy in a similar way as children with Prader-Willi syndrome.
Further studies are planned to investigate our hypothesis.

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Quantitative syndrome definition for translocation forms of monosomy 4p16.1-pter together with trisomy 8p23.1-pter

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Partial monosomy of the short arm of chromosome 4 has a strong effect on phenotype resulting as a rule in the Wolf-Hirschhorn syndrome (WHS) phenotype with characteristic facial appearance, organ malformations, functional impairment and developmental delay. Although WHS is known since early 1960's, the knowledge on correlations between partial monosomy 4p and resulting phenotypes according to different breakpoint positions is fragmentary. In addition high-resolution and molecular cytogenetic studies show that a proportion of the diagnosed WHS cases is associated with complex unbalanced chromosome rearrangements, involving both 4p and another (partner) chromosome. As imbalance of the partner chromosome may have impact on phenotype, the clinical diagnosis of WHS may be 'biased' by the effect of the other imbalanced segment.

The main aim of this work is a contribution for quantitative syndrome definition for monosomy 4p16.1-pter together with trisomy 8p23.1-pter obtained by systematic evaluation of clinical symptoms and anthropological traits. A group of 7 children with translocation form of monosomy 4p16.1-pter and trisomy 8p23.1-pter assessed by multiple FISH analyses and/or oligonucleotide-array-CHG has been studied at least twice at age between 1 month and 9 years and later. A catalogue of well-defined 807 dysmorphic and clinical features from the Munich Dysmorphology Database according to Stengel-Rutkowski was used for phenotype analysis and 55 common features were found. On this basis quantitative phenotype definition of monosomy 4p16.1 with trisomy 8p23.1-pter syndrome was obtained and compared according to age. Among clinical/developmental and anthropological traits identified in patients with these rearrangements, many traits corresponded to traits observed solely or predominantly in monosomy 4p16.1-pter cases. That domination of WHS signs should implicate support of patient's mental, emotional and medical needs that is required for children with that condition. Phenotype analyses based on the same systematic data acquisition may be useful in understanding the phenotypic effects of different chromosome regions in complex rearrangements.

Premature craniosynostosis in primordial dwarfism: A diagnostic challenge

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Establishing of an etiological diagnosis in patients with of microcephaly and dwarfisms is an intriguing challenge for the clinical geneticists; very recently several loci and genes had been identified and correlated to these clinical features.
Microcephalic osteodysplastic primordial dwarfism type II (MOPD II, MIM 210720) and Seckel syndrome belong to this primordial dwarfism group characterized by intrauterine growth retardation, severe proportionate short stature and pronounced microcephaly. Very recently also primary microcephaly (MCPH) was associated with severe dwarfism and proportionate short stature together with moderate to severe intellectual disabilities.
We report on a 17 weeks old baby, born at 33 weeks of gestation. Examination revealed proportionate growth deficiency. Distinct facial features, unilateral coronal craniosynostosis. The first weeks of life were characterized by severe feeding problems. Whole-genome array studies did not reveal an apparent disease causing copy number variation. Since craniosynostosis was reported as a feature of MOPD II cases in the older literature, we sequenced PCNTII, but did not find any mutation. Because of the striking features and similarities to other conditions sharing the clinical spectrum of dwarfism we checked for distinctive features present in our patient and we found that MCPH1 may be implicated in this specific case. MCPH1 links repair of DNA damage to chromatin remodelling by binding to the ATP-dependent chromatin remodelling complex SWI-SNF, which allows in turn specific recruitment to maintenance at DNA lesions. As a whole the primordial dwarfism genes are involved in cell cycle progression. Pathways and relationships exist between many of these genes, but must not necessary fall into the same pathway. We are now at an early stage of recognizing the role of dwarfism genes. To better define the unknown condition in our patient we initiated whole exome sequencing.

de novo tandem interstitial 19q13.2 microduplication in two unrelated children with macrocephaly, mental retardation, distinct face. Review of literature before and at the time of SNP-array technology

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Introduction

The discovery of Copy Number Variation in our genome has lead to better understand of genomic architecture and occurrence of disorders. Identification of interstitial tandem duplications always raise the question on the cause to phenotype. Based on sizing; 'de novo' vs inherited, genes involved as dosage and position effect together with read number and pair-ends methods may reinforce appropriate interpretation. Pure 'de novo' duplication on long arm of chromosome 19q13 was reported by Cotter in prenatal work-up for nuchal lucency; pregnancy was terminated. Baht et al., Qorri et al. and Palomares et al.[1-3] described interstitial duplication between bands q13.1 and q13.4. In these three unrelated sporadic patients growth retardation, microcephaly with a "flat face", a double hair crown and a downturned mouth were noted; malformation may encompass congenital heart malformation and hip dislocation and development is globally delayed. Constipation without feeding difficulties may be noted.

Patient report

Two unrelated caucasian patients (one girl and one boy) were evaluated for moderate mental retardation. Pregnancy and delivery were unremarkable. At birth, weight, height and OFC were proportionate (0 SD). The boy developed stridor (2 month-old) and mild laryngomalacia was noted. In both patients, hypotonia was noted from birth. A global psychomotor developmental delay was associated. Post natal macrocephaly became obvious and persist along +4SD at the age of 8 month and 1 year, respectively (while height and weight along the 25th to 50th centile). Constipation is recorded. No cerebral malformation was found. Craniofacial features include mild erythroderma on cheeks. Over time, the face became triangular with a pointed chin, the front is large with horizontal eyebrows and enophthalmia. No anatomic nor orthopaedic anomaly was found. Mental retardation leads to special education (2 years delay when compared to control). No specific behaviour pattern was noted while personality is outgoing and sociable.

Method

Phentoype features allowed to complete SNP-arrays screening for genomic architecture imbalance (Agilent 60k and Affimetrix human mapping 250k-Nsp1 were used respectively) and identified a 2.5 Mbs duplication on 19q13.33 encompassing 106 genes. Duplication was confirmed on inter- and metaphases FISH studies as the 'de novo' occurrence in both patients.

Discussion

Up to now, available publications on patients with *de novo* 19q13.33 interstitial tandem duplication do not precisely define a distinctive phenotype. The patients here described share common distinctive dysmorphic features together with post natal macrocephaly. Literature review and SNP-array findings will be commented

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X-exome analysis detects mutations in syndromic and non-syndromic forms of X-linked intellectual disability

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Intellectual disability (ID) has a prevalence of 1-3 % and is a major reason for consulting a clinical geneticist. Mutations in X-chromosomal genes account for approximately 10 % of male ID patients. Apart from fragile X syndrome, which is at cause in about 25 % of X-linked ID (XLID) and which has been part of the routine diagnostic work-up for many years, more than 90 other XLID genes are known. Because of the low prevalence of mutations in each individual gene, testing of these genes has so far not been routinely performed unless additional clinical problems indicated the involvement of a specific gene.

The advent of new sequencing technologies has enabled us to establish a platform combining in-solution enrichment of the coding regions of all X-chromosomal genes and subsequent next-generation sequencing (NGS). We have employed this platform in the setting of routine diagnostics for analyzing a cohort of more than 70 unselected male ID patients in whom chromosome aberrations and fragile X syndrome had already been excluded. As a result, novel mutations were detected in several known ID genes, e.g. *MED12, CUL4B, DLG3, NLGN3* and *ZDHHC9*. Clinical details of mutation-positive patients, results of co-segregation analyses and X-inactivation testing in the mothers will be presented.

In conclusion, X-exome analysis has been shown to be a valuable diagnostic tool in male patients with non-syndromic or atypical syndromic ID.

THE VARIABLE SPECTRUM OF SMAD4 MUTATIONS

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The SMAD4 gene on chromosome 18q21.1, previously known as MADH4, encodes a protein involved in
signal transduction of the TGF-beta superfamily and Bone Morphogenetic Proteins (BMP`s). SMAD 4 comprises 11 coding exons and pathologic allelic variants in the different domains can have various consequences. Several syndromes have been described as a result of mutations in SMAD4.
The SMAD4 gene was first identified as a tumor suppressor gene involved in human pancreatic carcinoma (Hahn et al. 1996) and later as one of the causes of Juvenile Polyposis Syndrome (JPS) (Howe, 1998). This syndrome is characterized by predisposition to hamartomatous polyps in the gastrointestinal tract, sometimes with malignant transformation. It is caused by mutations in BMPR1A or in SMAD4. About 15-22% of patients with JPS due to SMAD4 mutations also show symptoms of Hereditary Hemorrhagic Telangiectasia (JPS/HHT). HHT is characterized by the presence of multiple arteriovenous malformations, in the skin (telangiectasia), nose (frequent nose bleedings), lungs, liver and brain. The majority of cases is caused by mutations in the ENG gene or in the ALK1 gene. 1-2% Of persons with clinically HHT show a SMAD4 mutation.
Probably variable expressivity and/ or age related penetrance play a role and all patients with a SMAD4 mutation might be at risk for both conditions.
The most recent syndrome attributed to SMAD4 mutations is the Myhre syndrome, a developmental disorder with short stature, facial dysmorphism, muscular hypertrophy, deafness and developmental delay. Patients with this syndrome show heterozygous mutations in the MH2 domain of the SMAD4 gene, necessary for SMAD oligomerizaton and TGFB/ BMP signal transduction.
We present 3 patients with SMAD4 mutations, one with JPS/HHT and 2 patients with Myhre syndrome, and discuss the role of SMAD4 in the different disorders.

Congenital cutis laxa : an updated differential diagnosis

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This very rare autosomal recessive disorder has an alleged prevalence of 1/12000000 births. As a proof of extreme rarity, the affected children are very frequently, if not only, born to cansanguinous parents. Since its delineation in the seventies, one classifies ARCL according to its clinical features i.e. type 1 whenever pulmonary emphysema is present, type 2 for the Debré variant with developemental delay and large fontanelles, type 3 if cataracts and intellectual deficiency are present .It is characterized by redundant, overfolded skin and is caused by structural abnormalities of elastic fibres. Subsequently, each type was subdivided between A and B subtypes. After cloning of genes involved in the two main subtypes, the condition and its differential diagnoses has gained renewed interest. Through further studies in the last three years, seven genes are known to be causative at present. Therefore, classification has adopted a more aetiologic approach . Individuals with ARCL1 may have *FBLN5*-related cutis laxa , *EFEMP2 (FBLN4)*-related cutis laxa or *LTBP4*-related cutis laxa, while mutations in *ATP6V0A2,* and *PYCR1* have been identified in individuals with ARCL2A. In gerodermia osteodysplastica (GO) mutations in *GORAB* (formerly *SCYL1BP1*) are causative. Mutations in *PYCR1* have been also identified in a number of individuals with de Barsy syndrome. However, *PYCR1*-related cutis laxa (ARCL2B) is also shared with a phenotype encompassing Debré-type cutis laxa and Wrinkly skin syndrome. The phenotype of individuals with *ALDH18A1*-related cutis laxa resembles that of de Barsy syndrome. A form of cutis laxa with severe pulmonary, gastrointestinal and urinary abnormalities is caused by mutations in *LTBP4* . A distinct syndrome consisting of macrocephaly, alopecia, cutis laxa, and scoliosis (MACS) has also been recently described and renamed RIN2-related cutis laxa by Verloes et al. since macrocephaly and alopecia are not invariably present. Despite its rarity, cutis laxa thus offers a paradigm of genetic heterogeneity with a number of overlapping entities, hampering clinical recognition of different subtypes. Some key clinical features, however, allow stratification of molecular investigations e.g. pulmonary emphysema suggests mutations in *FBLN4* and *FBLN5* or in *LTBP4,* while developmental delay, seizures and delayed closure of fontanelles suggests mutations in *ATP6V0A4*.Clues to the diagnosis are to be presented.

Baraitser-Winter syndrome : delineation of the phenotypic spectrum in a large series of molecularly defined cases

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Baraitser-Winter (BWS) is a dominant MCA disorder. It was shown by exome sequencing of three trios to result from heterozygous missense mutations in one of the two ubiquitous cytoplasmic actin-encoding genes ACTB and ACTG1 (Rivière, Nat Genet 2012, 44: 440). We present detailed phenotypic description and neuroimaging of approx.. 30 patients with molecularly proved BWS, emphasizing the clinical variability of the syndrome, which also encompass Fyns-Aftimos syndrome. The major clinical anomalies are striking facial dysmorphism (present in all cases) with hypertelorism, broad nose with large tip, congenital ptosis, ridged metopic suture, and highly arched eyebrows. Iris or retinal coloboma is present in many cases, as does deafness. Pachygyria with antero-posterior gradient is present in most cases. Progressive joint stiffness and postnatal microcephaly may develop with time. Intellectual disability and epilepsy are variable and correlate with CNS anomalies.

THREE PATIENTS WITH NICOLAIDES-BARAITSER SYNDROME CAUSED BY IN FRAME DELETION AND MISSENSE MUTATIONS OF THE C-TERMINAL HELICASE DOMAIN OF SMARCA2

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Using high resolution molecular karyotyping with SNP arrays to identify candidate genes for etiologically unexplained intellectual disability, we identified a 32 kb *de novo* in frame deletion of the C-terminal helicase domain of the *SMARCA2* gene in a patient with severe intellectual disability, epilepsy, sparse hair, prominent joints, and distinct facial anomalies. Sequencing of the gene in patients with a similar phenotype revealed *de novo* missense mutations in this domain in two further patients, pointing to a crucial role of the SMARCA2 C-terminal helicase domain. The clinical features observed in all three patients are typical of Nicolaides-Baraitser syndrome, a so far only rarely reported syndrome with mainly moderate to severe intellectual disability and other typical aspects like sparse hair, epilepsy, wrinkling of the skin, prominent interphalangeal joints and broad distal phalanges. Notably, one of our patients with a p.Gly1132Asp mutation showed typical morphological features but an exceptional good development with borderline overall IQ and learning difficulties, thus expanding the phenotypic spectrum of Nicolaides-Baraitser syndrome.

SMARCA2 encodes Brahma (BRM), one of two mutually exclusive and specific ATPase subunits of the SWI/SNF ATP-dependent chromatin remodeling complex. Another group used whole exome sequencing to reveal de novo missense mutations in *SMARCA2* in 36 patients with Nicolaides-Baraitser syndrome. Only recently, mutations in another component of the SWI/SNF complex, *ARID1B*, were identified in patients with unspecific intellectual disability, and mutations in several additional components of this complex were identified in patients with Coffin-Siris syndrome.

SMALL DELETIONS DETECTED BY SNP ARRAY: GENES DO (NOT) TELL MORE

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A couple of years ago, our diagnostic cytogenetics laboratory switched from karyotyping to SNP array analysis as investigation of first choice in patients with mental retardation and/or congenital anomalies. We now use high-resolution arrays that may detect several minute imbalances in patients.

We present three examples of small deletions that pointed to the involvement of (part of) a specific gene. In two cases this information helped to interpret the clinical problems, in the third case we had high hopes to have found a candidate gene for Smith-Magenis (like) syndrome. We could not confirm this finding and eventually decided to wait for input from next generation sequencing. Very recently, exome sequencing data meant a new stimulus in finding the syndrome(s?) associated with this gene.

Case 1

A 42-year old male with clinical features of Sotos syndrome was referred because of intellectual deterioration. Additional SNP analysis showed an interstitial deletion of 1.8 Mb on chromosome 5q. The deleted region contained 39 genes, including *NSD1* and 4 other genes with a known function in disease. The most likely gene associated with the clinical course in this patient is the beta-synucleine gene *SNCB*. Mutations in this gene have been associated with Lewy body dementia. Until now deletions of this gene have not been reported, therefore it is not confirmed that haploinsufficiency of this region causes dementia. However, none of the other disease related genes (*FGFR4*, *SLC34A1*, *B4GALT7*) do have a function compatible with this disease course.

Case 2

A 44-year old female was seen because of severe mental retardation, seizures, and mild dysmorphic features.

SNP analysis showed an interstitial deletion on 9q34.11 of minimal 62 kb, including exon 1 through 9 of the syntaxin binding protein 1 (*STXBP1*) gene. Heterozygous mutations in STXBP1 are associated with Early Infantile Epileptic Encephalopathy (EIEE4, OMIM 612164). The deletion seems to explain the phenotype, though seizures started relatively late (after 10 months) and clinical reports on older patients are lacking. We are looking for older patients with mutations in *STXBP1* or with similar small deletions to compare with.

Case 3

A 12-year old male was referred because of autism spectrum disorder, sleeping problems, dysmorphic features and mild mental retardation. His clinical features were suggestive of Smith-Magenis syndrome.

SNP analysis showed a de novo interstitial deletion of minimal 85 kb on chromosome 10p, including a single gene of unknown function.

Assuming that we might have a candidate gene for Smith-Magenis (like) syndrome, we sequenced this gene in over 60 *RAI1*-negative cases with a Smith-Magenis phenotype, but we were unable to confirm the abnormality in a second patient. Very recently however, preliminary exome sequencing data showed a de novo mutation in this gene in an adult with severe mental retardation and behavioral problems, reminiscent of the Angelman/Pitt-Hopkins syndrome spectrum. The phenotype caused by haploinsufficiency of this gene is under study

DIAGNOSING KNOWN AND UNKNOWN MCA/ID SYNDROMES BY EXOME SEQUENCING.

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Whole-exome sequencing (WES) has led to the identification of disease genes for several known malformation syndromes in research settings e.g. *SETBP1* for Schinzel-Giedion syndrome, *MLL2* for Kabuki syndrome.
As many syndromic conditions have a monogenic etiology, the application of this technique to the clinical diagnosis of MCA/ID syndromes will substantially increase the diagnostic yield in sporadic cases.
It can be expected that sequencing the exomes of patients with MCA/ID will reveal causative mutations in genes that have been previously implicated in the syndromic condition of the patient.
On the other hand, WES will involve tremendous new challenges for the clinician with regarding the clinical interpretation of novel findings.
We had the exomes sequenced of some of our MCA/ID patients with a clinical diagnosis of a monogenic condition that was not confirmed by Sanger sequencing of the known disease genes. In this presentation we would like to show you some of these cases to highlight the strength of this novel technique

MYHRE SYNDROME: DESCRIPTION OF A CASE DUE TO A MUTATION IN THE *SMAD4* GENE AND EVOLUTION OF THE PHENOTYPE OVER TIME

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INTRODUCTION. Myhre syndrome (MYHRS) (OMIM 139210) is a developmental disorder characterized by short stature, generalized muscular hypertrophy, facial dysmorphism, deafness, intellectual disability, joint stiffness and skeletal anomalies. Two groups independently demonstrated that Myhre syndrome is caused by heterozygous mutations affecting the SMAD4 gene (Caputo et al. 2012; Le Goff et al. 2012). So far, missense changes affecting Ile500 have been identified as the causative event underlying this Mendelian trait. Here, we describe a patient with phenotype fitting Myhre syndrome with molecularly confirmed diagnosis, and underline the evolution of the phenotype over time and particular clinical feature, which is pericarditis with cardiac tamponade.

CLINICAL CASE: The boy is the first child of non-consanguineous parents. The child was born at 37 weeks gestation with vaginal delivery. He weighed 2.225 g and length was 43 cm. Aortic coarctation was diagnosed at birth. He started to walk at 12 months, and presented speech delay. On examination at age of 9 months his head circumference was 42.5cm (<3rd centile), length was 63 cm (<3rd centile) and weight 6.650g (<3rd centile). He had slightly short palpebral fissures, down-turned mouth, sticking-out ears in the upper part, normal skin. Hands: brachydactyly, hyper-convex nails, 5th finger clinodactyly. Feet: brachydactyly, hypoplastic and hyper-convex nails. He had recurrent respiratory infections in the first 3 years of life with otomastoiditis and pneumonia. Immunological tests demonstrated the following results: CD3 T lymphocytes: 44% CD19 B lymphocytes: 44% and a selective IgA deficiency. He also had transient hypocalcaemia without seizures. The clinical features led us to suspect a 22q11.2 deletion but the FISH analysis did not show any deletion and the karyotype was normal, 46, XY.
We saw the child again at age 8 years. He had: short palpebral fissures, midfacial hypoplasia, prognathism, brachydactyly, stiff and thick skin, muscular hypertrophy, generalized joint stiffness, with particular difficulty in fist-clenching and arm-raising. He also had short stature with bone age delay, bilateral conductive deafness, and mild intellectual disability. He weighed 27.8 Kg (75° centile), his height was 109 cm (<3° centile) and head circumference was 53 cm (90° centile). The X-rays demonstrated thick calvarium, broad ribs, large vertebral pedicles, hypoplastic iliac wings, brachydactyly. At age 8 years the clinical diagnosis of Myhre syndrome was made. At age 9 years he had pericarditis with cardiac tamponade. The following tests were carried out: karyotype was normal 46,XY. CGH Array was normal. Abdominal ultrasound was normal. The brain MRI demonstrated partial corpus callosum agenesis, with rostrum hypoplasia, mild ventriculomegaly with square-shaped lateral ventricles, periventricular frontal increased signal of white matter bilaterally. *SMAD4* mutation analysis: the entire coding sequence of the gene (NM_005359) was scanned for mutations using genomic DNA obtained from circulating leukocytes, hair and saliva. The *de novo* c.1499T>C nucleotide change (p.Ile500Thr) was detected in all the tissues. This mutation has been identified in two other Italian patients.

DISCUSSION Myhre syndrome is a rare condition with less than 30 individuals, mostly males, reported to date. Cardinal features of the syndrome, including short stature, a recognizable facial phenotype, brachydactyly, stiff and thick skin, muscular hypertrophy, generalized joint stiffness, with particular difficulty in fist-clenching and arm-raising and distinctive skeletal anomalies are sometimes recognizable after 5 years and are well evident after 8 years. In the first years of life the clinical diagnosis is really difficult, as demonstrated in our case and in the literature.
Germline nonsense, missense, splice-site changes and truncating mutations throughout the *SMAD4* gene as well as gene deletions are also known to cause juvenile polyposis syndrome (JPS; OMIM 174900) and JP-hereditary hemorrhagic telangiectasia syndrome (JP/HHT; OMIM 175050) and somatic mutations occurs in carcinomas of the pancreas, gastrointestinal tract and skin. Caputo et al. (2012) noted that the restrictive pattern of *SMAD4* missense mutations suggested genetic homogeneity of Myhre syndrome, which was reflected in the clinically homogeneous and uniform phenotype, with profound impact on development and growth. Probably this restricted spectrum of mutations has specific consequences on *SMAD4* function.
Of note, our patient presented a particular clinical feature, which is pericarditis with cardiac tamponade. This complication is really rare in childhood and it is interesting to note that another patient diagnosed with LAPS syndrome in 2003 had pericarditis with pericardial effusion at age 14 years with histological diagnosis of pericardial fibrosis non-specific which required pericardiectomy in adolescence [Lindor et al., 2002; Burglen et al., 2003; Lindor 2009]. A second patient diagnosed with LAPS syndrome in 2003 developed a constrictive pericardial sac requiring pericardiectomy. [Lindor et al., 2002; Lindor, 2009]. Lindor in 2012 found a heterozygous *SMAD4* mutation in both cases and demonstrated that mutations of *SMAD4* accounts for both LAPS and Myhre syndrome.

A GENETIC-ETIOLOGICAL STUDY OF INTELLECTUAL DISABILITY IN THE DEMOCRATIC REPUBLIC OF CONGO. Initial results

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Genetic mutations are a recognized cause of congenital malformations and intellectual disability (ID). However, in many African countries, mystical and traditional beliefs strongly influence how people view the cause of ID. For instance, in a survey of mothers of disabled children in a special institution in Nigeria, 35% ascribe the cause of the disability to evil spirits or witches, 18% to stepparents; 13% incriminate their husbands; 5% incriminate themselves but only 10% incriminate biological.

In the DRCongo, a country 10 times the size of the UK and with a population of 71 million, genetics is not part of the medical curriculum and no clinical genetic services currently exist. As one of the steps in our efforts to (re)introduce human genetics, we have initiated an genetic-etiological study of intellectual disability in 4 institutions in Kinshasa, the capital of DRC. Since we also wished to evaluate the use of different existing Fragile-X screening lists, we initially focused on males.

43 index cases were recruited. In all of them, Fragile-X was excluded. Of these, a clinical diagnosis could be made in 9 and confirmed by the appropriate genetic tests: 6 Down syndrome, 1 Williams syndrome, 1 Partington syndrome (carrying the classical 24 bp duplication in exon 2 of *ARX*).
9 dysmorphic cases were studied by means of array-CGH. Normal results were found in 4 cases, 2 unclassified variants were found: a 67 kb duplication including 15 kb of the *NUB1*-gene, and a 134kb intragenic deletion including exon 2 of the *KANK1* gene. *KANK1* has been implicated in parent-of-origin-dependent familial cerebral palsy (OMIM 612900). Parental studies are planned for a next mission. In three cases, a causal CNV was found: the classical 3.4 Mb deletion causing Smith-Magenis syndrome, a 6.2 Mb terminal deletion of chr 22q, including the *SHANK3* gene, and a 1.6 Mb interstitial deletion on chr20q11.22 including the *GDF5* gene (explaining the brachydactyly observed in this individual).

In conclusion, the present data indicate that genetic causes of ID are as real in the DRCongo as in any other population where such studies have been performed. However, the lack of recognition that genetic studies may have clinical utility, the lack of expertise in medical and clinical genetics and the total absence of technical facilities are major obstacles in reaching an etiological diagnosis of ID. Moreover, the recognition of specific genetic syndromes often is obscured by environmental influences such as birth trauma, malnutrition and infections. For instance, the boy with Williams syndrome was severely intellectually disabled and did not speak. This more severe expression is likely related to a meningitis at age 2 years, that was associated with a coma for 2 days. Likewise, in a family with X-linked adrenal hypoplasia congenita, the diagnosis was evocated based on the pedigree and dysmorphism (Lumaka et al., 2012 Eur J Ped). Finally, the clinical phenotype of certain syndromes may be more difficult to recognize in individuals with a different ethnic background, as illustrated by the failure to clinically diagnose the boy with Smith-Magenis syndrome.

Not "Ten Years After", but fifteen: would you still recognize now the (in the meantime proven) syndrome which was suspected and presented at this meeting in 1997 ?

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Key features

- postnatal short stature (adult height 132 cm)
- mild mental retardation with important speech delay
- anterior eye chamber defects (incomplete iris coloboma + corectopia)
- cerebral infarcts with hemiplegia due to occlusion of hypoplastic internal carotid arteries (Moya-Moya-like features)
- unilateral pseudarthrosis of clavicle
- hypernasal speech
- generalised osteopenia
- lipid myopathy
- premature ageing

Anything else you would like to know about the patient's history or clinical findings ? Just ask !

Phenotype

you will see the patient now at the age of 28 years, try and make a blitz diagnosis and then see her when she was 10 (so-called reversed syndromology).

If I tell you that the gene starts with S, has five letters, is located on chromosome 16p11.2, and all mutations of the syndrome in question are clustered in the last exon, then how many coding exons does the S.... gene have ?

Take home messages

- don't wait too long to make a diagnosis, as it could be more difficult with time
- but sometimes wait long enough to prove your suspected clinical diagnosis

N.B.

People

- making the diagnosis at the patient's age 28
- and telling me the name of the gene
- as well as the correct number of its coding exons

will receive a Swiss prize to be claimed at the end of the presentation

THE DELETION 15q11.2 AND INTELLECTUAL DISABILITY / AUTISM

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The 4 gene deletion 15q11.2 (BP1-BP2 region) is a susceptibility factor for neuropsychiatric impairment: developmental delay, autism spectrum disorder (ASD), obsessive compulsive disorder, epilepsy and schizophrenia. Evidence for this is based on clinical reports and association studies. However, this genomic region is variable in the population and in most clinical cases the deletion is inherited from an apparently unaffected parent. Therefore it is clearly not sufficient to cause a phenotype and since nothing is known on the cause of non-penetrance and variable expression, the impact of a familial deletion in a proband with a severe phenotype is unknown. As a result, genetic counseling for family members, in particular for unaffected carrier siblings, is a major challenge. To improve our understanding of the influence of this deletion on ASD and neurodevelopment we perform an exome sequencing study in families with a proband and an affected- or unaffected sibling, both with del15q11.2, inherited from an apparently unaffected parent. Variant filtering and interpretation is based on (1) gene networks and pathways implicated in ASD and/or intellectual disability, (2) the proposed genetic mechanism according to the family structure (dominant or recessive) and (3) *in silico* prediction of pathogenicity. Validation is done by functional studies. One of the 4 deleted genes, *CYFIP1*, encodes for a protein that is present in synaptosomal extracts. It interacts with FMRP, the protein product of the *FMR1* gene, which is responsible for the fragile X syndrome. Since fragile X is often associated with ASD, *CYFIP1* and other genes within the FMRP network are important candidate genes in this study. We hypothesize that additional variants contribute to the severity of the phenotypes of the probands (multi-hit model). We particularly focus on the remaining *CYFIP*-gene, on genes in the FMRP network and on genes known to be implicated in ASD and/or intellectual disability.

Report of a family affected with autism and non syndromic intellectual disability caused by a mutation in *PTCHD1*, an X-linked gene coding for a transmembrane protein expressed in postsynaptic dendritic spines.

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Recent advances in the identification of the causes of autistic spectrum disorders (ASD) have shown that genetic defects probably account for an important part, although the aetiology remains unknown in most cases. Rare and highly penetrant pathogenic mutations have been identified in several genes, particularly in genes coding for proteins involved in synaptic signaling. Several reports have emphasized the fact that the same gene can be responsible for autistic symptoms and/or intellectual deficiency (ID), even within the same family. Non inherited DNA copy number variations have also been described, accounting for 1% to nearly 30% of cases of ASD patients depending on the series, and have led in some cases to the identification of novel genes. In 2008, a 167 kb deletion including the first exon of the *PTCHD1* (patched domain-containing protein 1) gene at Xp22, was identified in two brothers with ASD/ID and their asymptomatic mother (Marshall *et al.* 2008). Several large deletions encompassing *PTCHD1* or located upstream the gene have been further characterized in familial or sporadic cases with autism and/or ID (Noor *et al.* 2010, Pinto *et al.* 2010, Whibley *et al.* 2010, Filges *et al.* 2011), but only variants of unknown significance have been identified in the coding sequence until now (Noor *et al.*, 2010).

We report here a French family with two male patients affected with non specific ID and ASD, in whom we have identified the first point mutation of the coding sequence of *PTCHD1*. The proband was aged 12 years ½. He had global delay of psychomotor development with retarded motor milestones and language, behavioural problems with outbursts of excitement, stereotypical movements and poor contact. Neurological examination and head circumference were normal. The patient had normal stature and there were no specific dysmorphic features. All previous investigations had been normal including metabolic screening, eye examination and hearing tests, EEG, brain MRI, fragile X testing, chromosome analysis and array-CGH. One maternal uncle was diagnosed as having autism and was living in an institution. Analysis of *PTCHD1* by PCR followed by DNA sequencing of the coding regions and the intron/exon junctions identified a one base-pair deletion (c.2128delC) which causes a frameshift in the coding sequence leading to a premature stop codon (p.Leu710CysfsX8). The predicted PTCHD1 protein is truncated at the C-terminus of 170 of its 888 amino-acids, including the last four transmembrane domains and the C-term intracellular end. The mutation was present in the proband and his asymptomatic mother, but absent in the unaffected brother and maternal cousins. More than 400 families from the European Consortium on X-linked ID (EuroMRX) were analyzed but no mutation was identified. As *PTCHD1* is expressed only in brain, the functional consequences of the mutation were tested on mouse primary hippocampal neurons. As our team has showed that the wild-type protein is localized at the neuronal synaptic membrane, we studied the subcellular localization of the mutated PTCHD1 protein by transfecting neuronal cultures. The mutated form was retained in the soma, showing that the cytosolic C-terminal end is essential for the protein targeting to the plasma membrane. These data further support the conclusion that *PTCHD1* has an important role in cognitive functions in humans and could be a novel cause of ASD and ID.

De novo microdeletion 2p14-p15 involving the *MEIS1* gene in a boy with developmental delay, facial dysmorphisms, sensorineural hearing loss and inner ear dysplasia

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During the past years interstitial microdeletions of various segments of the short arm of chromosome 2 were recognized as a cause of intellectual disability. Many of these deletions have no recurrent breakpoints which hampers precise genotype phenotype correlation. Recently, Wohlleber et al.[1] described two unrelated patients with small interstitial microdeletions 2p14-15. Both of them had mild mental retardation and minor dysmorphisms. The common deleted region in the two patients spans 1.6 Mb and contains 10 known genes, many of which play a known or suspected role in neuronal development.
We report a third patient with a de novo 2p14-15 microdeletion who presented at the age of 22 months with developmental delay, dysmorphisms, hypospadias and dysplasia of the inner ear leading to sensorineural hearing loss. The deletion in our patient overlaps with those previously described but in addition affects *MEIS1* which encodes a conserved homeobox protein belonging to the TALE-homeodomain class of conserved transcription factors. *Meis* genes are known to be required for the development of many organs in vertebrates and invertebrates[2,3]. So far constitutional aberrations in this gene have not been reported in humans but a recent study in chicken embryos showed that *MEIS1* is strongly expressed in the semicircular canals of the developing inner ear[4]. It is tempting to speculate that this gene is also involved in inner ear development in humans and that haploinsufficiency of *MEIS1* is the cause for inner ear dysplasia in our patient.

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Fetal case: twins with achondrogenesis type Ia

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The case is reported with parental consent. The case presented during the pregnancy, at 18 weeks routine ultrasound examination, which showed a severe polyhydramnios and twins with micromelia, short trunk, prominent abdomen, narrow thorax, short ribs and decreased skeleton mineralization. The pregnancy was from IVF due to 3 years infertility and the parents were first cousins from South Africa. The mother was 29 years old, the father was 30 years old. Both parents were previously healthy. The twins were diamniotic, dichoriotic, a male and a female. Both twins had small thorax with hypoplastic lungs. A lethal skeletal dysplasia was suspected. The CT examination confirmed skeletal phenotype as above and also showed "beaded ribs" (multiple fractures), absent mineralization of vertebral bodies and sacrum, small iliac bones and extremely short tubular bones. The pedicles of the vertebra were ossified. Diagnosis of achondrogenesis type IA was suggested and confirmed by skeletal radiograms which were performed after the pregnancy was terminated at week 20+6. Both twins had relative macrocephaly with puffiness around the eyes, upturned noses, low set ears, big tongue and flat faces. There was a severe micromely, with small hands and feet, where hands were more affected then feet. The diagnosis was confirmed by mutation analysis of the *TRIP11* gene, with a homozygous nonsense mutation. The radiograms and clinical pictures of the twins will be shown confirming a uniform phenotype in achondrogenesis type 1A.

Hydrocephaly, callosal defect and cleft lip/ palate representing frequent associations in fetuses with Peters' plus syndrome and *B3GALTL* mutations

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Objective: Fetal pathology aims to recognize syndromal patterns of anomalies for goal directed mutation analyses, genetic counselling, and early prenatal diagnosis in consecutive pregnancies. Here we report on five fetuses with Peters' plus syndrome from two distinct families aborted after prenatal ultrasound diagnosis of hydrocephaly.
Methods: We performed fetal autopsies and molecular analyses.
Results: Among 40 fetuses with prenatally diagnosed hydrocephaly, four fetuses of 16 to 21 gestational weeks presented with additional cleft lip/palate and/or agenesis of the corpus callosum. Other features were growth retardation, hypertelorism, anomalies of the eyes, in part consistent with Peters' anterior chamber anomalies, mild brachymelia, brachydactyly, and also internal anomalies. Suspected Peters' plus syndrome was confirmed by detection of *B3GALTL* mutations in these four fetuses and in one additional sib fetus, revealing homozygosity for the common c.660+1G>A donor splice site mutation in intron 8.
Conclusions: Autosomal-recessive Peters plus syndrome has not yet been diagnosed prenatally. We present the diagnosis of this disorder in growth retarded fetuses with (recurrent) hydrocephaly, callosal defect and cleft lip/palate and stress the more severe fetal manifestation, describing a first and second such case with additional Dandy-Walker cyst and occult meningoencephalocele.

PATERNAL UNIPARENTAL DISOMY 14: AN ENTITY TO INCLUDE IN OMPHALOCELE DIFFERENTIAL DIAGNOSIS

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Paternal uniparental disomy 14 (UPD14-pat) includes developmental delay; blepharophimosis; prominent philtrum; micrognatia; and small bell-shape thorax. We present a patient with paternal uniparental disomy 14 in which omphalocele was prenatally diagnosed.

Clinical report: F.J. Is the first gestation of a young spanish couple. During gestation, fetal omphalocele was diagnosed by echography at 22 week. Amniocentesis showed a 46, XY normal kariotype. At 28 week severe polyhydramnios was noted. Delivery by CST at 37 week. Breech presentation. Weigth: 3675 g (p>95) Apgar 2/5. After omphalocele surgical reparation he had persistent feeding problems needing gavage feeding until 4 months. In the follow-up presented developmental delay, hypotonia, coarse facies with prominent lips and philtrum, narrow thorax and scoliosis. No abnormal copy number variation was observed in array-CGH study. Metilation study of imprinted genes KCNQ1OT1, H19, MEG3 and SNRP, showed increase of metilation in MEG3 (Maternally Expresed 3) located in chromosome 14. Study with chromosomal makers showed paternal UPD14.

Omphalocele is an abdominal wall malformation frequently diagnosed in fetal echography. In classic textbooks differential diagnosis usually includes chromosomal imbalances, specific syndromes as Beckwith-Wiedemann, and different malformative entities as OEIS complex or pentalogy of Cantrell but not UPD14-pat. In our review of the literature, including our patient, we have identified 3 cases of omphalocele in 21 UPD14-pat (15%). UPD-14 pat is a serious condition that should be considered in fetal diagnosis of omphalocele.

MATERNAL AND PATERNAL UNIPARENTAL DISOMY OF CHROMOSOME 14

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Maternal and paternal uniparental disomy (UPD) of chromosome 14 are two rare but very distinct entities. We present two illustrative cases. One is a girl with pre- and postnatal growth retardation, mild developmental delay and irregular skin hyperpigmentations. She had a mosaic trisomy 14 with a maternal UPD(14). The second case is a girl with prenatally detected hychroma colli, small thorax, omphalocele and short extremities. She had a *de novo* and mosaic rob(14;14) translocation with a paternal UPD(14).

EARLY FETAL AKINESIA: AN UNUSUAL PRESENTATION OF TUBULINOPATHY

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In a G4 P3 woman, ultrasound examination performed at 12wg revealed no gross abnormality. Nuchal measurement was not available. Therefore one week later, NT was measured at 1,9mm for a CCL at 56,4mm, growth was normal, but no head and limb movements were detected, fetal akinesia was suspected.

At 14wg, control ultrasonography confirmed lack of movements with biometric data below the 5th percentile in particular for cephalic parameters. Furthermore, the upper limbs were fixed in flexion and lower limbs in extension. Third and fourth cerebral ventricles were dilated, brain middle line was not examinable.

At 15wg termination of pregnancy was performed with the informed consent of the parents. A complete autopsy revealed microcrania, micrognathia, cleft palate and no visceral malformation. Caryotype was normal 46, XY.

Neuropathological examination showed severe micrencephaly with absence of lamination of the cortical plate, along with some overmigration foci. Interestingly, spinal cord was strongly hypoplastic with major anomalies of basal plate development. Although this phenotype was not completely suggestive of LISII, analysis of cobblestone genes was carried out and was negative. Conversely, molecular analysis of Tubuline genes revealed a new heterozygous de novo mutation in *TUBB2B* gene: exon 4, c.716G<T, leading to a p.C239F substitution.

In conclusion: early fetal akinesia which is a highly heterogenous condition may be due to alteration of molecules which are involved in early central and peripheral nervous development.

CONGENITAL HEART DEFECTS IN A NOVEL RECURRENT 22Q11.2 DELETION HARBORING THE GENES *CRKL* AND *MAPK1*

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The proximal region of the long arm of chromosome 22 is rich in low copy repeats (LCR). Non-allelic homologous recombination (NAHR) between these substrates explains the high prevalence of recurrent rearrangements within this region. We have performed array comparative genomic hybridization in a normally developing girl with growth delay, microcephaly and truncus arteriosus, and have identified a novel recurrent 22q11 deletion that spans LCR22-4 and partially affects the common 22q11.2 deletion syndrome and the distal 22q11 deletion syndrome. This deletion is atypical as it did not occur by NAHR between any of the major LCRs found on 22q11.2. However, the breakpoint containing regions coincide with highly homologous regions. An identical deletion was reported recently as a *de novo* event in two patients with striking phenotypic similarity to the present case (Ogilvie *et al.*, 2009; Garavelli *et al.*, 2012). Interestingly, all three patients presented with a congenital heart defect (truncus arteriosus or septal defects), severe growth delay and microcephaly, but no or mild developmental delay. Computational gene prioritization methods and biological evidence denote the genes *CRKL* and *MAPK1* as the highest ranking candidates for causing congenital heart disease within the deleted region.

MALE WITH MOSAICISM FOR A SUPERNUMERARY DERIVATIVE X CHROMOSOME LACKING THE XIST GENE AND PHENOTYPIC FEATURES OF CRANIOFRONTONASAL SYNDROME

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Craniofrontonasal syndrome (CFNS, OMIM 304110) is an X-linked disorder with typical craniofacial dysmorphism (brachycephaly, facial asymmetry, coronal craniosynostosis, hypertelorism, broad nasal root, bifid nasal tip), syndactyly, broad halluces, and hypoplastic corpus callosum. Mutations in the gene for ephrin-B1 (*EFNB1*) located at Xq13.1 have been identified as the primary cause of CFNS which paradoxically shows a more severe phenotype in females than in males. In rare cases, CFNS can be caused by X-chromosome anomalies. We describe a five month old boy with severe dysmorphic features including a broad face, hypertelorism, broad nasal root, bifid nasal tip and multiple congenital anomalies (agenesis of the corpus callosum, patent ductus arteriosus, VSD and hypospadias). Cytogenetics including FISH analysis revealed mosaicism for a supernumerary derivative X chromosome lacking XIST: mos 47,XY,+der(X)del(X)(p11.1)del(X)(q13)[7]/46,XY[23]. Parental cytogenetic studies were normal, indicating that this derivative is likely de novo in origin. High resolution SNP array analysis showed a ~13 Mb duplication of Xp11.21-q13.1, mapped between 55,260,049 bp and 68,590,017 bp (Fig. 3). Copy number ratio was consistent with a mosaic abnormality. This region contains approx. 40 genes (such as *EFNB1*), the *XIST* gene is not included. The protein encoded by the EFNB1-gene, ephrin-B1, belongs to a group of signaling molecules involved in cell-cell-interaction and migration during development. It is assumed, that in males with inactivating EFNB1 mutations, ephrin-B1 may be replaced functionally by another B-class ephrin. Thus, the phenotypic effect of the mutation is absent or mild in males. The severe phenotype of CFNS in females with a heterozygous EFNB1 mutation is hypothesized to result from inequalities in gene dosage for EFNB1. X-inactivation in early embryogenesis leads to different cell populations: one with cells that do express EFNB1, the other one without EFNB1 expression. The patchy ephrin-B1 defect results in disturbed closure of cranial sutures by a process termed cellular interference. Mosaicism for a derivative chromosome expressing EFNB1 in one cell line due to a lack of XIST probably explains similar phenotypic features in the present male patient and one other previously published male case.

FEEDING DIFFICULTIES, HEART DEFECT AND CHARACTERISTIC FACIAL FEATURES AS PART OF THE 16p11.2-12.2 MICRODELETION SYNDROME

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We report on a 18 months old girl presenting with severe feeding difficulties since birth, a cardiac defect (ASD and ODB), hypotonia and dysmorphic features. She is the third child of non-consanguineous and healthy parents and family history is unremarkable.
She needed tube feeding in the first months after birth. Surgical intervention was required to repair her cardiac defect and she received physiotherapy to improve motor development.
Clinical facial features included narrow palpebral fissures, epicanthal folds, hypoplastic alae nasi, small chin and mouth, small low-set ears and flat facies.
High-resolution array-CGH showed a 7.7 Mb *de novo* microdeletion of 16p11.2-p12.2. This deletion is distinct from the more frequently reported 16p deletion associated with autism and obesity. It is recurrent, but relatively rare with less than 10 cases reported in literature so far.
We will discuss the findings in our patient in relation to earlier described cases in order to provide further clinical characterization.

WEST SYNDROME IN HALF-SIBS: A MICRODELETION EXPLAINS IT ALL !!

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The boy is the second child of non-consanguineous, healthy parents. Birth parameters were low and atrial and ventricular septal defects were diagnosed. At the age of 1 month he presented seizures, evolving to West syndrome. Psychomotor development was delayed and he has a severe intellectual disability. He had failure to thrive and his final height is 137cm.
The younger half-sister of the boy also presented intrauterine growth retardation. At the age of 4 months the diagnosis of West syndrome was made. She developed intellectual disability. At the age of 15 years she has a height of 112 cm.
Both children present similar facial characteristics.
In a recent new work-up, a microdeletion syndrome was diagnosed. Parental translocation is suspected, but has to be confirmed.

Biallelic SEMA3A defects cause a novel type of syndromic short stature

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Molecular karyotyping is commonly used to identify disease causing de novo copy number variants in patients with developmental delay and multiple congenital anomalies. In such a patient with multiple congenital anomalies we now observed an 150 kb deletion on chromosome 7q21.11 affecting the first exon of the axon guidance molecule gene SEMA3A. This deletion was inherited from the healthy father, but considering the function of SEMA3A and phenotypic similarity to the knock-out mice, we still assumed a pathogenic relevance and tested for a recessive second defect. Sequencing of the SEMA3A gene in the patient indeed revealed the de novo in-frame mutation p.Phe316_Lys317delinsThrSerSerAsnGlu. Cloning of the mutated allele in combination with two informative SNPs confirmed compound heterozygosity in the patient. While the altered protein structure was predicted to be benign, aberrant splicing resulting in a premature stop codon was proven by RT-PCR to occur in about half of the transcripts from this allele. Expression profiling in human fetal and adult cDNA panels, confirmed a high expression of SEMA3A in all brain regions as well as in adult and fetal heart and fetal skeletal muscle. Normal intellectual development in the patient was surprising but may be explained by the remaining 20% of SEMA3A expression level demonstrated by quantitative RT-PCR. We therefore report the first biallelic human mutations in the SEMA3A gene delineating a novel autosomal recessive disorder characterized by postnatal short stature with relative macrocephaly, camptodactyly, septal heart defect and several minor anomalies.

Clinical variability in partial Jacobsen Syndrome: report of a sporadic case and three affected family members

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Jacobsen syndrome is a contiguous gene deletion syndrome characterized by trigonocephaly, abnormal platelet function, thrombocyto- or pancytopenia, malformations of the heart, kidney, gastrointestinal tract, genitalia, partially agenesis of corpus callosum, minor skeletal anomalies, distinct facial dysmorphism and intellectual disability. It has an estimated frequency of 1:100.000 and more than 200 patients have been reported so far. Deletion sizes range from 7 to 20 Mb commonly with a proximal breakpoint within 11q23.3. 85% of reported cases occurred de novo and 15% resulted from parental balanced rearrangements. Intellectual disability varies from mild to severe and 3% of cases have been reported with normal or borderline IQ.

We report a novel sporadic and three familiar cases with partial Jacobsen syndrome identified by molecular karyotyping demonstrating broad clinical variability. Patient 1 is a 2.5 years-old girl with heterozygote 9.8 Mb deletion within 11q21-q22.3. Her main medical problems were hemophagozytosis syndrome due to Kawasaki syndrome, renal malformations, low CD4+T cell count, PDA, PFO, ASD II, hypotonia, and developmental delay. She also showed trigonocephalus, complete alopecia and onychodystrophia and facial dysmorphism. The same deletion could be identified in the father and in the older sister, both of which showed minor anomalies only. The second patient is a 12 years old boy with a de novo deletion about 6.6 Mb in 11q24.3-q25. He also had a heart defect (aortic isthmus stenosis) and developmental delay. The main clinical signs in this case were special behaviour, hypertrichosis, obesity and frequent respiratory infections.

An unknown case
Dysrmorphy
Skeletal anomaly
Eye anomalies
Dextrocardia
Asd II
Dental anomalies
Hypotonia/hypermobility
Normal intelligence

By

Eric Smeets, Maastricht University
Jean-Pierre Frijns, Leuven Universtity

UNKNOWN DIAGNOSIS - Tham E, Grigelioniene G,
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Family history: Consanguinous parents. One previous child with Prader-Willi syndrome and a deletion on chromosome 15. One healthy son. The mother of the case has a brother who has married the sister of the father of the case and they have a child with autism, cardiac malformation and abnormal skull shape who hopefully will visit me in the clinic soon.

Clinical findings: Routine ultrasound demonstrated cardiac malformation, growth retardation and polycystic kidneys. Karyotype: 46,XX. Intrauterine death in gestation week 25+3. Birth length 30cm (≤-3SD), birth weight 1kg (+1SD), head circumference 24cm (0SD), crown-rump length 23cm. Tower-shaped skull with dilated fontanelles. Bilateral telecanthus, hypertelorism. Low sitting, dysplastic ears. Long narrow nose with hypoplastic alae. Micrognatia. Short neck with extra skin folds. Thin lips. Rhizomelia, deformed left arm. Ulnar deviation of the fingers. Externally rotated deformed feet. Cardiac malformation with double outlet right ventricle, small left ventricle, dilated coronary sinus, open foramen ovale, ventricle septum defect, stenosis of the mitral valve. Kidney malformation with hypoplastic renal arteries, large polycystic kidneys with radial cysts and no clear cortex-medulla boundary. Hypoplastic ureters and bladder. Liver of normal size with fibrosis in the portal zones and ductal plate malformation and a cystic proliferation of the ducts. Bicornuate uterus and atrophic fibrotic changes in the ovaries. Protruberant abdomen. Skeletal radiograms demonstrated short long bones with flared, rounded metaphyses; lack of mineralisation of the cervical and sacral vertebral bodies (normal mineralisation of the pedicles). Platyspondyly. Lack of mineralisation of pubic bones. Eleven short ribs that end in axillary line. Narrow thorax. Hooked clavicles. No polydactyly, no atresias, normal tooth development. Normal ossification of calcaneus.

Conclusions: Due to the combination of cardiac malformation, polycystic kidneys, liver fibrosis in portal zones and skeletal dysplasia a ciliopathy was suspected. No known syndrome was identified.

If anyone has a similar case, please do contact me – for future research testing if possible
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Unknown syndrome in two sibs and their mother

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Here, we present two brothers with an unknown syndrome and their affected mother. At the age of three years, the first brother presented with bilateral radio-ulnar synostosis and a bilateral cutaneous 2,3 syndactyly. At the age of 7, his brother presented with cutaneous syndactylie of the hands (2,3 syndactyly of the right hand, and a 2,3/3,4/4,5 syndactyly of the left hand) as well as a cutaneous 2,3 syndactyly of the feet. The second brother did not have a radio-ulnar synostoses. Radiographically, their mother had a synostosis of the mertacarpals II and III of the right hand. During the pregnancy, the mother had used thyroid hormone supplementation. Both mother and the two brothers had dysmorphic features (deep-set eyes, epicantus folds, thin lips, pointy chin).
Chromosomal investigations of the first brother (chromosomes, BAC-array, subtelomere MLPA, 180K array-CGH) did not reveal a defect. DNA-analysis of HOXD13 and the NOG gene was normal. Genetic investigations of the second brother (180K array-CGH and Fragile X testing) were normal as well.

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