24th EUROPEAN MEETING ON DYSMORPHOLOGY

GENERAL PROGRAM

WEDNESDAY 4th 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 5th SEPTEMBER

8.55 a.m.		Opening address
9.00 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 6th 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.		Second session
7.30 p.m.	Dinner	

SATURDAY 7th SEPTEMBER

Breakfast - Departure

SCIENTIFIC PROGRAM

Note: This program is tentative and may be modified.

THURSDAY 5th SEPTEMBER

08.55 Opening address: FRYNS J.P.

09.00-11.00 FIRST SESSION: MCA/ID
Chair: STOLL C.

09.00 C. EVERS, D. MITTER, G. STROBL-WILDEMANN, J.W.G. JANSSEN, A. JAUCH, K. HINDERHOFER, B. MAAS, U. HAUG AND U. MOOG
De novo Xp11 duplications in female patients: clinical report and molecular cytognetic characterization.

09.15 C.STOLL, B.DOTT, Y. ALEMBIK AND M-P. ROTH
Associated nonurinary anomalies among infants with CAKUT.

09.30 B. ALBRECHT, K. BUITING, K. DE GROOT AND H.-J. LÜDECKE
A patient with clinical features of maternal uniparental disomy 14 caused by a 1.1Mb paternal deletion 14q32.2 Evidence for a novel microdeletion syndrome.

09.45 A. BARCIA,, L. ALONSO, A.M. LEAL, P. LOZANO AND A. CARMONA
7q11.22 deletion, involving AUTS2 gene, in a girl with delayed language development, mild intellectual disability and dysmorphic features.

10.00 E.K. BIJLSMA, S.L. GREVILLE-HEYGAT, S. BUNSTONE, B. CASTLE, E. HOWARD, D. ROBINSON, THE DDD STUDY, V. HARRISON, A. VAN HAERINGEN, C.A.L. RUIVENKAM AND, G.W.E. SANTEN
Mutations within MLL2 associated with a non-Kabuki syndrome phenotype.

10.15 B. CALLEWAERT, A. DHEEDENE, B. MENTEN, B. DELLE-CHIAIE[1] E. SNAUWAERT, K. DECAESTECKER, F. ROELENS, AND O VANAKKER
MED13L haploinsufficiency in isolated delayed neuromotor development: further delineation of the phenotypic spectrum.

10.30 Y. CAPRI, D. GRAS, M. GERARD, D. RODRIGUEZ, J. FABRE-TESTE, Y. LIU, A. VERLOES, D. SÖLL, O. BOESPFLUG-TANGUY and L. BURGLEN
First French family of cerebello-cerebral atrophy with new SEPSECS mutations.

10.45 C. FAUTH, S. SCHOLL-BÜRGI, B. KRABICHLER, AND J. ZSCHOCKE
Two siblings with hypotonia-cystinuria syndrome, a contiguous gene syndrome caused by homozygous 2p21 deletions.

11.00-11.30 *Coffee Break*

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

11.30 M .ISRIE, C. LAMBRECHT, C. WOUTERS, P. MOENS, M. MORREN AND H. VAN ESCH
X-linked dominant chondrodysplasia punctata revisited: novel missense mutation (p.w68c) in the EBP gene.

11.45 D.P. GERMAIN, N. MONNIER, J. LUNARDI, P.-S. JOUK, D. LECLAIR, B. ESTOURNET AND S. QUIJANO-ROY
Mutation in TNNT3 results in marked clinical variability in a French family with autosomal dominant distal arthrogryposis type 2B (Sheldon-Hall syndrome).

12.00 A. JACQUINET, H. VALDES-SOCIN, C. LIBIOULLE, J.H. CABERG AND A. VERLOES
Femoral facial syndrome: long term follow-up and associated array CGH abnormalities.

12.15 D.E. FRANSEN VAN DE PUTTE, M. KOOPMANS, D.Q.C.M. BARGE-SCHAAPVELD, N.S. DEN HOLLANDER AND E.K. BIJLSMA
Varying phenotypes in patients with WNT10A mutations.

AFTERNOON

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

14.30 H. KÄÄRIÄINEN, K. AVELA, P.SALO AND M. PEROLA
22q11.22 syndrome and multiple cases of ASD associated with personal facial features in a large sibship and their father.

14.45 J KOHLHASE, E BOUDRY-LABIS, B DEMEER, C LE CAIGNEC, B ISIDOR, M MATHIEU-DRAMARD, G PLESSIS, A M GEORGE, J TAYLOR, S AFTIMOS, A WIEMER-KRUEL, G ANNERÉN, H FIRTH, I SIMONIC, J VERMEESCH, A-C THURESSON, H COPIN, D R LOVE AND J ANDRIEUX
A novel microdeletion syndrome at 9q21.13 characterised by mental retardation, speech delay, epilepsy and characteristic facial features.

15.00 M. KUGAUDO, M. KUCHARCZYK, M. PELC, A. SKÓRKA, D. GIERUSZCZAK-BIAŁEK, K. CHRZANOWSKA AND M. KRAJEWSKA-WALASEK
Microdeletion of 12q12 region: report a new of case and a comparison with previously reported individuals.

15.15 A. LUMAKA, G. MUBUNGU, P. MUTANTU, P. MUKABA, G. UYEYE, B.-P. TADY, A. CORVENLEYN, P. LUKUSA AND K. DEVRIENDT
A novel heterozygous mutation of three consecutive nucleotides causing Apert syndrome in a Congolese family.

15.30 P. MARIN REINA, J. PANTOJA, F. MARTINEZ, C. ORELLANA, M. ROSELLO AND A.PEREZ-AYTES
Sotos-like phenotype with Marfanoid habitus in two patients with NFIX mutation.

15.45 M. MATHIEU, D. DJEDDI, G. JEDRASZAK, O. CRACCO, B. DEMEER N. SETA AND G.MORIN
Follow-up of a 33 year-old patient affected by CDG syndrome type 1a.

16.00-16.30 *Coffee Break*

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

16.30 A. RAUCH, K. STEINDL, S. AZZARELLO-BURRI, J. OBWEGESER AND AL. BAUMER
Atypical mild morphological features in a patient with Osteoglophonic dysplasia causing delayed diagnosis and treatment.

16.45 O.M. VANAKKER, U.I. FRÄNKEL AND A. DE PAEPE
Three generation family with kyphomelic dysplasia suggests autosomal dominant inheritance.

17.00 I.J.H.M. DE VOS, C.A.B. WEBER, A.P.A. STEGMANN AND C.T.R.M. STUMPEL
Atypical presentation of Axenfeld-Rieger Syndrome caused by a terminal 6p25.3 deletion resulting from a der(6)t(6;X) unbalanced translocation: some clinical lessons.

17.15 E.M.C. SCHWAIBOLD, B. ZOLL, P. BURFEIND, E. HOBBIEBRUNKEN, B. WILKEN, R. FUNKE AND M. SHOUKIER
The phenotypical differences between patients with 3p proximal deletions.

17.30 A. SKÓRKA , M. KUCHARCZYK, D. GIERUSZCZAK-BIAŁEK, M. KUGAUDO, A. CIEŚLIKOWSKA, K. CHRZANOWSKA AND M. KRAJEWSKA-WALASEK
Microduplication 22q11.2 in a child with Williams syndrome.

21.00-23.00 UNKNOWN
Chair: FRYNS J.P.

FRIDAY 6th SEPTEMBER

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

09.00 A. VOGELS, G. VAN BUGGENHOUT, R. CAEYENBERGHS, E. WEYTS AND E. LEGIUS
Copy Number Variations in a large cohort of adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders.

09.15 K. WRITZL
Minor abnormalities in Pitt-Hopkins syndrome.

09.30 C. ZWEIER, C. KRAUS, L. BRUETON, T. COLE, F. DEGENHARDT, H. ENGELS, G. GILLESSEN-KAESBACH, L. GRAUL-NEUMANN, D. HORN, J. HOYER, W. JUST, A. RAUCH, A. REIS, B. WOLLNIK, M. ZESCHNIGK, H.J. LÜDECKE AND D. WIECZOREK
A new face of Borjeson-Forssman-Lehmann syndrome? De novo mutations in PHF6 in seven females with a distinct phenotype.

09.45 M. ZENKER AND S. KANT
Copy number variants including RAS pathway genes – how much RASopathy in the phenotype?

10.00 L .GARAVELLI, A. WISCHMEIJER, S. ROSATO, C. GELMINI, E. LUSETTI ,A. IORI, F. BACCILIERI, C ADAMS, G. MIRZAA AND W.B DOBYNS
Megalencephaly capillary malformation (MCAP) and PIK3CA mutations: presentation of 3 clinical cases and evolution of the phenotype over time.

10.15 E.E.J. SMEETS, C.T.R.M. STUMPEL AND J.-P. FRIJNS
A complex clinical presentation with familial microphthalmia.

10.30 H. CHAABOUNI and F. MAAZOUL
Craniofacial anomalies associated to camptodactyly and chest deformity: cranio-facio-squelettal syndrome or new entity.

10.45 P.D. BRADY, H. VAN ESCH, J. DEPREST, P. MOERMAN, J. VERMEESCH, M. DE RADEMAEKER AND K. DEVRIENDT
Familial syndromic and non-syndromic congenital diaphragmatic hernia: the value of exome sequencing.

11.00-11.30 *Coffee Break*

11.30-13.00 SECOND SESSION: FETAL PATHOLOGY
Chair: BIJLSMA E. - SKORKA A.

11.30 D. HAYE, C. COLLET, C. SEMBELY-TAVEAU, G. HADDAD, C. DENIS, J. POINSOT, A.-L. SUC, A. LISTRAT AND A. TOUTAIN
Abnormal skull shape, bowing of the femora and tetralogy of Fallot as prenatal presentation of Carpenter syndrome.

11.45 D. LACOMBE, S. NAUDION, S. MOUTTON, M.P. CORDIER, A.L. DELEZOIDE, A. GOLDENBERG, P. LOGET, J. MELKI, S. ODENT, S. PATRIER, A. VERLOES, G. VIOT, B. ARVEILER, P. FERGELOT AND C. GOIZET
Fetal phenotype of OPD spectrum disorders.

12.00 D. GIERUSZCZAK-BIAŁEK , A. SKÓRKA, M. KUGAUDO, M. KRAJEWSKA-WALASEK AND K. CHRZANOWSKA
Achondroplasia with Di George's syndrome: a case report of the diagnosis of the extremely unusual association.

12.15 K. STEINDL, P. JOSET, D. BARTHOLDI, S. PAJAROLA, S. BÖHM, J. MICALLEF, A. BAUMER AND A. RAUCH
Further Delineation of the Johnston-Biesecker Multiple congenital anomalies-hypotonia-seizures syndrome caused by a single PIGA mutation

AFTERNOON

14.30-16.00 SECOND SESSION (Continued)
Chair: KÄÄRIÄINEN H. - BOTTANI A.

14.30 S. UHRIG, C. SOMMER, B. CSAPO, C. ROTKY-FAST, M. HAIM, F. REITERER AND C. WINDPASSINGER
Another infant with Pontocerebellar hypoplasia Type 5 (PCH5) and compound heterozygosity for the common TSEN54 mutation (p.A307S) plus a novel deletion of 25 bp in exon 8 (p.Ser376Cysfs*26). This supports the observation that PCH5 and PCH4 are allelic disorders.

14.45 A. VERLOES, S. PASSEMARD, V. LAMBERT, G. CARLES, J. GOULLE AND A. LAQUERRIERE
Maternal consumption of clay during pregnancy: an unexpected cause of recurrent congenital microcephaly with intracranial calcifications in babies from French Guyana (pseudo-Aicardi-Goutière syndrome).

15.00 GONZALES

15.15 O. CRACCO, G. JEDRASZAK, T. DERY, B. DEVAUCHELLE, V. STRUNSKI, L. BURGLEN, J.F. IKOLI, B. DEMEER, M. MATHIEU, A. LEKE AND G. MORIN
Tumoral risk in Sotos syndrome

15.30 TOUTAIN

15.45 BOTTANI

16.00-16.30 *Coffee Break*

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

DE NOVO Xp11 DUPLICATIONS IN FEMALE PATIENTS: CLINICAL REPORT AND MOLECULAR CYTOGNETIC CHARACTERIZATION

C. Evers[1], D. Mitter[2], G. Strobl-Wildemann[3], J.W.G. Janssen[1], A. Jauch[1], K. Hinderhofer[1], B. Maas[1], U. Haug[4], U. Moog[1]

[1] Institute of Human Genetics, Heidelberg University, Heidelberg, Germany
[2] Institute of Human Genetics, University Hospital Leipzig, Leipzig, Germany
[3] Humangenetik Ulm MVZ, Ulm, Germany
[4] Child Centre Maulbronn, Maulbronn, Germany

Duplication of Xp11.22-p11.23 has been shown to be associated with intellectual disability (ID) in males and females. The majority of patients had a ~4.5 Mb recurrent duplication, most affected females showed preferential activation of the duplicated X chromosome.

We describe a female patient carrying the recurrent microduplication at Xp11.22-11.23 and further present four female cases with novel Xp duplications. Two were sporadic cases with de novo ~9 Mb and ~5.5 Mb duplications of Xp11.23-11.4 and Xp11.23-p11.3, respectively. The others were monocygotic female twins carrying a de novo ~5 Mb duplication of Xp11.23-11.3. All five patients had developmental delay/intellectual disability with impaired language development and mild facial dysmorphism. Four of five patients presented with EEG abnormalities and seizures. Additional features were duplication of ureter and kidney in two unrelated patients. X chromomosome inactivation (XCI) analysis revealed preferential inactivation of the normal X in most patients. Selective inactivation of the normal X suggests that increased expression of a gene within the duplicated region leads preferential growth of the cells within the duplication. Functional disomy for genes within the duplication results in the described phenotype.

ASSOCIATED NONURINARY ANOMALIES AMONG INFANTS WITH CAKUT

C.STOLL, B.DOTT, Y. ALEMBIK, M-P. ROTH
Laboratoire de Genetique Medicale, Faculte de Medecine,
Strasbourg, France

BACKGROUND: Infants with congenital anomalies of the kidney and the urinary tract (CAKUT) often have other associated anomalies. The purpose of this investigation was to assess the prevalence, the nature and the types of associated anomalies in CAKUT in a defined population.
METHODS: The associated anomalies in CAKUT were collected in all livebirths, stillbirths and terminations of pregnancy during 26 years in 347,810 consecutive births in the area covered by our population based registry of congenital anomalies.
RESULTS: Of the 1703 infants with CAKUT born during this period (prevalence at birth of 49.1 per 10,000), 563 (33%) had associated malformations. There were 119 (7%) patients with chromosomal abnormalities including 33 trisomies 18, and 168 (10%) nonchromosomal recognized dysmorphic conditions. There were no predominant recognised dysmorphic conditions, but VA(C)TER(L) association. However, other recognised dysmorphic conditions were registered including Meckel-Gruber syndrome, and prune belly syndrome. Two hundred seventy six (16 %) of the patients had multiple congenital anomalies, non syndromic, non chromosomal (MCA). Anomalies in the musculoskeletal, the digestive, the cardiovascular and the central nervous systems were the most common other anomalies.
CONCLUSIONS: The overall prevalence of associated anomalies, which was one in six infants, emphasizes the need for a thorough investigation of infants with CAKUT. The most commonly associated major nonurinary anomalies involved the musculoskeletal system, followed by the digestive, the cardiovascular and the central nervous systems. A routine screening for other anomalies may be considered in infants and in fetuses with CAKUT

MUTATIONS WITHIN *MLL2* ASSOCIATED WITH A NON-KABUKI SYNDROME PHENOTYPE

E.K. BIJLSMA[1], S.L. GREVILLE-HEYGAT2[1], S. BUNSTONE[3], B. CASTLE[4], E. HOWARD[3], D. ROBINSON[5], THE DDD STUDY[6], V. HARRISON[2], A. VAN HAERINGEN[1], C.A.L. RUIVENKAMP[1], G.W.E. SANTEN[1]

[1]Centre for Human and Clinical Genetics (CHKG), Leiden University Medical Centre, Leiden, the Netherlands
[2] Wessex Clinical Genetic Service, Princess Anne Hospital, Southampton
[3] Regional Genetics Laboratories, Genetic Medicine, Saint Mary's Hospital, Manchester
[4] Department of Molecular Genetics, Royal Devon and Exeter NHS Foundation Trust, Exeter
[5] Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury
[6] The DDD study, Wellcome Trust Sanger Institute, Cambridge

Kabuki Syndrome (KS) is characterised by a recognisable facial appearance, skeletal anomalies, persistence of fetal fingertip pads, developmental delay and postnatal growth deficiency. Additional congenital abnormalities may also be present. KS is usually autosomal dominant with heterozygous mutations in *MLL2* identified in 56-76% of cases. To date, pathogenic *MLL2* mutations have not been associated with a non-Kabuki syndrome phenotype. We report two unrelated children with missense mutations within the *MLL2* gene who do not present with the typical facial or clinical features of KS.

Case 1 has severe speech and motor delay, truncal ataxia, seizures, stereotypies, poor sleep and recurrent respiratory tract infections. Additional features include long tapering fingers, joint hypermobility, a broad nasal bridge, bilateral hip dysplasia and early onset puberty. Whole exome sequencing was undertaken as part of the DDD study. This identified a de novo missense mutation (c.15485T>G p.Val5162Gly) within exon 48 of *MLL2*.

Case 2 has moderate to severe speech and language delay, truncal ataxia, oppositional behaviour, poor sleep and recurrent respiratory tract infections. Facial features include a broad forehead, epicanthic folds, hypertelorism and a low nasal bridge. Whole exome sequencing also detected a missense mutation (c.15685C>G p.Arg5229Gly) within exon 48 of the *MLL2* gene. Parental testing is pending.

These are the first two cases to describe a non-Kabuki syndrome phenotype in association with missense mutations in exon 48 of the *MLL2* gene and may represent a new genetically allelic condition.

MED13L haploinsufficiency in isolated delayed neuromotor development: further delineation of the phenotypic spectrum *B. Callewaert[1], A. Dheedene[1], B. Menten[1], B. Delle-Chiaie[1], E. Snauwaert[2], K. Decaestecker[3], F. Roelens[4], O. Vanakker[1].*

1)Center for Medical Genetics, Ghent University Hospital, Ghent, Ghent, Belgium; 2) Department of Pediatrics, Ghent University Hospital, Ghent, Belgium; 3) Department of Pediatrics, Stedelijk Ziekenhuis Roeselare, Roeselare, Belgium; 4) Department of Pediatrics, Heilig Hart Ziekenhuis Roeselare, Roeselare, Belgium .

A decade ago, a chromosomal translocation disrupting the MED13L (Mediator complex subunit 13-like) gene was found in a patient with transposition of the great arteries (TGA) and intellectual disability (ID). Three rare MED13L variants were subsequently identified in a cohort with isolated TGA. More recently, MED13L haploinsufficiency was detected in 2 patients with ID and conotruncal heart defects, while a copy number gain resulted in a ventricular septal defect, hypotonia and learning problems. We report 2 novel patients with a de novo intragenic MED13L deletion and further delineate the phenotype of this rare ID syndrome. Results: Both patients, respectively a 2-year old girl (patient 1) and a 3-year old boy (patient 2), presented with moderately delayed neuromotor development, generalized hypotonia, hypermetropia and a typical facial gestalt including a broad forehead, telecanthus, epicanthal folds, a bulbous nasal tip, rather small and low-set ears with a slight uplift of the earlobe. Staturoponderal evolution and head circumference were normal as was echocardiography. Brain MRI showed slightly delayed myelinisation in both patients. In addition, patient 1 had an episode of acute pyelonephritis. Abdominal ultrasound revealed a normal urogenital tract, but three small subdiaphragmatic liver cysts were noted. Patient 2 had a surgically corrected unilateral cryptorchidism. ArrayCGH analysis (180k Agilent array) revealed a 300kb deletion on chr. 12q24.21, deleting exons 2-22 of the MED13L gene in patient 1 and a 150kb deletion on chr. 12q24.21 deleting exons 2 and 3, likely resulting in a shift of the open reading frame in patient 2. Conclusion: We further document the clinical phenotype of intragenic MED13L deletions with moderate ID and consistent dysmorphic features. Particularly the morphology of the ear and earlobe should prompt MED13L analysis, even in the absence of cardiovascular defects. Hypermetropia in both patients suggests that refractive errors may also be part of the phenotypic spectrum. Besides this clinically recognizable ID syndrome, the mutation rate of the MED13L gene in patients with isolated neurodevelopmental delay remains to be determined.

A patient with clinical features of maternal uniparental disomy 14 caused by a 1.1Mb paternal deletion 14q32.2 Evidence for a novel microdeletion syndrome

Beate Albrecht[1], Karin Buiting[1], Karel de Groot[2], Hermann-Josef Lüdecke[1]

[1] Institut für Humangenetik, Universitätsklinikum Essen, Universität Duisburg-Essen, Germany
[2] MRC Holland, Amsterdam, The Netherlands

We report on a female patient with a upd(14)mat-like phenotype. The patient is the second child of non-consanguineous Tunisian-Lebanese parents. Pregnancy started as a twin pregnancy. Recurrent bleedings and reduced fetal movements were observed. The patient was born by cesarean section with normal birth measurements at 36 weeks of gestation. Muscular hypotonia and poor sucking led to tube and PEG feeding during the first year of life. She is severely delayed, walking with 2 ½ years and talking with 4 years. Precocious puberty occurred with 5 years. With 3 years all her body measurements lay below the 3rd centile, with 13 years she was short, but weight and head circumference were normal. She shows facial dysmorphism with long, narrow face and hypertelorism, behavioral problems started with 12 years.
Karyotyping was normal. SNP-array hybridization and quantitative real-time PCR for the *MEG3* gene revealed a 1.1 Mb *de novo* deletion, including most of the imprinted genes of the region and 14 not imprinted genes (arr[hg19]14q32.2q32.31(100.405.409-101.504.293)x1). Using MS-MLPA we detected hypomethylation of the *MEG3* promotor region, indicating that the deletion is of paternal origin.
Our patient carries the recurrent microdeletion 14q32.2 with breakpoints inside TGG repeats, as described for two patients by Bena et al in 2010, and two further patients, reported in 2012 by Ballif et al. She shows all clinical features of the previously described upd(14)mat-like phenotype, except for normal body measurements at birth. Haploinsufficiency of additional, non-imprinted genes may cause the intellectual disability of this novel microdeletion 14q32.2 syndrome.

7q11.22 DELETION, INVOLVING AUTS2 GENE, IN A GIRL WITH DELAYED LANGUAGE DEVELOPMENT, MILD INTELLECTUAL DISABILITY AND DYSMORPHIC FEATURES

A.BARCIA[1,2], L. ALONSO[1], A.M. LEAL[1], P. LOZANO[2] AND A. CARMONA[2]

[1] Servicio de Pediatría y Neonatología, Hospital de Valme, Sevilla (Spain)
[2] Instituto Hispalense de Pediatría, S.L. Sevilla (Spain)

Autism spectrum disorders and intellectual disability are neurodevelopmental disorders of complex and multifactorial aethiology, with increasing number of involved genes described till now, AUTS2 among them, located in 7q11.22, which contributes to both autism disorders and mental retardation, specially speech and language development. We report a 3.5 year-old girl with dysmorphic features, intellectual disability and mild autistic behaviour disorders, in whom it has been detected a 2.39 Mb deletion in 7q11.22, which implies AUTS2, and also a 1.52 Mb deletion in Xp22.31, associated to X-linked congenital ichthyosis.

3.5 year-old girl, only child of non-consanguineous and healthy parents, who presents dysmorphic features and mild intellectual disability. **Personal background**: Natural gestation, with no interesting incidents; eutocic term delivery, Apgar score 10/10; normal birth somatometry. Slight delay in neurodevelopmental items adquisition, with some autistic behaviour disorders related to an important speech delay. **Physical examination:** Weight in P48, Height in P9 and HC in P25; Inespecific dysmorphic features (frontal bossing, prominent and posterior rotated ears, mild ptosis, downslanting palpebral fissures, broad nasal root, bulbous nose, downturned mouth, micrognathia), broad neck, mild pectus excavatum, spaced nipples, joints hypermobility, pes valgus, 4th and 5th feet fingers clinodactyly, mild dry skin. Very mild autistic behaviour disorders and mild intellectual disability, with poor language. **Diagnostic tests:** Echocardiography: minimal pulmonar insuficiency; Brain MRI, EEG, metabolic disorders tests: All normal; Karyotype 46, XX; Array CGH qChipPost 60000 probes: 2.39 Mb deletion in 7q11.22 (67679077-70071727), 1.52 Mb deletion in Xp22.31 (6533520-8057511), and 3 CNVs described in general population, one of them a 569 Kb duplication in 15q11.2, described as a CNV related to a higher risk of neurodevelopmental disorders. Parents´ karyotype and a-CGH: not realised yet.

With the few cases of 7q11.22 deletion described in literature until nowadays, it´s not possible to define a common syndrome, as the phenotypes are highly variable. The 2.39 Mb 7q11.22 deletion found in our patient involves AUTS2 gene, altering its dose. This gene is implied in neurodevelopmental disorders, such as autism, and speech and language delay, although its function is not well known yet. There are also some CNVs in this patient, one them also related to a higher risk of neurodevelopmental disorders and intellectual disability. The array-CGH analysis in our patient has also allowed to diagnose an Xp22.31 deletion associated to X-linked congenital ichthyosis, being our patient an asymptomatic carrier of this disease, which is an important information to be taken in account for her future offspring.

FIRST FRENCH FAMILY OF CEREBELLO-CEREBRAL ATROPHY WITH NEW *SEPSECS* MUTATIONS

Y. CAPRI[1], D. GRAS[2], M. GERARD[3], D. RODRIGUEZ[4,5,6], J. FABRE-TESTE[1], Y. LIU[7], A. VERLOES[1,5], D. SÖLL[7], O. BOESPFLUG-TANGUY[2,5] and L. BURGLEN[5,6,8]

[1] Department of Genetics, APHP – Robert Debré University Hospital, Paris, France
[2] Reference center for "leukodystrophies", Child Neurology and Metabolic Disorders, APHP – Robert Debré University Hospital, Paris, France
[3] Department of Genetics, Caen University Hospital, Caen, France
[4] Department of Pediatric neurology, APHP –Trousseau University Hospital, Paris, France
[5] *Inserm, U676, Paris, France*
[6] Centre de référence des malformations et maladies congénitales du cervelet, APHP-Trousseau University Hospital, Paris, France
[7] Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, USA
[8] Department of Genetics, APHP – Trousseau University Hospital, Paris, France

Progressive cerebello-cerebral atrophy is an extremely rare entity described in 2003 in less than 10 patients (Ben-Zeev *et al.*). Clinical findings consist of severe spasticity, profound mental retardation with progressive microcephaly. Brain imaging shows progressive cerebellar atrophy followed by severe cerebral atrophy. The disease is caused by mutations in the *SEPSECS* gene. The Sepsecs protein needs a cofactor, pyridoxal phosphate (PLP), and is involved in the syntheses of Selenocysteine, an essential component of the active sites of some enzymes (selenoenzymes). We describe a family with 2 affected children. Patient A is the 2nd child of non-consanguineous parents. The boy was born with normal parameters, after an uneventful pregnancy. Bilateral adductus thumb were noticed at birth and generalized stiffness appeared rapidly with tetra spastic paraplegia. He developed with a profound mental retardation. His best milestones were smiling at 4.5 months and head control at 24 months. Spontaneous movements were very poor. He developed severe postnatal microcephaly (-3SD at 6 months and -7SD at 7 years). Successive brain MRI found progressive cerebellar atrophy, rapidly followed by severe cerebral atrophy. Patient B is the 4th child of the family. Recurrence of the disease was suspected in the young sister of patient A because she displayed dystonic movements, stiffness of the trunk at 3 months and progressive microcephaly. *SEPSECS* sequencing revealed in the affected children, 2 novel mutations: a splice mutation predicted to affect splicing of exon 1, and a missense predicted to disrupt folding of the protein or affect binding with PLP.

Two siblings with hypotonia-cystinuria syndrome, a contiguous gene syndrome caused by homozygous 2p21 deletions

C. Fauth,[1] S. Scholl-Bürgi,[2] B. Krabichler,[1] J. Zschocke[1]
[1] Division of Human Genetics
[2] Division of Neuropediatrics and Inherited Metabolic Diseases, Medical University Innsbruck, Austria

Muscular hypotonia in childhood is a rather unspecific sign which can be part of over 500 different genetic disorders (Lisi and Cohn, 2011). Hence, finding the correct diagnosis is often challenging. Key elements of clinical work-up are a thorough clinical, neuropaediatric and dysmorphological examination complemented by electrophysiological and laboratory tests. In some patients metabolic abnormalities may yield diagnostic clues beyond individual inborn errors of metabolism as shown in the present case of two brothers with hypotonia-cystinuria syndrome.
The index patient is an 8 year old boy with muscular hypotonia, mild developmental delay, mild facial dysmorphism, hypospadias, cryptorchidism, and short stature (length 117,5 cm; 1 cm <P3). During the first years of life he had a failure to thrive followed by hyperphagia and rapid weight gain (current BMI 21,4 kg/m2, >P97). His parents are consanguineous. Molecular testing for Prader-Willi syndrome gave a normal result. However, metabolic screening including urinary amino acid analysis showed reduced absorption of the dibasic amino acids and cystine, compatible with cystinuria.
Evaluation of other family members showed that his younger brother who is currently 3 years old also had hypotonia as well as nephrolithiasis caused by cystinuria. Based on these findings hypotonia-cystinuria syndrome (HCS) was suspected. This was confirmed by molecular karyotyping which showed a homozygous deletion in chromosome band 2p21 with a size of 30-40 kb in both brothers. The deletion affects parts of the *SLC3A1*-gene coding for a renal cystine transporter, mutations of which cause cystinuria type I, and the *PREPL*-gene coding for a serin oligopeptidase supposed to be involved in secretion and/or processing of peptide hormones. Similar homozygous deletions have already been described in other patients with HCS. Clinical hallmarks of this syndrome are severe generalized hypotonia at birth, nephrolithiasis due to cystinuria, growth hormone deficiency with short stature, and initial failure to thrive followed by obesity in late childhood. Intellectual development may be normal or mildly delayed.
Urinary amino acid analysis or at least a nitroprusside test (Brand reaction) should be part of the biochemical work-up in children with muscular hypotonia, in particular in those with a Prader-Willi-like phenotype who test negative for Prader-Willi syndrome.

X-LINKED DOMINANT CHONDRODYSPLASIA PUNCTATA REVISITED: NOVEL MISSENSE MUTATION (p.W68C) IN THE *EBP* GENE

M.ISRIE[1], C. LAMBRECHT[2], C. WOUTERS[3], P. MOENS[4], M. MORREN[2] AND H. VAN ESCH[1]

[1] Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium
[2] Department of dermatology, University Hospitals Leuven, Leuven, Belgium
[3] Department of pediatric rheumatology, University Hospitals Leuven, Leuven, Belgium
[4] Department of pediatric orthopedics, University Hospitals Leuven, Leuven, Belgium

We report on a 7 months old girl presenting with ichthyosis, erythematous alopecia spots on the scalp, strabismus, cataract and subtle facial dysmorphism. She is the first child of non-consanguineous parents. The mother had a history of cicatricial alopecia for which she was treated with hair implants. She also had follicular atrophoderma on the forearms, small lens opacities and scoliosis.

The combination of symptoms and signs in the proband and her mother, along with absence of photophobia, led to the clinical diagnosis of Conradi-Hünermann-Happle syndrome. However, stippling of the epiphyses was absent on X-rays. DNA analysis of the *EBP* gene revealed a novel missense mutation (c.204G>T) in exon 2, which was inherited from the mother. The clinical phenotype as well as additional investigations supported pathogenicity of this variant.

Conradi-Hünermann-Happle syndrome, also known as X-linked dominant chondrodysplasia punctata type II (CDPX2) is a type of chondrodysplasia punctata which primarily affects the skin, bones and eyes. There is strong clinical and intrafamilial variability. We will review the clinical spectrum as well as the differential diagnosis of CDPX2. In addition, other *EBP* mutations in both males and females will be discussed.

Mutation in *TNNT3* results in marked clinical variability in a French family with autosomal dominant distal arthrogryposis type 2B (Sheldon-Hall syndrome)

Dominique P. GERMAIN 1,2, Nicole MONNIER 3, Joel LUNARDI 3, Pierre-Simon JOUK 4, Danielle LECLAIR 5, Brigitte ESTOURNET 5, Susana QUIJANO-ROY 5

1. Service de Génétique Médicale, CHU Raymond Poincaré (AP-HP), 92380 Garches, France
2 EA2493, Université de Versailles - St Quentin en Yvelines, 78180 Montigny, France
3. Laboratoire de Biochimie et Génétique Moléculaire, CHU de Grenoble, Grenoble, France
4. Service de Génétique Médicale, CHU Grenoble, 38000 Grenoble, France
5. Service de Pédiatrie, CHU Raymond Poincaré (AP-HP), 92380 Garches, France

Distal arthrogryposis (DA) is a group of rare, clinically and genetically heterogeneous disorders primarily characterized by congenital contractures of the limb joints. Recently, mutations in genes encoding the fast-twitch skeletal muscle contractile myofibers complex, including troponin I2 (TNNI2), troponin T3 (TNNT3), tropomyosine 2 (TPM2), and embryonic myosin heavy chain 3 (MYH3), and the slow-twitch skeletal muscle myosin binding protein C1 (MYBPC1) were found to cause DA1, DA2A, and DA2B. Sheldon-Hall syndrome (SHS; OMIM 601680, or DA2B) is a rare multiple congenital contracture syndrome characterized by contractures of the distal joints of the limbs. SHS is intermediate to DA1 and DA2A (also known as Freeman-Sheldon syndrome, FSS; OMIM 193700). We report a French family with SHS over two generations in which affected individuals showed marked clinical variability. The index case presented with distal arthrogryposis, marked cervical webbing, facial dysmorphism and cyphoscoliosis. His mother and younger sister were subsequently found to also be affected with SHS, although to a lesser extend. For both pregnancies, fetal movements had been diminished. Sequencing revealed a mutation at a hot-spot site in *TNNT3* (c.187C>T; p.Arg63Cys). This mutation was confirmed to cosegregate with the DA phenotype in affected individuals. PolyPhen analyse suggested that the mutation is pathogenic. Interestingly, all previously reported mutations in *TNNT3* occurred at codon 63. There is no specific therapy for SHS. Our index case benefited from early intervention with occupational, physical therapy, serial casting and surgery.

FEMORAL FACIAL SYNDROME: LONG TERM FOLLOW-UP AND ASSOCIATED ARRAY CGH ABNORMALITIES

A. JACQUINET[1], H.VALDES-SOCIN[2], C.LIBIOULLE[1], J.H.CABERG[1] AND A.VERLOES[1,3]

[1] Center for Human Genetics, CHU & University of Liège, Liège, Belgium
[2] Department of Endocrinology, CHU & University of Liège, Liège, Belgium
[3] Department of Medical Genetics and INSERM U676, APHP-Robert Debré University Hospital, Paris, France

Daentl femoral-facial syndrome (FFS) includes bilateral femoral hypoplasia and particular facial features: long philtrum with thin upper lip, micrognathia with or without cleft palate, upward-slanted palpebral fissures, and hypoplastic alae nasi with a broad tip. The syndrome is clinically heterogeneous, and other malformations have been associated. Psychomotor and cognitive developments are usually normal. Etiology of this syndrome remains currently unknown. Most of the cases are sporadic. Non-genetic factors as maternal diabetes mellitus have been associated. Reports of familial cases have otherwise suggested autosomal dominant inheritance.

Our patient was the first child of unrelated parents. Very short femora were detected at fourth month of pregnancy. Birth height was 40 cm at term. FFS was diagnosed at birth, based on severe bilateral femoral hypoplasia and characteristic facial features with Pierre Robin sequence. Early psychomotor development was normal and walking alone was acquired at age two despite the absence of hip joints. At age seventeen, she was investigated for primary amenorrhea and was shown to have uterine aplasia, and thus Mayer-Rokitansky-Kuster-Hauser syndrome. Endocrine workup noted hyperandrogenism due to both ovarian and adrenal androgen overproduction. Recently, array CGH investigation identified a 1485 kb duplication at 9q31.1, including the gene *SMC2,* and a 853 kb deletion at 12q24.33 including the genes *P2RX2, PEGAM5, GOLGA3, POLE1, CHFR, ZNF26, ZNF140, ZNF10* and *ZNF268*. Unfortunately, samples of parents were not available. Long term follow up of our patient underlined orthopedic problems as the major handicap in the FFS syndrome, cognitive development being normal. Unexpected discover was the association with mullerian agenesis. Both may reflect different defects in the primary axial mesodermal development, being the consequences of same environmental or/and genetic factors during blastogenesis. Among these genetic factors, we suggest the possible involvement of the two copy number variants reported here. Reports of other patients would be required to confirm this.

VARYING PHENOTYPES IN PATIENTS WITH WNT10A MUTATIONS

D.E. FRANSEN VAN DE PUTTE [1], M. KOOPMANS [1], D.Q.C.M. BARGE-SCHAAPVELD [1], N.S. DEN HOLLANDER [1], E.K. BIJLSMA [1].

[1] Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands

Homozygous mutations in the WNT10A gene cause various types of ectodermal dysplasia (ED). Recently, both homozygous and heterozygous mutations in this gene have been reported to be present in a large proportion of patients with isolated oligodontia and in patients with oligodontia associated with minor signs of ectodermal dysplasia. Homozygous and (compound) heterozygous mutations appear to be associated with similar, but highly variable phenotypes. No individuals carrying two WNT10A mutations without any ED symptoms have been described so far.
We describe six probands and several family members with WNT10A mutations. Phenotypes in patients with two mutations varied from odontoonychodermal dysplasia (ODDD) in a 32-year-old proband to asymptomatic in the mother of an oligodontia patient. Most heterozygous parents were asymptomatic or had mild ED features.
Our cases illustrate the variable phenotype in patients with WNT10A mutations. Moreover, this is the first report of an asymptomatic patient carrying two mutations in this gene.

22Q11.22 SYNDROME AND MULTIPLE CASES OF ASD ASSOCIATED WITH PERSONAL FACIAL FEATURES IN A LARGE SIBSHIP AND THEIR FATHER

HELENA KÄÄRIÄINEN[1,2], KRISTIINA AVELA[2], PERTTU SALO[1], MARKUS PEROLA[1]:.

1) National Institute for Health and Welfare, Helsinki, Finland
2) Dpt of Medical genetics, Helsinki University Hospital, Helsinki, Finland

We report a family with multiple cases of atrial septal defects (ASD) and one individual with 22q11.22 syndrome. The index patient is a girl with ASD secundum (percutaneous operation), cleft palate, dysmorphic facies suggesting 22q11.22 syndrome and learning difficulties. As expected, a 22q11.22 deletion was found in a FISH study. As 4/5 of her siblings also had ASD (one necessitated open heart surgery, two were closed by percutaneous operation and one is in follow up), the parents were studied with 22q11.22 FISH and their chromosomes were investigated to rule out balanced translocations. In addition, molecular karyotyping (180K oligonukleotide microarray) was performed in both of them with normal results. The four affected siblings (ages 15-20 years) do not have learning difficulties nor cleft palate, but some of them have dyslexia as also has the father. They all had personal facial features resembling the father (long facies, large ears) but not suggesting 22q11.22 syndrome (which had been ruled out with FISH in some of them). During the investigations of the family, the father had a transient cerebral ischemic attack and an echocardiogram was performed to rule out an atrial shunt. The atrial septum was found to be intact but exceptionally thin, like a membrane only. The father had three daughters from a previous marriage, in echocardiogram one had a possible atrial shunt at foramen ovale but not an ASD, the other two had normal echocardiograms. Cardiologic examination of the mother is pending. Additional molecular studies in this family are ongoing.

A novel microdeletion syndrome at 9q21.13 characterised by mental retardation, speech delay, epilepsy and characteristic facial features.

J Kohlhase[1], E Boudry-Labis[2], B Demeer[3], C Le Caignec[4], B Isidor[4], M Mathieu-Dramard[3], G Plessis[5], A M George[6], J Taylor[7], S Aftimos[7], A Wiemer-Kruel[8], G Annerén[9], H Firth[10], I Simonic[10], J Vermeesch[11], A-C Thuresson[9], H Copin[12], D R Love[6], J Andrieux[2]

2 Institut de Génétique Médicale, Hopital Jeanne de Flandre, CHRU de Lille, France
3 Service de Génétique Médicale, CHRU d'Amiens, France
4 Service de Génétique Médicale, CHU Nantes, France
5 Service de Génétique, CHU Clémenceau, Caen, France
6 Diagnostic Genetics, LabPLUS, Auckland City Hospital, New Zealand
7 Genetic Health Service New Zealand- Northern Hub, Auckland City Hospital, New Zealand
8 Epilepsy Center, Kehl-Kork, Germany
1 Center for Human Genetics, Freiburg, Germany
9 Department of Immunology, Genetics and Pathology, ScilifeLab, Uppsala University, Uppsala, Sweden
10 Dept of Medical Genetics, Box 134, Addenbrooke's Hospital, Cambridge, United Kingdom
11 Center for Human Genetics, Katholieke Universiteit Leuven, Belgium
12 Médecine et Biologie reproduction et cytogénétique, Centre de Gynécologie-Obstétrique, Université Picardie, CHU d'Amiens, France

The increased use of array-CGH and SNP-arrays for genetic diagnosis has led to the identification of new microdeletion/microduplication syndromes and enabled genotype/ phenotype correlations to be made. In this study, nine patients with 9q21 deletions were investigated and compared with four previously Decipher reported patients. Genotype-phenotype comparisons of 13 patients revealed several common major characteristics including significant developmental delay, epilepsy, neuro-behavioural disorders and recognizable facial features including hypertelorism, feature-less philtrum, and a thin upper lip. The molecular investigation identified deletions with different breakpoints and of variable lengths, but the 750 kb smallest overlapping deleted region includes four genes. Among these genes, *RORB* is a strong candidate for a neurological phenotype. To our knowledge, this is the first published report of 9q21 microdeletions and our observations strongly suggest that these deletions are responsible for a new genetic syndrome characterised by mental retardation with speech delay, epilepsy, autistic behaviour and moderate facial dysmorphy.

MICRODELETION OF 12q12 REGION: REPORT A NEW OF CASE AND A COMPARISON WITH PREVIOUSLY REPORTED INDIVIDUALS

M. KUGAUDO[1,2], M. KUCHARCZYK[1], M. PELC[1], A. SKÓRKA[1,3], D. GIERUSZCZAK-BIAŁEK[1,3], K. CHRZANOWSKA[1], M. KRAJEWSKA-WALASEK[1]

[1] Department of Medical Genetics, The Children's Memorial Health Institute, Poland
[2] Department of Child and Adolescent Psychiatry, Medical University of Warsaw, Poland
[3] Department of Pediatrics, Medical University of Warsaw, Poland

Interstitial deletion of 12q12 is a rare cause of psychomotor delay/ learning disability with craniofacial dysmorphy. In 2010, genotype-phenotype correlation was refined by Adam et al. based on similar proximal deletion of 12q12 in six individuals. Reported patients had an overlapping phenotype: psychomotor retardation (6/6), growth retardation (6/6), microcephaly (6/6), upslanting palpebral fissures (3/6), broad nose (4/6) with anteverted nostrils (3/6), low set ears (5/6), sensorineural hearing loss (2/6), widely spaced nipples (3/6), small hands (5/6) with fifth finger clinodactyly (3/6).

Here we present molecular and clinical findings of another patient a 12-year-old girl with de novo deletion at 12q12q13.11 region. Our patient is the first child of healthy and non-consanguineous parent. She was born by cesarean section at 42 weeks of gestation with 3-7-9 Apgar score. Birth weight was 2180g (↓3rd centile), length – 50cm (↓3rd centile), head circumference – 32cm (25th centile). Bilateral dysplasia of the hip was diagnosed in neonatal period. Her developmental milestones were delayed (sitting - 15m, walking – 2y, words – 1.5y). Her height and weight at 8y and 10 y were below 3rd centile, head circumference measurements 3-10 centile. Sensorineural hearing loss was diagnosed at 10 y. She was also operated because of bilateral inguinal hernia.

Her facial features include: prominent metopic ridge, slightly coarse face with upslanting palpebral fissures, low-set fleshy ears with thick helix and uplifted ear lobe, short and broad nose with anteverted nares, wide mouth with downturned corners, deeply grooved philtrum, high-arched palate. Other anomalies were: sparse hair, webbed neck, a low posterior hairline, widely set nipples, small hands and feet, unilateral single palmar crease and keratosis pilaris on extremities.

Genetic investigation with CGH-array revealed a 5,7 Mb deletion in the 12q12 q13.11 encompasses the most known genes of this region implicated in early embryonic development. A comparison between the clinical and molecular findings of our patient and the previously reported cases will be presented.

This study was supported in part by a grant from the Polish Ministry of Science and Higher Education (Contract No. 0193/IP1/2013/72).

A novel heterozygous mutation of three consecutive nucleotides causing Apert syndrome in a Congolese family

Aimé LUMAKA[1,2,3], Gerrye MUBUNGU[2,3], Pierre MUTANTU[2,3], Papino MUKABA[4], Getty LUYEYE[5], Bruno-Paul TADY[2], Anniek CORVENLEYN[1], Prosper LUKUSA[1,2,3] & Koen DEVRIENT[1]

1. Center for Human Genetics KULeuven, Belgium
2. Center for Human genetics, University of Kinshasa, DR.Congo
3. Institut National de Recherche Biomédicale (INRB-RD.Congo),
4. Department of Surgery, University Hospital Kinshasa, DR.Congo
5. Imaging Department, Hôpital Général de Référence de Kinshasa, DR.Congo.

Apert syndrome (AS) is a rare genetic condition characterized by craniosynostosis and syndactyly of hands and feet. There exists intrafamilial clinical variability, the basis of which is presently unclear. Causal mutations in the Fibroblast Growth Factor Receptor 2 (FGFR2) are restricted to the linker region between the immunoglobulin-like domains II and IIIa of the ectodomain. Two mutations are responsible of the vast majority of cases: Ser252Trp (65%) and Pro253Arg (34%). Besides this, a few cases carry multiple substitutions of consecutive nucleotides in the linker region. Here we present a Congolese male patient and his mother, both affected with Apert syndrome and variable severity. Both carrying a previously unreported heterozygous mutation of three consecutive nucleotides in the IgII-IgIIIa linker region. This is the seventh distinct mutation to be reported in Apert syndrome, and it adds to the range of alternative substitutions of the Pro253 amino acid. Remarkably, this novel mutation was detected in the first Central African patient ever to be studied molecularly. To discriminate between a hitherto unreported mutation and an ethnic specific polymorphism for one position of this mutation, we tested 60 Congolese controls, and this variant was not detected.

Key words: Craniosynostosis, clinical variability, ectodomain, polymorphism.

SOTOS-LIKE PHENOTYPE WITH MARPHANOID HABITUS IN TWO PATIENTS WITH *NFIX* MUTATION

Marin Reina P (1,4), Pantoja J (2), Martinez F (3), Orellana C (3), Rosello M (3), Perez-Aytes A (4)
mail:
(1) S.Pediatría, Hospital General de Valencia (2) S.Pediatría, Hospital de La Plana, Villareal
(3) S. Genética (4) U. Dismorfologia, Hospital La Fe. Valencia (Spain)

Sotos-like phenotype associated to *NFIX* mutations has been reported in patients negative for mutations in *NSD1*. Mutations in *NFIX* are also associated to Marshall-Smith syndrome, an overgrowth syndrome with more severe phenotype than Sotos and Sotos-like. We present two patients with Sotos-like phenotype with de novo mutations in *NFIX*.

Case 1: P.S. is a female, referred to Dysmorphology clinic at 12 year old to discard Marfan syndrome. She was studied because of hypotonia and scoliosis. Karyotype: 46, XX normal. Brain MRI: Normal. Normal cardiac examination. No ectopia lentis. Phenotype was suggestive of Sotos syndrome. He presented weight: 33.5 kg (p 10), height: 164 cm (p>97), OFC: 55 cm (p 98). *NSD1* mutational study was normal. Study of *NFIX* showed a heterozygous missense mutation c.161G>C in exon 2 (p.Arg54Pro). This change was absent in both parents. She is mildly retarded.

Case 2: A.M. is a 6 year old male. In the first year of life retarded motor development was noted. Karyotype and Fragile-X testing were normal. Brain MRI: No anomalies. In the follow-up, Marfan syndrome was suspected. Cardiac and Ophthalmological examination were normal. He was referred to Dysmorphology Clinic with suspected Sotos syndrome. He presented weight: 25.5 kg (p 90), height: 135 cm (p>97), OFC: 59.5 cm (p>98). He had high forehead, thin mandible, large and slender digits (almost aracnodactyly), moderate joint hyperextensibility. Carpal X-ray showed advanced bone age. *NSD1* study did not show a pathogenic mutation. *NFIX* was then studied and a heterozygous c.112C>T change was observed. This change was absent in both parents. The child attends to normal school but has learning difficulties needing special support in expressive language.

The two changes observed in our patients are novel missense mutations in *NFIX*. In both patients a slender phenotype with tall stature lead to an initial diagnosis of Marfan syndrome. *NFIX* study should be considered not only in patients with Sotos-like phenotype but also in Marfanoid phenotype associated to developmental delay.

Follow-up of a 33 year-old patient affected by CDG syndrome type 1a

M. Mathieu[1], D. Djeddi[2], G. Jedraszak[1], O. Cracco[2], B. Demeer[1], N. Seta[3], G.Morin[1].

(1) Service de Génétique Clinique - CHU - Amiens - France
(2) Service de Pédiatrie - CHU - Amiens - France
(3) Service de Biochimie – Groupe Hospitalier Bichat – Paris – France

Congenital disorder of glycosylation is a group of autosomal recessive metabolic diseases caused by defective glycosylation of glucoconjugates. Type 1a is the most frequent and is characterized by high variable clinical manifestations from birth including feeding problems, chronic diarrhea, failure to thrive, peculiar facies, hypotonia and scoliosis, severe mental retardation, peripheral neuropathy and stroke-like episodes. Cortical atrophy and evolutive cerebellar hypoplasia are constant on cerebral MRI imaging.

Letality or neonatal death is a dependency of severe mutations in the gene encoding phosphomannomutase 2 (PMM_2).

We report the observation of a patient aged 33 years. The parents and 2 sons are healthy. Diagnosis was confirmed at the age of 10 years by biological values and identification of mutations in PMM_2gene.

Atypical mild morphological features in a patient with Osteoglophonic dysplasia causing delayed diagnosis and treatment

Anita Rauch[1], Katharina Steindl[1], Silvia Azzarello-Burri[1], Joachim Obwegeser[2], Alessandra Baumer[1]

1) Institute of Medical Genetics, University of Zurich, Schwerzenbach-Zurich, Switzerland
2) Craniofacial surgery, University Hospital Zurich, Zurich, Switzerland

Osteoglophonic dysplasia (OGD) is a rare autosomal dominant skeletal disorder characterized by severe growth retardation and craniofacial malformations. OGD is caused by certain mutations in the fibroblast growth factor receptor 1 gene and only about 14 cases are published to date. We followed a boy with normal growth and mild facial dysmorphism presenting with non-eruption of teeth and multiple giant cell granulomas of the jaw at the age of 4 years. At that time molecular testing for Noonan syndrome and Cherubism revealed normal results. Treatment consisted of repeated curettage, local injection of corticosteroids and daily subcutaneous injections of calcitonin. At the age of 5 ½ years he presented with unexplained intracranial hypertension which was considered idiopathic and calcitonin as a potential trigger was discontinued. He also received symptomatic therapy with acetazolamide. At the age of 7 years he developed lower limb pain. Complete radiological work-up revealed gross non-ossifying lesions of the long bones suggestive of OGD. Subsequently, diagnosis of craniosynostosis was established by CT scan, explaining the intracranial hypertension and enabling successful treatment by expansive cranioplasty. Targeted FGFR1 sequencing confirmed the clinical diagnosis and revealed the de novo heterozygous missense mutation c.1115A>G/=; p.Y372C/=. This mutation was already described in a typical case with OGD indicating a potentially broad phenotypic variability. Our case demonstrates that due to the therapeutic implications OGD should be considered in all cases with lack of eruption of teeth even in the absence of short stature.

Three generation family with kyphomelic dysplasia suggests autosomal dominant inheritance

O.M. Vanakker[1], U.I. Fränkel[2], A. De Paepe[1]
1. Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium
2. Department of Paediatrics, Zorgsaam Hospital, Terneuzen, The Netherlands

Kyphomelic dysplasia (KD) is a rare skeletal dysplasia belonging to the group of bent bone dysplasias. It represents a heterogenous group of disorders, with at least three distinct entities identified: Schwartz-Jampel syndrome (SJS), Cartilage Hair Hypoplasia (CHH) and 'true' KD. For the latter, the genetic background is unknown and autosomal recessive inheritance is presumed based on several sporadic cases with parental consanguinity.
We report a three-generation family presenting with a true KD phenotype. The proband was born at term after an uneventful pregnancy. Her length and weight at birth were 37cm and 1578g respectively. She had severe rhizomelic shortening of upper and lower limbs and radiographs showed stubby femora which were extremely curved. Iliac wings were short and widened; the humeri were also short and dumbbell-shaped.
The mother of the proband has a similar disproportionate short stature phenotype. Radiographs taken at birth revealed severe femoral bowing, though less prominent compared to her daughter. Follow-up radiographies in the mother demonstrated gradual improvement of the bowing over several years. The maternal grandfather of the proband had an identical phenotype. All had a normal neuromotor development. There were no signs of myotonia or ocular problems (SJS) nor evidence for immune deficiencies or anaemia (CHH).
This family, suffering from true KD, suggests that at least a subtype of KD has an autosomal dominant mode of inheritance. This observation has important consequences for genetic counselling of patients with KD, and identification of other families may allow clarification of the genetic background.

Atypical presentation of Axenfeld-Rieger Syndrome caused by a terminal 6p25.3 deletion resulting from a der(6)t(6;X) unbalanced translocation: some clinical lessons.

Ivo JHM de Vos[1], *Carroll AB Webers*[2], *Alexander PA Stegmann*[1], *Constance TRM Stumpel*[1,3]

[1,3]Department of Clinical Genetics and School for Oncology & Developmental Biology (GROW), Maastricht UMC+, Maastricht, the Netherlands
[2]Department of Ophthalmology, Maastricht UMC+, Maastricht, the Netherlands

Axenfeld-Rieger Syndrome (ARS) is an autosomal dominant multisystem disorder with an estimated incidence of 1 in 200,000. Key clinical features include varying degrees of ocular anterior segment dysgenesis predisposing for glaucoma and a wide spectrum of associated extra ocular malformations such as umbilical hernia, cardiac anomalies and facial dysmorphism. At least six genetic loci/genes are associated with ARS, among which the Forkhead Box C1 (FOXC1) gene at 6p25.3.

Here we present a case of a 21-year-old woman with a mild iris coloboma and posterior embryotoxon of the left eye, and bilateral increased intraocular pressure. She experienced radial head luxation in the past. Reason for referral now was a moderate bilateral mid-frequency sensorineural hearing loss since 1.5 years. Family history was negative for similar features.

Physical examination demonstrated a pleasant woman with short stature and small head circumference (both <2 SD), microretrognathism, thin upper lip, full everted lower lip, and a mild scoliosis. Genetic analysis by combined FISH and microarray testing revealed an aberrant karyotype i.e. an unbalanced chromosomal translocation 46,XX,der(6)t(6;X)(p25.3;q28). This unbalance effectively results in a terminal 6p25.3 microdeletion (1.8Mb) encompassing the FOXC1 gene and thus consistent with a diagnosis of ARS, and a terminal Xq28 microduplication (1.5Mb), of as of yet unknown clinical significance. Mutation analysis of the FOXC1 gene revealed no mutation.

ARS is a primary neurocristopathy, in which structures of neural crest origin such as the ocular anterior segment and facial bones, and structures that rely on neural crest derivatives for development such as the vestibuloacoustic ganglia, are affected. It has been demonstrated that FOXC1 plays a major role in development of neural crest cells. Previously reported cases of haploinsufficiency of FOXC1 all show anterior segment dysgenesis; hearing loss has been described in several cases, although other clinical findings differ from our patient.

This case of an atypical presentation of genetically confirmed ARS in which classical signs such as dental hypoplasia, midface hypoplasia and involuted periumbilical skin are lacking underscores the great clinical variability of ARS, even among patients with FOXC1 haploinsufficiency. We would have missed the diagnosis if we had analyzed the FOXC1 gene only!

THE PHENOTYPICAL DIFFERENCES BETWEEN PATIENTS WITH 3P PROXIMAL DELETIONS

EMC. SCHWAIBOLD[1], B. ZOLL[1], P. BURFEIND[1], E. HOBBIEBRUNKEN[2], B. WILKEN[3], R. FUNKE[3] and M. SHOUKIER[4]

1 Institute of Human Genetics, Georg August University, Göttingen, Germany
2 Department of Pediatrics and Pediatric Neurology, Georg August University, Göttingen, Germany
3 Sozialpädiatrisches Zentrum, Department of Neuropediatrics, Kassel, Germany
4 Pränatal-Medizin München MVZ, München, Germany.

In the last decades an increasing number of patients with proximal 3p deletions were described in the literature. Their main features were speech and motor developmental deficits, intellectual disability, sometimes autistic features and varying degrees of major anomalies and dysmorphisms. With the implementation of array-CGH in routine genetic diagnostics, a more concise relation between the deleted region of 3p and the phenotype of these patients seemed to be possible.
Here, we report on two monozygotic twin brothers and an 18-year-old man with proximal 3p deletions detected by array-CGH: the male twin brothers of 3 years showed a 6.32 Mb *de novo* deletion of 3p14.1p14.3 and the 18-year-old man an overlapping 4.76 Mb deletion of 3p14.1p14.2, respectively. All three of them displayed psychomotoric delay, almost no external malformations and only little facial dysmorphisms. Moreover, they had a severe intellectual disability with no development of a active speech in the 18-year-old man. In contrast, many previously reported patients with slightly more distally or proximally located 3p interstitial deletions demonstrated a more severe phenotype, especially regarding their dysmorphisms. Therefore, we compared our patients with molecularly wellcharacterized patients with proximal 3p deletions from the literature and the DECIPHER database (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources; http://decipher.sanger.ac.uk/). This led us to the hypothesis of a potential core region in 3p proximal deletions, a finding that could be helpful for genetic counselling.

MICRODUPLICATION 22Q11.2 IN A CHILD WITH WILLIAMS SYNDROME.

A. SKÓRKA[1,2], M. KUCHARCZYK[1], D. GIERUSZCZAK-BIAŁEK[1,2], M. KUGAUDO[1,3], A. CIEŚLIKOWSKA[1], K. CHRZANOWSKA[1], M. KRAJEWSKA-WALASEK[1]

[1] Department of Medical Genetics, The Children's Memorial Health Institute, Poland
[2] Department of Pediatrics, Medical University of Warsaw, Poland
[3] Department of Child and Adolescent Psychiatry, Medical University of Warsaw, Poland

The chromosome 22q11.2 region is susceptible to rearrangements due to the low-copy repeats spanning the region that predispose to homologous recombination events and mediate nonallelic homologous recombination. The region has long been implicated in such genomic diseases as DiGeorge/VCF syndromes, der(22)t(11;22) syndrome, and cat-eye syndrome associated with either decreased or increased gene dosage. Chromosome duplication of the region that is deleted in patients with DGS/VCF has been reported with up till now less that 100 unrelated cases presented.

The phenotype of this new genomic duplication syndrome is extremely variable, ranging from multiple defects/lethal major cardiovascular defects to mild learning difficulties or even asymptomatic carriers, sharing many features with DGS/VCF. There is high frequency of familiar duplication and marked intrafamiliar variability. The large majority of affected individuals have identical 3 Mb duplication.

Here we present a case of a little 3-years of age girl who presented with coarctation of aorta, hypertension, characteristic for Williams syndrome dysmorphic features and delayed psychomotor development. She is a third child (her sibling are healthy) of healthy parents. She was born on time, with normal birth weight and length. Due to respiratory distress in early neonatal period investigations revealed coarctation of aorta and enlarged thymus. She required cardiac surgery at 2 month of age (end-to-end reanastomosis) and 6 months later reoperation (balloon angioplasty) due to recoarctation. Her psychomotor development is delayed, she started to sit unaided at the age of 1 year 6 months, started to walk only recently at 3 years of age, and her speech is very much delayed (she speaks only few words). So far she presented no calcium metabolism abnormalities. Her karyotype was normal, MLPA (with probe set of P064) and FISH studies revealed deletion in Williams syndrome region with a duplication in DiGeorge region (TUPLE 1 probe x3). Both aberrations were confirmed and precisely characterized by array CGH.

This study was supported in part by a grant from the Polish Ministry of Science and Higher Education (Contract No. 0193/IP1/2013/72).

Copy Number Variations in a large cohort of adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders

VOGELS A., VAN BUGGENHOUT G., CAEYENBERGHS R., WEYTS E., LEGIUS E.

Centre for Human Genetics, University Hospital of Leuven, Belgium
Sint-Camillus Psychiatric Hospital, Bierbeek, Belgium

Background

The term "developmental disorder" is used to refer to a range of conditions characterised by a deviation from the normal brain development and usually becoming manifest during childhood. They include intellectual disability and a variety of neuropsychiatric disorders such as autism, attention deficit disorder, schizophrenia and bipolar disorder.

Data from recent studies show that copy number variations are found at an increased frequency in these neurodevelopmental disorders.
Almost all CNV regions that have been shown to be associated with intellectual disability are also associated with one of the neuropsychiatric disorders indicating clinical heterogeneity. Second, different CNV's are found in intellectual disability as well as in each of these neuropsychiatric disorders indicating genetic heterogeneity. All developmental disorders are associated with CNV's and these CNV's overlap between the different neurodevelopmental disorders. We therefore expect a higher prevalence of CNV's in patients with a dual diagnosis of intellectual disability and a neuropsychiatric disorder.

Methods

We examined the prevalence of CNV's in a cohort of adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders. Results

CNV's were found in 32 % of the adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders. Discussion

CNV's are found in one third of adults with a dual diagnosis of intellectual disability and neuropsychiatric disorders. There is a clinical as well as genetic heterogeneity confirming previous studies suggesting that different causative genes converge in common biological pathways.

MINOR ABNORMALITIES IN PITT-HOPKINS SYNDROME

K. WRITZL

Institute of Medical Genetics, University Medical Centre Ljubljana, Slovenia

Pitt-Hopkins syndrome is an autosomal dominantly inherited intellectual disability syndrome. Next to an unusual face the main characteristics are seizures and breathing abnormalities. The characteristic facial features are often less obvious in an infant, and the abnormal breathing pattern may begin in the second half of the first decade or even later, so minor anomalies can form important clues to the clinical diagnosis.

We report on a 3-year-old boy who presented with severe motor and speech delay. He had no seizures or breathing abnormalities. He was described as a happy child with stereotypic hand movements, teeth grinding and constipation. Examination showed brachycephaly, enophtalmia, long eyelashes, prominent nasal bridge, wide mouth, full lips, widely spaced teeth with fused lower teeth, overfolded helix with indentations on the lower part of the posterior helix, fetal pads on fingers and toes, and bilaterally a single palmar crease.

Prominent fetal pads have been observed before in individuals with PHS, but fused teeth and helical indentations have not previously been reported to be associated. These signs may be coincidental although both are infrequent in the general population. We suggest it is worth looking for these in infants and children with an Angelman / Rett-like phenotype.

A NEW FACE OF BORJESON-FORSSMAN-LEHMANN SYNDROME? *DE NOVO* MUTATIONS IN *PHF6* IN SEVEN FEMALES WITH A DISTINCT PHENOTYPE

C. ZWEIER[1], C. KRAUS[1], L. BRUETON[2], T. COLE[2], F. DEGENHARDT[3], H. ENGELS[3], G. GILLESSEN-KAESBACH[4], L. GRAUL-NEUMANN[5], D. HORN[6], J. HOYER[1], W. JUST[7], A. RAUCH[1,8], A. REIS[1], B. WOLLNIK[9], M. ZESCHNIGK[10], H.J. LÜDECKE[10], D. WIECZOREK[10]

[1]Institute of Human Genetics, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany
[2]Birmingham Women's Hospital Healthcare NHS Trust, Edgbaston, Birmingham, United Kingdom
[3]Institute of Human Genetics, Rheinische Friedrich Wilhelms-Universität, Bonn, Germany
[4]Institut für Humangenetik, Universität zu Lübeck, Lübeck, Germany
[5]Ambulantes Gesundheitszentrum, Charité Campus Virchow, Berlin, Germany
[6]Institute for Medical and Human Genetics, Charité Universitätsmedizin Berlin, Berlin, Germany
[7]Institute of Human Genetics, University of Ulm, Ulm, Germany
[8]Institute of Medical Genetics, University of Zurich, Zurich-Schwerzenbach, Switzerland
[9]Institute of Human Genetics; CMM; CECAD; University of Cologne, Cologne, Germany
[10]Institut für Humangenetik, Universitätsklinikum Essen, Universität Duisburg-Essen, Essen, Germany

Borjeson-Forssman-Lehmann syndrome is an X-linked recessive intellectual disability (ID) disorder caused by mutations in the *PHF6* gene and characterized by variable cognitive impairment, a distinct facial gestalt, obesity and hypogonadism. Female carriers are usually not or only mildly affected, and so far only two females with *de novo* mutations or deletions in *PHF6* have been reported.

Trio exome sequencing in one female patient with a distinct appearance of sparse hair, remarkable facial features, hypoplastic nails, linear hyperpigmentation, and teeth anomalies revealed a *de novo* missense mutation in *PHF6*. We subsequently performed targeted mutational and single exon deletion/duplication analysis of this gene in four female patients with a very similar clinical phenotype. This revealed two truncating mutations and two duplications of exons 4 and 5, respectively. Furthermore, two female patients with *PHF6* deletions were identified by routine molecular karyotyping and also showed a similar phenotype. Further studies revealed skewed X-inactivation in blood lymphocytes, while it was normal in fibroblasts, thus indicating functional mosaicism.

Our findings indicate that *de novo* defects in *PHF6* in females result in a recognizable phenotype which might have been under-recognized so far and which comprises variable ID, a characteristic facial gestalt, hypoplastic nails, brachydactyly, clinodactyly mainly of fingers IV and V, dental anomalies, and linear skin hyperpigmentation. The distinct facial gestalt includes bitemporal narrowing with sparse hair, prominent supraorbital ridges, high arched eyebrows with synophrys, and a short nose with a high nasal root and a bulbous nasal tip. The phenotype shows overlap with Borjeson-Forssman-Lehmann syndrome but also additional distinct features, thus adding a new facet to this disorder.

COPY NUMBER VARIANTS INCLUDING RAS PATHWAY GENES – HOW MUCH RASOPATHY IN THE PHENOTYPE?

M. ZENKER[1] and S. KANT[2]

[1] Institute of Human Genetics, University Hospital Magdeburg, Germany
[2] Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

The RASopathies comprise a heterogeneous group of multiple congenital anomaly syndromes the common pathogenetic basis of which is dysregulated (usually activated) signal flow through the RAS-MAPK signalling cascade. Gain-of-function point mutations in several components or modifiers of the pathway have been identified in Noonan syndrome and related disorders. The shared phenotypic features of the RASopathies include congenital heart defects, short stature, variable developmental delay, predisposition to cancer, as well as a distinct and overlapping pattern of dysmorphological anomalies.

Over the past years various copy number variants (CNVs) including RAS pathway genes (e.g. PTPN11, RAF1, MEK2) have been reported in children with developmental syndromes. These observations have raised the speculations that their phenotypes represent RASopathies, implicating that it is the increased or reduced expression of the respective RAS pathway component and a resulting dysregulation of RAS-dependent signalling that is mainly responsible for the clinical picture.

We present a novel case of a 19p13.3 duplication including the MEK2 locus in a family with short stature and learning difficulties, review the previous literature on CNVs including RAS pathway genes, and interpret the current knowledge in the light of the known pathophysiology of RASopathies. Clinically, patients with those CNVs commonly share with RASopathies some non-specific symptoms like short stature, heart defects, and developmental delay, whereas the characteristic "gestalt" is lacking. Pathophysiologically, substantial doubt remains that a modest (+/-50%) quantitative aberration in the expression of a functionally normal signalling component of the RAS-MAPK cascade could be able to exert similar effects as a qualitatively abnormal mutant protein.

We argue that the current evidence is still insufficient to allow the conclusion that an increased or decreased copy number of the RAS pathway component is indeed the phenocritical mechanism in CNVs including RASopathy gene loci. The phenotypes associated with such genomic aberrations still have to be regarded as contiguous gene syndromes for which the contribution by these genes is still unclear and may be of minor significance.

MEGALENCEPHALY CAPILLARY MALFORMATION (MCAP) AND *PIK3CA* MUTATIONS: PRESENTATION OF 3 CLINICAL CASES AND EVOLUTION OF THE PHENOTYPE OVER TIME

L.Garavelli (1), A. Wischmeijer (1,2), S. Rosato (1), C. Gelmini (1), E. Lusetti (1,3) A. Iori (1,3), F. Baccilieri (1,3), C Adams (4), G. Mirzaa (4) and W.B Dobyns (4)
1) Clinical Genetics Unit, Obstetric and Paediatric Department, Istituto di Ricovero e Cura a Carattere Scientifico, S. Maria Nuova Hospital, Reggio Emilia, Italy. 2) Department of Medical Genetics, Policlinico Sant'Orsola-Malpighi, University of Bologna, Bologna, Italy. 3) Post-Graduate School of Pediatrics, University of Modena and Reggio Emilia, Italy 4) Division of Genetic Medicine, Department of Pediatrics, Center for Integrative Brain Research, University of Washington, Seattle Children's Research Institute, Seattle, WA, USA

INTRODUCTION Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) is characterized by cutaneous capillary malformation in association with megalencephaly with a tendency to progressive enlargement, cortical brain malformations, most distinctively polymicrogyria, abnormalities of somatic growth with body and brain asymmetry, developmental delay, and typical face with full cheeks, frontal bossing, and nevus flammeus of the nose, philtrum and/or upper lip. Some cases of MCAP have been found to have somatic mutations in the PIK3CA gene on chromosome 3q26 with evidence of postzygotic mosaicism in most affected individuals [Riviere et al., 2012]. All reported cases occurred sporadically. Increased paternal age was noted. Significant overlap has been observed with megalencephaly polymicrogyria-polydactyly hydrocephalus (MPPH; see this term); in fact MCAP and MPPH result from mutations in the same pathway, emphasizing a central role of PI3K-AKT signaling in vascular, limb and brain development.

Here, we present 3 unrelated patients with MCAP and we underline the evolution of the phenotype over time.

CLINICAL CASES

1st PATIENT This female infant is the first child born by vertex delivery at 35 weeks of gestation to healthy non-consanguineous parents. The pregnancy was unremarkable with no known exposures to potential teratogens. Birth weight was 4.240 g (>99th centile) and length of 52 cm (>98th centile). She had neonatal hypoglycaemia. On examination in the newborn period she showed generalized hypotonia and a congenital generalised "marbled" or "mottled" skin appearance, most prominent on the face and right arm and exaggerated by crying. In addition there was a nevus flammeus of the philtrum, full cheeks and bilateral 2/3 syndactyly of the toes. She had mild developmental delay, with particular involvement of expressive language. She walked at 24 months. At the age of 10 years and 7 months, her height was 146 cm (75th centile), weight was 50 kg (>97th centile) and head circumference 58.5 cm (+7-8 SD). In addition to the features mentioned above, she had hypertelorism, epicanthic folds and body asymmetry with left hemihypertrophy .

Chromosome analysis of cultured lymphocytes at 450 band resolution and skin fibroblasts were normal and did not reveal any chromosomal mosaicism. Ultrasound of the abdomen did not show any evidence of haemangiomata of the abdominal viscera. Left kidney length was 8.2 cm, right kidney 7.7 cm. Radiographs of the lower limbs showed the right leg was shorter than the left by 0.9 cm. MRI scan of the head showed left hemimegalencephaly, mild ventriculomegaly, periventricular increased signal of white matter and a Chiari type I malformation. Doppler of the legs was negative for arteriovenous fistulae. Electrocardiogram and fundoscopy were normal. Genetic investigations (performed Seattle Children Research Institute) revealed a mutation in *PIK3CA* (p.E970K). The mutation is de novo and mosaic (only present in saliva with a mutant allele frequency of 27%. It was undetectable in blood by Sanger sequencing) Ongoing: deep sequencing in the blood to see if the mutation could be present at low level of mosaicism(less then 20%). This mutation was identified in another MCAP patient, found in L8 cell line (not published).

2nd PATIENT This child is the first born boy at 40 weeks gestation to healthy non-consanguineous parents. The pregnancy was unremarkable. He was born by vertex delivery, with a birth weight of 3.700 g (75th centile) and a length of 52 cm (75th centile). On examination at the age of 5 years, his head circumference was 56 cm (+3-4 SD), weight 18,6 kg (50th centile) and height 103 cm (10th centile). There was generalised mottling of the skin, especially apparent on the face, trunk, abdomen, hands, feet and right arm. He had a nevus flammeus of the philtrum, the occiput and over the back. There was also a cavernous haemangioma of the back and body asymmetry with left hemihypertrophy involving the face, and foot. He had minimal cutaneous syndactyly of the 2nd and 3rd toes bilaterally. He had normal psychomotor development. Chromosome analysis of cultured lymphocytes at 550 band resolution was normal. Ultrasound of the abdomen was also normal, as was a sacral spine x-ray and Doppler examination of the legs. Echocardiogram and fundoscopy were normal. MRI of the head showed left hemimegalencephaly and periventricular increased signal of white matter

Genetic investigations (Seattle Children Research Institute): *PIK3CA* analysis in saliva, buccal swab and blood: ongoing

3rd PATIENT This female is the first child born by cesaren delivery at 34 weeks gestation to healthy non-consanguineous parents. The pregnancy was unremarkable with no known exposures to potential teratogens. Chromosome analysis of cultured amniocyte were normal. Birth weight was 2.900 g (90th-97th centile) She had mild developmental delay, with particular involvement of expressive language, and she walked at 24 months. She had hydrocephaly (operated at the age of 12 months). On examination at the age of 6 years and 1 month, she had a congenital generalised "marbled" or "mottled" skin appearance, prevailing on the face and left arm and exaggerated by crying. In addition there was asymmetry of the face, hypertelorism, a nevus flammeus of the philtrum, upper lip and glabella, gingival hypertrophy, full cheeks, right 2/3 syndactyly of the toes. In addition to the features mentioned above she had body asymmetry with left hemihypertrophy and scoliosis. At the age of 6 years and 1 month her height was 124 cm (97th centile), the weight was 28 kg (>97th centile) and the head circumference 60.5 cm (+5-6SD). Ultrasound of the abdomen did not show any evidence of haemangiomata of the abdominal viscera. Computerised tomography and MRI scan of the head showed left hemimegalencephaly, ventriculomegaly, periventricular increased signal of white matter and a Chiari type I malformation. Laryngoscopy demonstrated epiglottis asymmetry Echocardiography showed an atrial septal defect.

Genetic investigations (Seattle Children Research Institute): *PIK3CA* analysis in saliva, buccal swab and blood: ongoing

CONCLUSIONS: The clinical diagnosis of MCAP is possible at birth and may be supported by MRI brain findings of a CNS phenotype and by molecular analysis of the PIK3CA gene (blood/saliva/buccal swab). Variable levels of mosaicism depending on the tissue tested have been observed.

Management requires a multidisciplinary approach (involving neurology, ophthalmology, cardiology, orthopedics, ultrasound and Doppler ultrasound, radiology, audiometrics, physiotherapy, psychology and dermatology)

A complex clinical presentation with familial microphthalmia.

Eric E. J. Smeets, Connie T.R.M. Stumpel, Jean-Pierre Frijns

Department clinical genetics, Maastricht University Medical Center, Maastricht, The Netherlands

Clinical history and diagnostics will be presented.
An unknown finally resolved.

CRANIOFACIAL ANOMALIES ASSOCIATED TO CAMPTODACTYLY AND CHEST DEFORMITY: CRANIO-FACIO-SQUELETTAL SYNDROME OR NEW ENTITY.

H. CHAABOUNI[1], F. MAAZOUL[1].

1Charles Nicolle Hospital, Tunis, Tunisia, Department of congenital and hereditary disorders.

We report the case of a Tunisian boy with unusual face, marked flat occiput, camptodactyly, chest deformity ,normal thrive and normal intelligence. He had brachycephaly with marked flat occiput, flat supraorbital ridges,hypertelorism , epicanthal fold and bilateral ptosis. The palpebral fissures were short and downslanting. He had depressed nasal bridge, broad nasal tip with wide nostrils. The philtrum was long with thin upper lip. He had maxillary hypoplasia , high and narrow palate , oligodontia and dental malocclusion . His ears were stickled with severe lobulehypoplasia. The hair was normal and his neck was short. He hadthorax asymmetry, pectus excavatum and depressed low sternum.He presented moderate restrictive lung disease. Wenotedbilateralcamptodactyly of all fingers, and multiple cutaneous nevi.There wasno other abnormality ,neurological examination was normal, and therewas no clinical features of visceral malformation.

He had normal psychomotor evolution and intelligence was normal. A skeletal survey was unremarkable except skull roentography showing deformity and thoracic narrowing. The karyotype was 46 XY. Ophthalmologic examination confirmed ptosis, lacrimalducts obstruction andmore recently amblyopia. There was not hearing loss.

The patient was born to consanguineous parents.The motherpresented moderate bilateral ptosis, unilateral left deafness and she hadabnormal teeth position but normal teeth number. His two brothers and sister, his grand parents,uncles and ants were phenotypically normal.

Our patient's phenotype could match with previously reported cases of faciothoracoskeletal syndrome in facial appearance and thoracic deformity. The main discrepancies are the absence of vertebral anomalies, the normal growth and intellect and of course the inheritance pattern. Faciothoracoskeletal syndrome is reported as an autosomal recessive entity while in our case the mother shares some clinical features with the affected son.

Familial syndromic and non-syndromic congenital diaphragmatic hernia: the value of exome sequencing.

Paul D. Brady[1], Hilde Van Esch[1], Jan Deprest[2], Philippe Moerman[3], Joris Vermeesch[1], Marjan De Rademaeker[4], Koen Devriendt[1].

[1]Centre for Human Genetics, KU Leuven, University Hospital Leuven, Belgium.
[2]Obstetrics & Gynaecology, Department Woman & Child, University Hospital Leuven, and Development & Regeneration, KU Leuven, University Hospital Leuven, Belgium
[3]Department of Pathology, KU Leuven, University Hospital Leuven, Belgium.
[4]Centre for Medical Genetics, University Hospital Brussels, Belgium.

Congenital Diaphragmatic Hernia (CDH) may occur as an isolated defect or in syndromic form for which the prognosis is worse. Results from conventional karyotyping and more recently genomic arrays support a substantial role for genetic factors as a cause. Many genomic loci and candidate genes are associated with CDH. To unravel the etiology of CDH in familial cases where no clinical diagnosis could be reached, we have undertaken exome sequencing in 3 families.

The first family has 2 fetuses affected with isolated CDH. Exome sequencing showed a FOG2 or ZFPM2 mutation, c.C334T or p.R112X. This mutation has previously been described in a fetus with diaphragm eventration. Further studies in the family revealed that this mutation was maternally inherited and also present in a male sibling with total anomalous pulmonary venous return. The same mutation was also detected in the maternal grandfather and maternal aunt, who are asymptomatic. No additional functional variants were identified in CDH-related genes in affected individuals.

The second family has 2 affected male newborns with multiple congenital anomalies. The first sibling presented left-side CDH, microphthalmia and retinal coloboma and an ASD. The second boy had bilateral microphthalmia, dense intra-ocular tissue; spina bifida; hydronephrosis; hypospadias. The initial diagnosis of Matthew-Woods syndrome could not be confirmed after mutation analysis of the STRA6-gene in the first boy. Exome sequencing reveals a mutation in the PORCN-gene, c.G470A : p.G157D. Carrier females were shown to have skewed X-inactivation pattern. Mutations in this gene are known to cause X-linked – Focal Dermal Hypoplasia. A single case of CDH has previously been reported in a female with FDH.

In a third family, three affected boy presented a syndromic form of CDH, with an X-linked inheritance pattern. The index patient had a right diaphragmatic hernia, renal cystic disease, hypospadias, and cryptorchidism and 2-3 th finger and toe syndactyly and nail hypoplasia. His development was delayed. He had a maternal uncle who had died neonatally over 20 years ago, with CDH, ambiguous genitalia and cystic kidneys. More recently, a third affected fetus was diagnosed antenatally in this family, presenting CDH and ambiguous genitalia. Pathological examination did not reveal additional anomalies. His carrier mother had a completely skewed X-inactivation. Exome sequencing of the two affected males failed to yield a causal mutation in this family thus far.

Abnormal skull shape, bowing of the femora and tetralogy of Fallot as prenatal presentation of Carpenter syndrome.

Damien HAYE[1], Corinne COLLET[2], Catherine SEMBELY-TAVEAU[3], Georges HADDAD[4], Christèle DENIS[5], Jacques POINSOT[6], Annie-Laure SUC[6], Antoine LISTRAT[6], Annick TOUTAIN[1,9]

1) Service de Génétique, CHU de Tours, France 2) Service de Biochimie et Biologie Moléculaire, Hôpital Lariboisière, Paris, France 3) Service de Radiologie Pédiatrique, CHU de Tours, France, 4) Service de Gynécologie Obstétrique, CH de Blois, France 5)) Service de Gynécologie Obstétrique, CHU de Tours, France 6) Service de Médecine Pédiatrique, CHU Tours, France 7) Service de Médecine Néonatale, CHU de Tours, France 8) Service de Neurochirurgie Pédiatrique, CHU de Tours, France 9) UMR_INSERM U930, Faculté de Médecine, Université François Rabelais, Tours, France.

Carpenter syndrome, also known as 'acrocephalopolysyndactyly type II' is a rare autosomal recessive disorder characterized by multiple suture craniosynostosis, brachydactyly of the fingers, post-axial polydactyly of the hands, pre-axial polydactyly of the feet, and soft-tissue syndactylies. It is caused by mutations of the *RAB23* gene which encodes a Rab protein acting as a negative regulator of the Sonic hedgehog signaling pathway. Twelve different mutations in the *RAB23* gene have been identified in 33 patients from 25 independant families until now.

We report here the prenatal description of a case of Carpenter syndrome with a *RAB23* mutation. It was the fifth pregnancy of healthy consanguineous Turkish parents. Cystic hygroma and bowed femora were seen on ultrasound scan since 14-15th weeks of gestation. In addition, at 22 weeks a complex heart defect (double outlet right ventricle of Fallot type) was detected. At 28 weeks abnormal skull shape with irregular outlines and too easily visible brain structures, associated with bowing of the femora raised the question of osteogenesis imperfecta. This was reinforced by the fetal bone CT scan which showed the same skeletal anomalies and suggested a depressed fracture of the skull. However, physical examination and skeletal X-rays of the newborn patient lead to the diagnosis of Carpenter syndrome. In addition to the heart defect and bowing of the femora, the patient had a typical clinical picture with trigonocephaly and scaphocephaly, dysmorphic facial features, pre-axial polydactyly of both feet, cutaneous syndactylies of the toes and hypoplastic middle phalanges. Direct sequencing of the *RAB23* gene identified a novel homozygous frameshift mutation c.481G>C (p.Val161Leu).

This observation illustrates the difficulty of prenatal diagnosis of Carpenter syndrome in the absence of a previous case in the family. Abnormal skull shape and limb anomalies, mainly polydactyly, are sometimes detected on prenatal US scan. However, to our knowledge, prenatal diagnosis of Carpenter syndrome has been made in only one case. Tetralogy of Fallot and bowing of the femora were never described prenatally but are both rare postnatal findings which were reported in a few cases. Carpenter syndrome should therefore be considered in case of abnormal skull shape with bowed femora, and cardiac defects on prenatal imaging.

Fetal phenotype of OPD spectrum disorders

D. LACOMBE[1], S. NAUDION[1], S. MOUTTON[1], MP CORDIER, AL DELEZOIDE, A. GOLDENBERG, P. LOGET, J. MELKI, S. ODENT, S. PATRIER, A. VERLOES, G. VIOT, B. ARVEILER[1], P. FERGELOT[1], C. GOIZET[1],

[1] Service de Génétique Médicale, CHU de Bordeaux ; Laboratoire Maladies rares: Génétique et métabolisme, EA4576, Université Bordeaux, Bordeaux, France.

The otopalatodigital (OPD) spectrum disorders includes OPD syndromes type 1 and 2 (OPD1 and OPD2), Melnick-Needles syndrome (MNS), and frontometaphyseal dysplasia (FMD). These conditions are clinically characterized by skeletal dysplasia with various degrees of undertubulation of long bones, cortical irregularity and campomelia. Extra skeletal malformations, observed in severely affected males, include brain malformation, cleft palate, cardiac anomalies, omphalocele and obstructive uropathy. Mutations in the X-linked *FLNA* gene are reported in the majority of FMD and OPD2 cases and in all typical OPD1 and MNS patients. Some phenotype-genotype correlations have emerged in postnatal cases affected with the OPD syndrome spectrum disorders.

We report a series of 7 fetuses (1 female and 6 males) and 1 male newborn displaying a MCA phenotype evocative of the OPD spectrum disorders. A *FLNA* gene mutation was identified in 3 cases. A mutation was found in two OPD2 cases and a specific MNS mutation was characterized in one fetus. Hypertelorism, cleft palate, abnormal hands and feet, heart defects and brain anomalies are relevant criteria for an OPD2 diagnosis in fetuses. For MNS, abnormalities of the anterior segment of the eye seem to be good criteria for diagnosis orientation. Molecular diagnosis may help to refine the clinical diagnosis according to the *FLNA* gene mutation type and localization and to provide an appropriate genetic counseling.

ACHONDROPLASIA WITH DI GEORGE'S SYNDROME: A CASE REPORT OF THE DIAGNOSIS OF THE EXTREMLY UNUSUAL ASSOCIATION

D.Gieruszczak-Białek [1,2], A.Skórka [1,2], M.Kugaudo [2], M.Krajewska-Walasek [2], K.Chrzanowska[2]
[1] Medical University of Warsaw
[2] The Children's Memorial Health Institute

Background : The association of achondroplasia and chromosomal disorder is very rare. To date only a few cases of achondroplasia and diferent chromosomal abmormalities (Down syndrome, Klinefelter syndrome) have been previously reported.
We describe the first case of association of achondroplasia and di George's syndrome.
Case presentation : The 3 years old girl was born at term with prenatal diagnosis od 22q11 deletion The amniocentesis was performed because of heart anomaly (interrupted aortic arch) After birth surgical treatment was performed.
Clinical features of achondroplasia or hypochondroplasia were observed prenatally (shortening of the femur) and after birth (disproportionate stature). FGFR3 mutation screening showed that she is heterozygous for the G380R mutation.
Conclusion: Specific mutation analysis is needed to confirm the clinical diagnosis, especially when the chromosomal analysis (first diagnosis) does not explain the abnormal, clinical findings

Further Delineation of the Johnston-Biesecker Multiple congenital anomalies-hypotonia-seizures syndrome caused by a single PIGA mutation

Katharina Steindl[1], Pascal Joset[1], Deborah Bartholdi[1], Sandra Pajarola[1], Sebastian Böhm[2], John Micallef[2], Alessandra Baumer[1], Anita Rauch[1]

1) Institute of Medical Genetics, University of Zurich, Schwerzenbach-Zurich, Switzerland
2) Eastern Swiss Pediatric Hospital, St. Gallen, Switzerland

Somatic mutations in the X-linked PIGA gene [MIM 311770] encoding phosphatidylinositol glycan class A are known to cause paroxysmal nocturnal hemoglobinuria, while germline mutations were assumed embryonic lethal. Johnston and colleagues only recently described a PIGA nonsense mutation p.Arg412* with residual function in a family segregating with an X-linked lethal disorder involving cleft palate, neonatal seizures, contractures, central nervous system structural malformations and other anomalies (Johnston et al. Am J Hum Genet 2012). While three boys of this family were affected, two carrier females with 100% skewing of X-inactivation were healthy.

We now identified the same p.Arg412* mutation in an unrelated boy by whole exome sequencing. Like the previous cases this boy was born with macrosomia, short neck, facial dysmorphism and cerebral anomalies such as hypoplastic cerebellum and immature white-matter. The neonatal course was complicated by absence of spontaneous movements, respiratory insufficiency and intractable myoclonic-tonic seizures. The boy developed sepsis from necrotizing enterocolitis and deceased at the age of 15 days. In addition to the reported features this boy showed hepatosplenomegaly and remarkable short tubular bones verified by X-ray measurements to approximately correspond to the 3rd centile. The healthy carrier mother showed only mild skewing of X-inactivation in blood (83:17). The family history was remarkable for one male stillbirth of the sister of the maternal grandmother.

We therefore confirm that boys with the PIGA p.Arg412* mutation show a distinct pattern of morphological anomalies and are prenatally viable, but die soon after birth due to respiratory failure and intractable seizures.

Another infant with Pontocerebellar hypoplasia Type 5 (PCH5) and compound heterozygosity for the common TSEN54 mutation (p.A307S) plus a novel deletion of 25 bp in exon 8 (p.Ser376Cysfs*26). This supports the observation that PCH5 and PCH4 are allelic disorders.

S. Uhrig [1], C. Sommer [2], B. Csapo [3], C. Rotky-Fast [2], M. Haim [2], F. Reiterer [2], C. Windpassinger [1]
1. Institute of Human Genetics, Medical University of Graz, Austria
2. Division of Neonatology, Department of Pediatrics, Medical University of Graz, Austria
3. Department of Obstetrics and Gynecology, Medical University of Graz, Austria

Autosomal recessive Pontocerebellar hypoplasias (PCHs) are a group of neurodegenerative disorders characterized by prenatal onset of progressive atrophy predominantly affecting cerebellum, pons and olivary nuclei. Eight different subtypes have been described so far (PCH1-8). The most severe subtype PCH5 is characterised by intrauterine seizure-like movements of the fetus and was first described 2006 by Patel et al. in a non-consanguineous family with three affected children. In 2011 Navarmar et al. identified compound-heterozygote mutations for the common TSEN54 mutation (p.A307S) plus a novel splice site mutation in this family. Thus the genetic findings in PCH5 were similar to that of PCH4. Here we report a patient, first child (2nd pregnancy) of a healthy unrelated couple. Prenatal ultrasound including first trimester screening and second trimester organ scan were unremarkable besides polyhydramnios seen at 23+6th week of gestation. At 30th week of gestation the mother was admitted to hospital due to preterm labor. Fetal ultrasound showed polyhydramnios and a large cisterna magna and severe pontocerebellar hypoplasia. Amniocentesis was performed and karyotyping including array CGH showed a normal male karyotype. Preterm rhythmic fetal movements were noticed. The boy was delivered at 31+5th week of gestation by caesarean section due to uncontrollable preterm labor. Apgar scores were 7/8/8. He weighed 1700 g (~25th centile), birth length was 43 cm (~50th centile) and had a head circumference of 27,5 cm (10th centile). The neonate was unresponsive and had generalized symmetrical hypertonia. Central respiratory impairment required mechanical ventilation. Generalized clonus provoked by handling occurred. MRI showed severe hypoplasia of the cerebellar hemispheres, severe vermal hypoplasia, immaturity of cerebral cortex and enlarged ventricles compatible with the diagnosis of PCH4/5. Molecular genetic analysis of exon 8 of the TSEN54 gene detected the common TSEN54 missense mutation (p.A307S) seen in PCH2A, 4 and 5 plus a novel deletion of 25bp (c.1127_1151delCCAGCTGGCGGGAGTACAAGGAGCT) leading to frame shift and loss of function of the second allel (p.Ser376Cysfs*26) thus confirming the clinical diagnosis of PCH4/5. The boy died due to respiratory distress on the 30th day of life. In the subsequent third pregnancy chorionic villus sampling showed homozygosity for the wild type allel and a healthy boy was born. Up to now 20 families have been reported with a PCH4 phenotype and one family with the more severe PCH5 phenotype. In all 10 families where molecular genetic analysis was done the children were compound heterozygote for the common missense mutation (p.A307S) and a more severe mutation on the second allel. Our case supports the results that PCH5 is allelic to PCH4 and shows that sequencing of exon 8 of the TSEN54 gene is a fast way to confirm clinical diagnosis of PCH2A, 4 or 5 thus allowing a more precise prognosis and prenatal diagnosis in subsequent pregnancies.

Maternal consumption of clay during pregnancy: an unexpected cause of recurrent congenital microcephaly with intracranial calcifications in babies from French Guyana (pseudo-Aicardi-Goutière syndrome)

A. Verloes[1], S. Passemard[1], V. Lambert[2], G. Carles[2], J. Goullé[3], A. Laquerrière[4]

1) Department of Genetics, Robert DEBRE University Hospital and INSERM UMR 676, Paris, France; 2) Department of Obstetrics , Regional Hospital, Saint-Laurent du Maroni, French Guyana, France; 3) Department of Toxicology, Rouen University Hospital, Rouen, France; 4) Department of Pathology, Rouen University Hospital, Rouen, France

Eating clay ("pemba") during pregnancy is a traditional behavior in the Bushinengue population living on the border of the Maroni river, in the French department of Guiana. Clay consist in aluminium silicate. It is a powerful chelator of iron, and this practice (linked to traditional medicine), is responsible for a high incidence of severe anemia of pregnancy in this area. We report on two sibs born to a pemba-eater mother. The first child was born at term with IUGR severe microcephaly. Intracranial "calcifications" were observed by ultrasound screening during the second trimester. CT scan confirmed massive radio-opaque deposits in the brain basis. The clinical diagnosis of TORCH or Aicardi-Goutières syndromes were suggested initially. The child survived with major developmental delay. At age 7y, she has an OFC of 39 cm (-10 SD) and a height of 10 cm (-4SD). CSF interferon and TORCH screening were negative. Recurrence of microcephaly during the second pregnancy lead to TOP, after diagnosis of a similar microcephaly. Neuropathological examination confirmed severe microcephaly, with extensive microcalcifications dispersed throughout the brain. Electron microscopy made it possible to visualize intraneuronal aluminium silicate deposits, resembling aluminium deposition observed in post-vaccinal myofasciitis.

The most likely mechanism to explain this recurrence is an association of IUGR secondary to severe maternal anemia combined with accumulation of exogenous silicates in the neural cells. This appears to be the first description of fetal brain disruption secondary to ingested clay. The syndrome superficially mimics Aicardi-Goutières syndrome, and convey a high risk of recurrence.

Tumoral risk in Sotos syndrome

Cracco O[1], Jedraszak G[1], Dery T[1], Devauchelle B[2], Strunski V[3], Burglen L[4], Ikoli JF[5], Demeer B[1], Mathieu M[1], Leke A[6], Morin G[1].

1 Clinical Genetics - Amiens University Hospital, 2 Maxillofacial Surgery - Amiens University Hospital, 3 Otolaryngology - Amiens University Hospital, 4 Genetic Department - Trousseau Hospital Paris, 5 Pathology Laboratory - Amiens University Hospital, 6 Pediatric Reanimation - Amiens University Hospital

Overgrowth syndromes (OGS) form a heterogeneous group of disorders in which the main characteristic is a weight, height or head circumference over +2 standard deviations. Benign tumours and neoplasms are not exceptional in OGS. Sotos syndrome (OMIM 117550), is characterized by cerebral gigantism, distinctive craniofacial appearance, and variable learning disabilities. Haploinsufficiency of the *NSD1* gene was identified as the cause of the disorder.

A case of Sotos syndrome with cystic lymphangioma is retrospectively described. This male patient was the third child of related healthy parents. Pregnancy was unremarkable. Delivery occurred by caesarian section at 37 weeks of amenorrhea in a context of acute foetal suffuring and umbilical cord procidence. Neonatal period was difficult with prolonged trachcal ventilation, E Coli sepsis and ulcero-necrotizing enterocolitis. In the first years of life he developed psychomotor retardation, hyperactivity, advance stature (+3SD), weight (+4SD), and macrocephaly (+2.5SD). The diagnosis of Sotos syndrome was made at the age of 4, and a heterozygous mutation of *NSD1* gene was identified (c.3659_3660delAG / p.Glu1220AlafsX5 – Burglen L). At the age of 9 years, a subcutaneous tumour of the neck was discovered. Ultrasound examination and CT scan confirmed the presence of a well delimited mixed tumour. This tumour was surgically removed and pathological examination confirmed the diagnosis of cystic lymphangioma.

To our knowledge, this is the first reported case with Sotos syndrome and cystic lymphangioma. This association could be coincidental. However in the literature, 10 other cases of Sotos syndrome with benign tumour and 37 individuals with neoplasms have already been reported. Among them, many cases were not molecularly documented. If all these patients were really affected by Sotos syndrome, with approximately 500 reported cases of Sotos syndrome worldwide, the risk of tumour development could be estimated as high as 9%. In this presentation we detail the literature concerning the tumoral risk in Sotos syndrome and discuss the necessity of a specific follow-up.

Participants 24th European Dysmorphology Meeting 2013

Name	First name	E-mail
ADDOR	Marie-Claude	Marie-Claude.Addor@chuv.ch
ALBRECHT	Beate	beate.albrecht@uni-due.de
BARCIA RAMIREZ	Ana	ana1barcia@gmail.com
BIJLSMA	Emilia	E.K Bijlsma@lumc.nl
BOTTANI	Armand	armand.bottani@unige.ch
CALLEWAERT	Bert	Bert.Callewaert@Ugent.be
CAPRI	Yline	yline.capri@rdb.aphp.fr
CHAABOUNI-BOUHAMED	Habiba	habiba.chaabouni@rns.tn
DEVRIENDT	Koen	Koen.Devriendt@med.kuleuven.be
EL CHEHADEH	Salima	salima.elchehadeh@chu-dijon.fr
EVERS	Christina	Christina.Evers@med.uni-heidelberg.de
FAUTH	Christine	Christine.Fauth@i-med.ac.at
FRANSEN VAN DE PUTTE	Dietje	D.E.Fransen_van_de_Putte@lumc.nl
FRYNS	Jean-Pierre	Jean-Pierre.Fryns@med.kuleuven.be
GARAVELLI	Livia	livia.garavelli@asmn.re.it
GERMAIN	Dominique P.	dominique.germain@uvsq.fr
GIERUSZCZAK-BIALEK	Dorota	dorekgier@gazeta.pl
GONZALES	Marie	marie.gonzales@trs.ap-hop-paris.fr
HAYE	Damien	Damien.haye@univ-tours.fr
JACQUINET	Adeline	adeline.jacquinet@chu.ulg.ac.be
KAARIAINEN	Helena	helena.kaariainen@thl.fi
KOHLHASE	Jürgen	jkohlha@t-online.de
KUGAUDO	Monika	mkugaudo@mp.pl
LACOMBE	Didier	didier.lacombe@chu-bordeaux.fr
LUKUSA	Tshilobo	Prosper.Lukusa@uzleuven.be
LUMAKA ZOLA	Aimé	aime.lumaka@uzleuven.be
MARIN REINA	Purificacion	pmarinreina@gmail.com
MATHIEU-DRAMARD	Michèle	mathieu-dramard.michele@chu-amiens.fr
MISRA-ISRIE	Mala	mala.isrie@uzleuven.be
MORIN	Gilles	morin.gilles@chu-amiens.fr
PEREZ-AYTES	Antonio	Perez_ant@gva.es
RAUCH	Anita	anita.rauch@medgen.uzh.ch
SCHWAIBOLD	Eva	eva.schwaibold@med.uni-goettingen.de
SKORKA	Agata	askorka@wum.edu.pl
SMEETS	Eric	eric.smeets@mumc.nl
STEINDL	Katharina	steindl@medgen.uzh.ch
STOLL	Claude	cstoll@unistra.fr
STUMPEL	Connie	c.stumpel@mumc.nl
TOUTAIN	Annick	annick.toutain@univ-tours.fr
UHRIG	Sabine	sabine.uhrig@medunigraz.at
VANAKKER	Olivier	Olivier.vanakker@ugent.be
VERLOES	Alain	alain.verloes@gmail.com
VOGELS	Annick	Annick.Vogels@uzleuven.be
WRITZL	Karin	karinwritzl@gmail.com
ZENKER	Martin	martin.zenker@med.ovgu.de

Name	First name	E-mail
ZWEIER	Christiane	Christiane.Zweier@uk-erlangen.de