TWENTY-FIFTH EUROPEAN MEETING ON DYSMORPHOLOGY

10 – 12 SEPTEMBER 2014

25th EUROPEAN MEETING ON DYSMORPHOLOGY

LE BISCHENBERG

GENERAL PROGRAM

WEDNESDAY 10th SEPTEMBER

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

THURSDAY 11th SEPTEMBER

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

FRIDAY 12th SEPTEMBER

8.30 a.m. to 1.00 p.m.		Fourth and fifth sessions
1.00 p.m.	Lunch	
2.30 p.m. to 6.00 p.m.		Sixth and seventh sessions
7.30 p.m.	Dinner	

SATURDAY 13th SEPTEMBER

Breakfast – Departure

SCIENTIFIC PROGRAM

Note: This program is tentative and may be modified.

WEDNESDAY 10th SEPTEMBER

9.30 UNKNOWN SESSION
Chair: FRYNS J.P.

H. VAN ESCH
Case 1

H. VAN ESCH
Case 2

H. JILANI, S. HIZEM, I. REJEB, F. DZIRI AND L. BEN JEMAA
Developmental delay, dysmorphic features and hirsutism in a Tunisian girl. Cornelia de Lange syndrome?

L. VAN MALDERGEM, C. CABROL, B. LOEYS, M. SALEH, Y. BERNARD, L. CHAMARD AND J. PIARD
Megalophthalmos and thoracic great vessels aneurisms

E. SCHAEFER AND Y. HERENGER
An unknown diagnosis associating facial dysmorphism, developmental delay, posterior urethral valves and severe constipation

P. RUMP AND T. VAN ESSEN
What's in the name

G. MUBUNGU, A. LUMAKA, K. DEVRIENDT AND P. LUKUSA TSHILOBO
An unknown syndrome of congenital hypoplasia of the lateral abdominal wall muscles

THURSDAY 11th SEPTEMBER

08.15 Opening address: FRYNS J.P.

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

08.30 K. KEYMOLEN, R. MAUEL, M. DE RADEMAEKER, C. ERNST, W. LISSENS, S. SENECA AND A. LAUMEN
Severe renal involvement in multicentric carpotarsal osteolysis syndrome

08.45 C. STOLL, B. DOTT, Y. ALEMBIK AND M.-P. ROTH
Associated noncardiac congenital anomalies among infants with congenital heart defects

09.00 H. CAVE, A. CAYE, A. DIEUX COESLIER, O. BOUTE, C. BAUMANN, C. VINCENT-DELORME, P. BOUVAGNET, A. DAVID, D. LACOMBE, P. BLANCHET, B. ISIDOR, M. RIO, D. HERON, S. SAUVION, J.-L. ALESSANDRI, V. DROUIN-GARRAUD, B. DORAY, N. POUVREAU AND A. VERLOES
Noonan syndrome due to RIT1 mutations: further clinical and molecular delineation in 32 cases

09.15 J. PIARD , H. CAVÉ, E. LEGIUS, L. CHAMARD AND L. VAN MALDERGE
KRAS-related multiple schwannomatosis

09.30 B. MIKAT, B. ALBRECHT, H.-J. LÜDECKE, P. OSTERGAARD, G. JONES, S. MANSOUR, T.M. STROM AND D. WIECZOREK
Three patients with mutations in *KIF11* with microcephaly and intellectual disability

09.45 D. LACOMBE, J. VAN GILS, I. COUPRY, C. ROORYCK-THAMBO, J. DEFORGES, G. LANCELOT, B. ARVEILER AND P. FERGELOT
Phentotype-genotype correlations in Rubinstein-Taybi syndrome in 20 patients with *EP300* gene mutations

10.00 J. KOHLHASE, I. BADER, M. COHEN, S. MARKUS, M. HEMPEL, E. HOLINSKI-FEDER AND S. RITTHALER
Novel *MLL* (*KMT2A*) mutations and atypical clinical presentation in Wiedemann-Steiner syndrome

10.15 L. BERGER, J. VERHAGEN, K. DIDERICH, A. PAULUSSEN, A. BROOKS AND Y. VAN BEVER
Unusual presentation of Kabuki syndrome

10.30 C.W. OCKELOEN, M.H. WILLEMSEN, S. DE MUNNIK, B.W.M. VAN BON, N. DE LEEUW, A. VERRIPS, S.G. KANT, E.A. JONES, H.G. BRUNNER, R.L.E. VAN LOON, E.E.J. SMEETS, M.M. VAN HAELST, G. VAN HAAFTEN, A. NORDGREN, H. MALMGREN, G. GRIGELIONIENE, S. VERMEER, P. LAURO, L. RAMOS, T.J.J. MAAL, C.C. VAN HEUMEN, H.G. YNTEMA, C.E.L. CARELS AND T. KLEEFSTRA
Further delineation of the KBG syndrome phenotype caused by *ANKRD11* aberrations

10.45 C. MARCELIS, M. ROIFMAN, T. PATON, C. MARSCHALL, R. SILVER, J. LOHR, H. YNTEMA, H. VENSELAAR, H. KAYSERLI, B. VAN BON, G. SEAWARD, H. BRUNNERAND D. CHITAYAT
De novo WNT5A-associated autosomal dominant Robinow syndrome suggests specificity of genotype and phenhotype

11.00-11.30 *Coffee Break*

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

11.30 D. HAYE, E. CARPENTIER, N. FAKHRI, N. SOULE, C. ROZE, S. ELLARD AND A. TOUTAIN
A novel *HOXA1* mutation in a Moroccan patient with Athabaskan brainstem dysgenesis syndrome and review of the literature

11.45 I. IVANOVSKI, L. GARAVELLI, S. ROSATO, A. WISCHMEIJER, G. CHIARA, R. PASCARELLA, M. ALDERS AND R.C. HENNEKAM
Van Maldergem syndrome with a *FAT4* mutation in sibs

12.00 M. DE RADEMAEKER, A. VAN DEN BOGAERT, L. DEMEIRLEIR AND K. KEYMOLEN
The diagnosis of Mowat Wilson syndrome in two cases with severe eye anomalies

12.15 K. STEINDL, L. ABELA, P. JOSET, B. SCHMITT, B. PLECKO AND A. RAUCH
Further delineation of the Snyder Robinson syndrome presenting with unusual features

12.30 M.E.H. SIMON, M. JOOSTEN, J.H.J.M. BESSEMS, L.P. KOOPMAN, F. MALFAIT AND B.J. SIBBLES
Disorders caused by *B3GALT6* mutations: the severe end of the spectrum

12.45 E. DAGYTĖ, A. MATULEVIČIENĖ, R. MEŠKIENĖ, L. AMBROZAITYTĖ, A. MORKŪNIENĖ, Š. BERNOTAS, J. KOHLHASE AND W. BOROZDIN
Nail patella syndrome: two patients with the same mutation and different clinical manifestation

AFTERNOON

14.30-16.00 *SECOND SESSION: New genes*

Chair: GARAVELLI L. – PEREZ-AYTES A.

14.30 M. ISRIE, M. BREUSS, A. SIFRIM, L. DEHASPE, G. PEETERS, C.M. RODRIGUEZ RODRIGUEZ, E. PORTA DAPENA, KU. DOONANCO, N. LEONARD, F. TINSA, S. MOORTGAT V. MARTON, A.BARCIA RAMÍREZ, H. ULUCAN, E. KOPARIR, E. KARACA, G. TIAN, N. COWAN, D.A. KEAYS AND H. VAN ESCH
Exome sequencing in patients with circumferential skin creases Kunze type: evidence for locus heterogeneity

14.45 A.V. POSTMA, M. ALDERS, C.M. BILARDO, E. PAJKRT, R.R. VAN RIJN, S. BULK, A. ILGUN, P. BARNETT, M.M.A.M. MANNENS, A.F.M. MOORMAN, R.-J. OOSTRA AND M.C. VAN MAARLE
Sacral agenesis, abnormal vertebral ossification and persistent notochordal canal caused by a mutation in the t (brachyury) gene

15.00 J. LOUW, A. CORVELEYN, C. VERDOODT, Y. JIA, S. IQBAL, D. BOSHOFF, M. GEWILLIG, H. PEETERS, P. MOERMAN AND K. DEVRIENDT
Exome sequencing and linkage analysis as tools in solving uncommon cardiomyopathies in small families

15.15 A. RAUCH, S PAPUC, J. PASCAL, M. ZWEIER, L. GOGOLL, M. PAPIK, A. KLEIN, B. PLECKO AND K. STEINDL
Exome sequencing identifies SMARD1 as frequent diagnosis in early infancy onset respiratory distress with multiple congenital anomalies

15.30 E. DENAYER, J. VAN DER WERFF TEN BOSCH, M. DE RADEMAEKER, C. KLEIN, K. KEYMOLEN
Two siblings with a congenital neutrophil defect syndrome caused by homozygous VPS45 mutations

15.45 R. ACUNA-HIDALGO, D. SCHANZE, A. KARIMINEJAD, A. NORDGREN, P. CONNER, G. GRIGELIONIENE, D. NILSSON, M. NORDENSKJÖLD, A. WEDELL, D. WIECZOREK, G. GILLESSEN-KAESBACH, H. KAYSERILI N. ELCIOGLU, S. GHADERI-SOHI, P.GOODARZI, H. SETAYESH, M. VAN DE VORST, M. STEEHOUWER, B. KRABICHLER, C. CURRY, M. G MACKENZIE, K. M BOYCOTT, C. GILISSEN, A. R JANECKE, A. HOISCHEN AND M. ZENKER
Neu-Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the l-serine biosynthesis pathway

16.00 G. MORIN, N. ORTIZ BRUECHLE, A. RABBIND SINGH, C. KNOPP, G. JEDRASZAK, M. ELBRACHT, D. BRÉMOND-GIGNAC, K. HARTMANN, H. SEVESTRE, P. DEUTZ, D. HÉRENT, P. NÜRNBERG, B. ROMÉO, K. KONRAD, M.MATHIEU-DRAMARD, J. OLDENBURG, E. BOURGES-PETIT, Y. SHEN, K. ZERRES, H. OUADID-AHIDOUCH, AND J. ROCHETTE
Gain-of-function mutation in STIM1 (p.R304W) is associated with Stormorken syndrome

16.15-16.45 *Coffee Break*

16.45-18.00 THIRD SESSION: Clinical dysmorphology
Chair: STUMPEL C.- KOHLHASE J.

16.45 C. DE DIE-SMULDERS, A. COUMANS, S. ROBBEN, Y. ARENS, R. PFUNDT AND A. PAULUSSEN
Prenatal presentation of more common and rare skeletal dysplasias

17.00 J. VAN DEN ENDE, N. VAN DER AA AND B. LOEYS
Lines of Blaschko as a manifestation of functional

17.15 J. BRECKPOT, A. LUMAKA, J. VERMEESCH AND K. DEVRIENDT
Congenital anterolateral bowing of the tibia with ipsilateral polydactyly of the hallux associated with cerebral cyst: a new entity?

17.30 C. FAUTH, M. RAUCHENZAUNER, S. TINSCHERT AND J. ZSCHOCKE
PHACE syndrome in a girl with segmental facial hemangioma and posterior fossa brain malformation

18.00 KEY-NOTE LECTURE
J. CHELLY
Understanding cortical development: insights from genetics of neuronal migration disorders and malformations of cortical development (MCD)

21.00-23.00 UNKNOWN
Chair: FRYNS J.P.

FRIDAY 12th SEPTEMBER

08.30-11.00 FOURTH SESSION: Cytogenetics
Chair: ALBRECHT B. – VERLOES A.

08.30 A. LUMAKA, H. PEETERS, P. LUKUSA AND K. DEVRIENDT
Copy number variations in congolese patients with ID

08.45 A. VAN DIJCK, I. VAN DER WERF, G. MORTIER, M. AZAGE, J. MOKRY AND R.F. KOOY
Macrocephaly and overweight in two patients with 1q21.1 triplication

09.00 A. MATULEVIČIENĖ, B. ALEKSIŪNIENĖ, V. MIKŠTIENĖ, N. KRASOVSKAJA, L. GRIŠKEVIČIUS, A. UTKUS AND V. KUČINSKAS
Dup (1) (q43–q44) & del (21) (q22.2–q22.3) characterized by facial dysmorphism, congenital heart defect and mental retardation

09.15 L. GARAVELLI, A. VETRO, A. FORLINO, R. CICCONE, E. LONDON, C.A. STRATAKIS AND O. ZUFFARDI
Carney complex: clinical hystory of a patient with gain of function of *PRKACB*

09.30 C. SNIJDERS BLOK, N. CORSTEN-JANSSEN, D.R. FITZPATRICK, C. ROMANO, M. FICHERA, G.A. VITELLO, M.H WILLEMSEN, J. SCHOOTS, R. PFUNDT, C.M.A. VAN RAVENSWAAIJ-ARTS, L. HOEFSLOOT AND T. KLEEFSTRA
Definition of 5q11.2 microdeletion syndrome reveals overlap with charge syndrome and 22q11 deletion syndrome phenotypes

09.45 P. MARIN REINA, A. HERRERO, G. CABEZUELO AND A. PEREZ-AYTES
Mixed phenotype Langer-Giedion/Cornelia de Lange in Microdeletion 8q23.3-q24.1

10.00 S. NAMBOT, A.-L. MOSCA-BOIDRON N. MARLE, S. EL CHEHADEH, A. MASUREL, M. LEFEBVRE, J. THEVENON, J.V. DE MONTLÉON, S. PEREZ-MARTIN, M. CHOUCHANE, E. SAPIN, J.-D. METAIZEAU, V. DULIEU, F. HUET, C. THAUVIN-ROBINET, L. CHATEL, V.ABADIE, G. PLESSIS, J. ANDRIEUX, P.-S. JOUK, G. BILLY-LOPEZ, C. COUTTON, F. MORICE-PICARD, M.-A. DELRUE, C. ROORYCK-THAMBO, A. GOLDENBERG, G. JOLY-HÉLAS, P. CHAMBON, P. SAUGIER-VEBER AND L. FAIVRE
9q33.3q34.11 microdeletion: delineation of a new contiguous gene syndrome involving the *STXBP1, LMX1B* and *ENG* genes assessed using reverse phenotyping

10.15 M.T. BONATI, C. CASTRONOVO, A. SIRONI, M. CRIPPA, L. LARIZZA AND P. FINELLI
A new case of 9q34.3 microduplication syndrome: further delineation of the clinical spectrum

10.30 C. ZWEIER, M. KRUMBIEGEL, H. PETERS AND A. REIS
Overgrowth and developmental delay associated with a 200 kb deletion in 16p11.2 in two families

10.45 S.BULK, G. PIERQUIN, S. GAILLEZ, J.-S. GATOT AND J.H. CABERG
Evaluation of distal 22q11 deletion and duplications. A highly variable phenotype

11.00-11.30 *Coffee Break*

11.30-13.30 FOURTH SESSION (Continued)
Chair: BIJLSMA E. – DONNAI D.

11.30 E. COTTEREAU, A. PAUBEL, S. VONWILL, N. CHASSAING, M.-A. BARTHEZ, S. PONDAVEN, C. HOARAU AND A. TOUTAIN
X-linked agammaglobulinemia and Mohr-Tranebjaerg syndrome (XLA-MTS): a rare contiguous gene syndrome caused by a deletion of the genes *BTK* and *TIMM8A*

11.45 K. WRITZL, N. TERAN, A. LIEDÉN AND B. PETERLIN
Xq26.2q26.3 microduplication in a boy with developmental delay, distinct facial appearance and genitourinary abnormalities

12.00-12.30 FIFTH SESSION: Monogenic disorders non syndromology

12.00 L.M. HILLEN, E.J. KAMSTEEG, J. SCHOOTS, A. TIEBOSCH, E.J. SPEEL, G.M. ROEMEN, C.J. PEUTZ-KOOSTRA AND C.T.R.M. STUMPEL
Congenital nephrotic syndrome: not always the Finnish type!

12.15 F. MORICE-PICARD, E. LASSEAUX, C. PLAISANT, C. ROORYCK, D. LACOMBE, A.TAIEB AND B. ARVEILER
Molecular genetics of patients with oculocutaneous albinism

12.30 M. POLLAZZON, L. GARAVELLI1, S. ROSATO, A. WISCHMEIJER, C. GELMINI, I. IVANOVSKI AND O. ZUFFARDI
A patient with a paternal UPD-14 like phenotype due to maternal 14q microdeletion

12.45 S. WHALEN, V. LÓPEZ-GONZÁLEZ, A. DIEUX, S. JULIA, D. HÉRON, C. GAREL, A. LEGALL, B. DORAY-ROY, S. JAGADEESH, D. RODRIGUEZ AND L. BURGLEN7
Description of seven novel patients with Schinzel-Giedion syndrome and mutation in SETBP1 gene. Further delineation of the neuroradiological phenotype

AFTERNOON

14.30-16.00 SIXTH SESSION: Reverse phenotyping: mutation first (by exomes)
Chair: KÄÄRIÄINEN H. – RAAS-ROTHSCHILD A.

14.30 E. BIJLSMA, M. HOFFER, M. KRIEK, E. ATEN, A. VAN HAERINGEN, M. BREUNING, S. KANT, N. DEN HOLLANDER AND W. ARINDRARTO, M. LOSEKOOT, G. SANTEN AND C. RUIVENKAMP
Is exome sequencing of single patients with intellectual disability an effective diagnostic strategy?

14.45 L. GOGOLL, M. ZWEIER, P. JOSET, M. PAPIK, O. HASSELMANN, K. STEINDL AND A. RAUCH
New case of Biallelic TRMT10A deficiency identified by exome sequencing confirms the associated phenotype of primary microcephaly with intellectual disability and short stature

15.00 L.B. OUSAGER, C.R. FAGERBERG, M. THOMASSEN AND M. LARSEN
PIGA mutation identified by WES in a boy with overgrowth, epileptic encephalopathy and dysmorphic features

15.15 E. SMEETS, T. KLEEFSTRA AND C. STUMPEL
CTNNB1 related neurodevelopmental disorder, a recognizable syndrome

15.30 H.E. VEENSTRA-KNOL, H.A. KOETSE, A.H. VD VLUGT, J.C. HERKERT AND C.M.A. VAN RAVENSWAAIJ-ARTS
A novel KAT6B mutation; expanding the phenotype?

15.45 B. ALBRECHT, K. CREMER, H.-J. LÜDECKE, T. STROM, H. ENGELS AND D. WIECZOREK
Broadening the phenotype of *SOX2* mutations and microdeletions by array analyses and exome sequencing

16.00 C.R. FAGERBERG, L.B. OUSAGER, M. BURTON AND L. LONE
Features of a patient with ARID1B mutation

16150-16.45 *Coffee Break*

16.45-18.30 SEVENTH SESSION: Genetic Counselling (broad issues in clinics)
Chair: DEVRIENDT K.. – MATULEVIČIENĖ A.

16.45 D. DONNAI
Modern dilemmas; impact of uncertain findings on a second generation

17.00 H. KÄÄRIÄINEN AND K. AVELA
Difficulties in interpreting molecular findings in fnlb gene and predicting their consequences in two families with Larsen syndrome

17.15 K. DEVRIENDT AND M. HOLVOET
Multifactorial familial intellectual disability: a clinical study in schools for special education

17.30 L. BASEL-VANAGAITE' AND L. WOLF
Is a computer-based facial dysmorphology novel analysis ready for the clinic?

17.45 L. BOER, W.M. KLEIN, R.-J. OOSTRA AND A. SCHEPENS-FRANKE
A contemporary approach to exhibit a collection of teratological fetuses of the museum for anatomy and pathology in Nijmegen.
The use of computed tomography, magnetic resonance imaging and 3d reconstructions to visualize, describe and educate

18.00 L. BOER, W. KLEIN, R.-J. OOSTRA AND A. SCHEPENS-FRANKE
Imaging the collection of fetuses with sirenomelia from the teratological collection of the museum for anatomy and pathology in Nijmegen

UNKNOWN CASE 1

H. VAN ESCH

Center for Human Genetics UZ Leuven, Leuven, Belgium.
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We present an 11 years old girl with moderate intellectual delay.
She is the only child of a Belgian mother and a Greek father. Normal birth.
Mean clinical features: microcephaly, long and coarse face, large mouth and smooth philtrim.
Large hands with broad thumbs and spatula shaped terminal phalanges and fetal pads on fingers and toes.
High resolution molecular karyotyping is normal.

UNKNOWN CASE 2

H. VAN ESCH

Center for Human Genetics UZ Leuven, Leuven, Belgium.
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We present an 6 years old girl with moderate-severe intellectual and motor delay. She is the only child of a Belgian
couple, non-related.
Preterm birth at PMA 33 weeks and weight and length below centile 3.
Progressive postnatal microcephaly, weight and length slightly below centile 3.
Strabism and mild nystagmus. Sloping forehead and large mouth.
High resolution molecular karyotyping is normal.
Exome: no clear pathogenic variants.

DEVELOPMENTAL DELAY, DYSMORPHIC FEATURES AND HIRSUTISM IN A TUNISIAN GIRL. CORNELIA DE LANGE SYNDROME?

H. JILANI[1], S. HIZEM[1], I. REJEB[1], F. DZIRI[2] AND L. BEN JEMAA[1]

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[2] Ezzahra, Tunis, Tunisia.

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This case is about a Tunisian girl with development delay and dysmorphic features. She is the second child of young, healthy, unrelated parents. During gestation, fetal echography showed no abnormalities. No pregnancy complication was detected.
The proband was born at term vaginally with good Apgar score. Her birth weight and height were normal. She also had a normal head circumference for age gestation.
The examination at the age of eleven months showed brachycephaly but with no microcephaly, a short neck with a low posterior hairline. Her eyebrows and palpebral fissures were down slanting. She had hirsute forehead, synophrys and long curled eyelashes. She had a broad depressed nasal bridge with anteverted nares. The palate was high and arched, teeth were absent at the age of 13 months. Her ears were prominent and low set. In her lower limbs, she had malimplantation of the right big toe. Psychomotor development was delayed. She was unable to sit alone. In addition, she had a marked hypotonia. Although she had a massive gastrointestinal reflux due to a malposition of the cardia, weight and height remain between -2 and -1 standard deviation.
Chromosome analysis showed a normal caryotype 46,XX.
This description may correspond to the Cornelia de Lange syndrome, but our patient didn't have the minimum diagnostic criteria. She had neither growth retardation nor a microcephaly. Eyebrows are not arched, philtrum is not long. She had no major limb malformations such as oligodactyly. This mild phenotype could match with a mutation in SMC1A or SMC3 genes.

MEGALOPHTHALMOS AND THORACIC GREAT VESSELS ANEURISMS

L. VAN MALDERGEM[1], C. CABROL[1], B. LOEYS[5], M. SALEH[2], Y. BERNARD[3], L. CHAMARD[4] AND J. PIARD[1]

[1] Centre de génétique humaine
[2] services d'ophtalmologie
[3] de cardiologie
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This girl was born at term to unrelated Caucasian parents with normal growth parameters. Her infancy was uneventful. At 6 years, visual impairment was noted at school and an ophtalmological work-up indicated severe rapidly progressive myopia. At 7 years, uveitis developed and responded only partially to prednisone in the context of HLAB27 leukocyte antigen. It relapsed at 8 and 9 years. A major dilatation of aortic root required reconstructive surgery (aortic tube). A diagnosis of Takayasu arteritis was suggested, but could not find confirmation.
Between 12 and 25 years, her clinical status remained stable. At 26 years, rapid enlargement of her eyeballs occurred, alongside with acute neurological symptoms: right hemiparesia, dizziness, right central facial palsy with recovering within 72 y. Brain MRI indicated three small T2 fronto-parietal cortical hypersignals and bilateral megalophthalmos. Orbital CT scan indicates a eyeball diameter of 28.8 mm (left) and 26 mm (right) and a circumference of of 35.9 mm (left) and 35.5 mm (right). She reported a history of progressive enlargement of her eyeballs. There was no glaucoma, thus suggesting a pure anterior chamber megalophthalmos. Due to its rapidly increasing size culminating at +5 SD and the mechanical limits of bone, eye pain could only be alleviated by morphin derivatives delivered by a pump. Routine blood chemistry did not indicate any argument for an inflammatory or autoimmune process. Concomitantly, retinal detachment resulted in complete loss of vision on the left side and a 1/10 visual acuity on the right side despite attempts at reverting the process by laser. Heart ultrasound indicates a Dilatation of 45 mm at the leval of Valsalva sinuses and a 22 mm aneurysm of brachiocephalic trunk. On clinical examination, Megalophthalmos and a relative shortness of limbs (height/span 164/ 144 cm). Karyotype on peripheral lymphocytes was 46, XX, aCGH was [46, XX] x1 (Agilent 180K). Whole exome sequencing trio analysis discarded a convincing *de novo* mutation of any valuable candidate gene. Megalophtalmos of the anterior chamber, to be differentiated from buphtalmos by the absence of glaucoma and the apparent primary nature of the phenomenon, is a very rare condition described by Seefelder in 1914. It usually occurs sporadically, with at least two sib pair and one sibship with three affected females reported sofar, emphasizing its probable monogenic basis. Since her thoracic aneurisms are suggestive of a connective tissue disorder, collagen immunolabeling and electrophoresis have been scheduled.

AN UNKNOWN DIAGNOSIS ASSOCIATING FACIAL DYSMORPHISM, DEVELOPMENTAL DELAY, POSTERIOR URETHRAL VALVES AND SEVERE CONSTIPATION

E. SCHAEFER AND Y. HERENGER

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We present the case of a male patient who is the first child of an unrelated couple without any family history.
The history of the disease of our patient begins in the antenatal period. A diagnosis of dilatation of the bladder, ureters and kidneys was made during the second trimester of the pregnancy. A hydramnios at 34 weeks of gestation led to the delivery induction. Birth parameters were at -2SD for the height and the head circumference but weight was normal
A diagnosis of posterior urethral valves was established explaining the dilatation of the urinary tract.
The clinical examination found facial dysmorphism with hypertelorism, ptosis, blepharophimosis and arched eyebrow, associated with congenital torticollis, bilateral cryptorchidism, sacral dimple and enlarged hands. The neurological examination found hypotonia.
The clinical evolution was marked by mild motor and intellectual developmental delay, delayed weight gain, development of severe constipation and gastroesophageal reflux and the diagnosis of obstructive and central apnea. The ophthalmological examination found strabismus, severe hyperopia and heterogeneity of the retinal pigmentary epithelium with normal fundus and normal electroretinogramm. The audition was tested and found no anomalies.
Explorations with cerebral MRI, medullar echography, heart and renal ultrasound and skeleton radiographies found no major anomalies.
To date, genetic investigations were normal: conventional karyotype, array-based comparative genomic hybridization and sequencing of the *BRAF, MEK1, MEK2* and *KRAS* genes.

WHAT'S IN THE NAME

P. RUMP AND T. VAN ESSEN

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Whole-exome sequencing revealed an unanticipated diagnosis in a 10-year-old boy with severe intellectual disability and congenital anomalies. The boy has an atypical presentation of the syndrome and an unusual long survival when compared to previously reported cases.

AN UNKNOWN SYNDROME OF CONGENITAL HYPOPLASIA OF THE LATERAL ABDOMINAL WALL MUSCLES

G. MUBUNGU, A. LUMAKA, K. DEVRIENDT AND P. LUKUSA TSHILOBO

SEVERE RENAL INVOLVEMENT IN MULTICENTRIC CARPOTARSAL OSTEOLYSIS SYNDROME

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The boy we present is the first child of Caucasian, non-consanguineous parents. Both parents were in good health and family history was without particularities. Pregnancy was complicated by maternal diabetes. At birth hypospadias and mild facial dysmorphism were noticed.
Motor development was slightly delayed but social interaction was adequate for age.
Painful swelling of several articulations occurred in early childhood, leading to limited joint movements. Initial radiological evaluation did not show specific findings.
Proteinuria and chronic renal insufficiency were diagnosed around the same time.
The combination of the renal and joint manifestations, led to the clinical hypothesis of Multicentric Carpotarsal Osteolysis syndrome (MCTO) and this was confirmed by radiological re-evaluation.
Sequencing of the MAFB gene revealed a pathogenic mutation, giving molecular confirmation of the diagnosis. The mutation was absent in DNA from peripheral lymphocytes of both parents.
Acute decline of the renal function caused end-stage renal insufficiency and multi-organ failure. The child deceased at the age of 4 years.
MCTO is a rare autosomal dominant disorder mainly affecting the skeleton and the kidney. The majority of the reported patients represent de novo mutations, but parent-to-child transmission has been described. The skeletal phenotype consists of progressive osteolysis, especially in the carpal and tarsal bones. Craniofacial anomalies and mental impairment have been reported in some patients. Renal involvement with hypertension and chronic renal insufficiency leading to end-stage kidney disease is often present but usually at an older age.
With the present case, we want to illustrate that severe renal involvement can even occur during infancy and can lead to fatal complications.

ASSOCIATED NONCARDIAC CONGENITAL ANOMALIES AMONG INFANTS WITH CONGENITAL HEART DEFECTS

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Background: Although the majority of congenital heart defects (CHD) occur in isolation, a significant number occur with noncardiac anomalies. The purpose of this investigation was to assess the prevalence and the types of associated anomalies in infants with CHD in a defined population.
Methods: The associated anomalies in CHD were collected in all livebirths, stillbirths and terminations of pregnancy during 26 years in 346,831 consecutive births of known outcome in the area covered by our population based registry of congenital anomalies.
Results: Of the 4005 infants with CHD born during this period (prevalence at birth of 116 per 10,000), 1055(26.3 %) had associated anomalies. There were 354 (8.8%) patients with chromosomal abnormalities including 218 (62 %) trisomies 21, and 99 (2.5%) 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 Noonan syndrome and fetal alcohol syndrome. Six hundred two (15.0 %) of the patients had multiple congenital anomalies, non syndromic, non chromosomal (MCA). Anomalies in the urinary tract, the musculoskeletal, the digestive, and the central nervous systems were the most common other anomalies. **Conclusions:** The overall prevalence of associated anomalies, which was one in four infants, emphasizes the need for a thorough investigation of infants with CHD. The most commonly associated major noncardiac anomalies involved the urinary system, followed by the musculoskeletal, the digestive, and the central nervous systems. A routine screening for other anomalies may be considered in infants and in fetuses with CHD. One should be aware that the anomalies associated with CHD can be classified into a recognizable anomaly, syndrome or pattern in one out of nine infants with CHD.

NOONAN SYNDROME DUE TO RIT1 MUTATIONS: FURTHER CLINICAL AND MOLECULAR DELINEATION IN 32 CASES

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Noonan syndrome is a heterogeneous dominant disorder, due to mutations in at least 8 different genes involved in the RAS/MAPK signaling pathway. Recently, RIT1 was shown to be involved in the pathogenesis of some Noonan patients. We report a series of 32 patients from 22 pedigrees with mutations in RIT1. The patients show a typical Noonan Gestalt and facial phenotype. Among the 22 probands, 5 % showed postnatal growth retardation, 71 % had congenital heart defect, 37 % had hypertrophic cardiomyopathy, 52% had speech delay, 62 % have learning difficulties, but only 10% had intellectual disability. None of them has major skin anomalies. Compared to the canonic Noonan syndrome phenotype linked to PTPN11 mutations, RIT1 mutants appear to be less severely growth retarded and intellectually impaired. Incidence of cardiomyopathy was lower than previously observed. Based on our experience, we estimate that RIT1 may be the cause of 3 to 5 % of Noonan syndrome, and should be prioritized in patients with normal growth and cognitive development.

KRAS-RELATED MULTIPLE SCHWANNOMATOSIS

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Schwannoma is a peripheral nerve sheath benign tumor. Its multiple occurence is rare and can take two forms: associated with neurofibromatosis type 2 when located at the level of acoustic nerves or non NF2-related when located elsewhere. The molecular basis of the former is clearly identified with mutations in the gene encoding merlin on chromosome 22 accounting for most cases while the latter remains poorly characterized. Rare familial cases of these non-NF2 multiple schwannomas were reported in association to *SMARCB* mutations and a single case report describes a KRAS mutation in a patient with multiple schwannomas. More recently, Messiaen et al. demonstrated a multiple-hit mutational process involving 22q11 and KRAS in case of germ-cell *LZTR1* mutation in familial cases. We describe the second KRAS-related multiple schwannomatosis case in an adult patient with signs and symptoms of Noonan syndrome. This 45 y-old lady was born at term to unrelated parents with normal birth parameters. Her milestones were mildly retarded with walking without assistance obtained at 20 months, learning difficulties and delayed puberty (21 y). Turner syndrome was suspected during adolescence and a peripheral karyotype indicated a 46, XX complement. At 37 y, her first schwannoma appeared on the left arm, a few years later on the thigh, later in the bladder, then again on the upper limb. On clinical examination, her length was at the lower limit of normal range (-1.8SD) and her phenotype included downward slant of palpebral fissures, pterygium colli, a low M-shaped posterior hairline, cubitus valgus and multiple naevi. Coagulation factor XI plasma concentration was 54% (NR 65-150) and heart ultrasound was unremarkable. Based on her noonanoid features, a panel of genes belonging to ras pathway were sequenced and a *KRAS* c.40G>A heterozygous missense mutation was identified, resulting in a substitution of valine in position 14 by isoleucine (p.Val14Ile). It confirms that a subgroup of patients with multiple schwannomatosis harbour *KRAS* mutations.

THREE PATIENTS WITH MUTATIONS IN *KIF11* WITH MICROCEPHALY AND INTELLECTUAL DISABILITY

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Mutations in KIF11 cause the autosomal dominant condition microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR, MIM #152950). It is a rare condition, and so far only 22 families with mutations in KIF11 have been reported. Overall 85% of the previously published individuals with mutations in KIF11 have microcephaly, learning disabilities are documented in 73%. Chorioretinopathy is reported for 59% and lymphedema for 46% of cases (Jones et al., 2013). Here we present three patients from two families with mutations in KIF11. The first family, an affected mother and her affected daughter, was examined in our department. We made the tentative diagnosis MCLMR on the basis of the clinical presentation of the mother and her daughter and the publication of Ostergaard et al. 2012. The molecular analysis of KIF11 revealed a nonsense mutation [c.1159C>T, p.(Arg387*)]. The mother and her daughter both had primary microcephaly [OFC mother 48.5 cm (-4 SDS), OFC daughter 45.8 cm (-4.6 SDS)], mild intellectual disability (ID) and visual impairment. They showed resemblances to the previously published patients with prominent noses, thickened eyebrows, thick lower lips and prominent chins. Both patients are included in the publication of Jones et al. 2013. The third patient is the daughter of healthy parents. She presented with congenital microcephaly and mild ID few years ago in our genetics consultation. She was born after 40 weeks of gestation with congenital microcephaly [OFC 30.5 cm (-3.6 SDS)], low birth weight [2720 g (-2 SDS)] and normal lenght [50cm (-1 SDS)]. She reached milestones of motor development within the normal range but showed speech delay. At the age of four years her measurements were within normal range except for her head circumference [OFC 43 cm (-5.5 SDS), weight 13.6 kg (BMI 14.4), height 97 cm (-1.6 SDS)]. With a prominent nose, thickened eyebrows, thick lips, and in relation to her head circumference, and large ears, she also resembles the previously published patients (Vasudevan et al., 2005, Ostergaard et al., 2012, Jones et al., 2013, Hazan et al., 2012). Whole exome sequencing within a cohort of patients with ID identified a missense mutation in KIF11 [c.427A>T, p.(Ile143Phe)], which was verified with Sanger sequencing and was assumed to be disease causing by three different algorithms (PolyPhen-2, MutationTaster and SIFT).
We present the clinical and molecular data of these three patients and give a short review on the rare condition MCLMR with its wide clinical spectrum.

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PHENTOTYPE-GENOTYPE CORRELATIONS IN RUBINSTEIN-TAYBI SYNDROME IN 20 PATIENTS WITH *EP300* GENE MUTATIONS

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Rubinstein-Taybi syndrome (RSTS) is a rare autosomal dominant developmental disorder, characterized by typical facial dysmorphism, intellectual disability, and skeletal anomalies of thumbs and halluces. Two genes are involved in RSTS, *CREBBP* (16p13.3) and *EP300* (22q13.2) with identified anomalies in about 65% and 3-8% of cases, respectively. These paralogs act in chromatin remodeling and encode transcriptional co-activators interacting with more than 300 proteins. Since 2005, fourteen RSTS cases with EP300 anomalies have been described. The presentation seems less severe than in *CREBBP* patients. Here we describe the phenotype and genotype of 20 RSTS patients with *EP300* anomaly. Clinical data have been gathered from specific forms for each patient. Growth retardation was present in 89% of cases (16/18). The most frequent cranio-facial anomalies were microcephaly (85%, 17/20), columella below alae nasi (90%, 18/20) associated with prominent (80%, 16/20) and broad (65%, 13/20) nose, highly arched eyebrows (75%, 15/20), and long eyelashes (80%). Palpebral fissures orientation was either down slanted (55%) or horizontal (45%). Typical limb anomalies were also observed with broad thumbs (75%) and halluces (90%, 18/20). By contrast, radial deviation of thumbs was never seen. Intellectual disability was described in 17/19 patients (90%) at less or more severe degrees: a severe form was described in only one case whereas two patients had no mental delay. Cardiac (40%, 8/19) and renal (38%, 7/19) defects were the most frequent visceral anomalies. We identified 1 intragenic deletion and 2 large deletions at 13q13.2, 17 truncating mutations and interestingly 5 non truncating mutations in the HAT domain: 1 splicing mutation, 1 in-frame deletion and 3 *de novo* missense mutations.

Our study shows that EP300 phenotype, though variable, recapitulates most of the typical features of RSTS. Microcephaly, highly arched eyebrows and low columella are inconstant; and radial deviation of thumbs is absent. Intellectual disability is often moderate. Large deletions of *EP300,* identified by pan genomic array-CGH, were associated with atypical phenotypes. Three additional mutated cases showed an atypical phenotype, two of them bearing mutations in the last exon of the gene. This work underlines the need for enlarged, multicenter series to precise EP300 phenotypes associated with rare molecular events like missense mutations in the HAT domain and large rearrangements that are the landmarks of the clinical spectrum.

NOVEL *MLL* (*KMT2A*) MUTATIONS AND ATYPICAL CLINICAL PRESENTATION IN WIEDEMANN-STEINER SYNDROME

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Wiedemann-Steiner syndrome (WSS) is characterized by hypertrichosis cubiti associated with short stature, intellectual disability, and a distinctive facial appearance with arched, thick eyebrows, hypertelorism, narrow palpebral fissures, broad nasal bridge and tip. Stubby hands and feet were also described. The causative gene was identified im 2012 by whole exome sequencing. Five mutations have so far been described in the gene *MLL* (*KMT2A*) as causative for WSS, which are one nonsense mutation and four frameshift mutations (three short deletions and one short insertion), most likely resulting in haploinsufficiency for MLL. We present six further patients with *de novo* novel mutations in the *KMT2A* gene, two nonsense mutations, three frameshift mutations (two duplications, one deletion) and the first missense mutation. While the loss of function mutations are predicted to have a similar effect as the mutations reported previously, the missense mutation p.R1154W affects a highly conserved amino acid witin the CXXC zinc finger domain of the protein and results in a slightly aberrant phenotype.

UNUSUAL PRESENTATION OF KABUKI SYNDROME

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Background

Kabuki syndrome is characterized by typical facial features, intellectual disability, skeletal anomalies, persisting fetal pads and postnatal growth deficiency. Facial dysmorphisms include long palpebral fissures with eversion of the lateral third of the lower eyelid, arched eyebrows with sparse lateral third, short columella and large, prominent or cupped ears. Structural anomalies are present in a considerable part of patients with Kabuki syndrome, mainly consisting of heart defects (40-50%) and urogenital anomalies (30-40%)[1] .
Here we present 4 Kabuki syndrome patients with atypical features.

Patients

Our first patient presented with central hypotonia, a cleft palate and dysmorphic features, consisting of epidermoid cyst, dysplastic ears, a short stature with a microcephaly and short hands. She suffered from extreme hypoglycemia. Moreover, the lens of her left eye was absent with the iris possibly missing. Due to her complex eye anomalies, the relatively subtle periocular features of Kabuki syndrome were masked. Only at revision at the age of 10 years, she could be diagnosed with Kabuki syndrome.
The second patient presented with intellectual disability, short stature and dysmorphic features, consisting of a striking shape of the breasts, microcornea, a high palate, clinodactyly of the fifth fingers, relatively big halluces and multiple naevi. MRI of the cerebrum revealed corpus callosum hypoplasia. Although her facial features were not striking, Kabuki syndrome could be established 13 years after her first presentation.
Patient 3 was admitted because of mild respiratory distress and multiple congenital anomalies, consisting of anal atresia with rectoscrotal fistula, bilateral microphthalmia with iris and retinochoroidal coloboma, rocker bottom deformity of the right foot, bicuspid aortic valve and multiple sacral segmentation defects. Moreover, he suffered from transient hypoglycemia, panhypopituitarism and bilateral moderate hearing loss. Despite of this unusual presentation, diagnosis of Kabuki syndrome was suggested at the age of 2 years based on his facial features and the presence of developmental delay, hypodontia and fetal pads.
Our fourth patient was referred by a hematologist because of immune thrombocytopenic purpera (ITP) in combination with an intellectual disability and unilateral microtia. Medical history consisted of an eventration of the diaphragm, multiple patellar luxations and a hearing deficit. It was not until the age of 33 years that he came under the attention of a clinical geneticist, who diagnosed Kabuki syndrome based on his dysmorphic features.

Discussion

Our patients demonstrate that Kabuki syndrome is not always an easy diagnosis, especially when patients initially present with unusual features. The importance of early recognition of uncommon features was recently underlined [2] by pointing out Kabuki syndrome as a cause of neonatal hypoglycemia, which was also present in patient 1 and patient 3. Rare clinical features can set the dysmorphologist to choose the wrong diagnostic path. For example, Kabuki syndrome might be confused with CHARGE syndrome as was demonstrated by our third patient[3]. Although ear anomalies are well known in Kabuki syndrome, microtia has, to our best knowledge, only previously been reported in three patients with Kabuki syndrome. The average age of diagnosis is 2,5 years[4] , however typical facial features may not be striking at a young age, as is shown by two of our patients, which emphasizes the importance of follow-up of patients with an undiagnosed disorder.

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FURTHER DELINEATION OF THE KBG SYNDROME PHENOTYPE CAUSED BY *ANKRD11* ABERRATIONS

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Loss-of-function mutations in *ANKRD11* were identified as the cause of KBG syndrome, an autosomal dominant syndrome with specific dental, neurobehavioural, craniofacial and skeletal anomalies. We present the largest cohort of KBG syndrome cases confirmed by *ANKRD11* mutations reported so far, consisting of twenty patients from thirteen families. Sixteen patients were molecularly diagnosed by Sanger sequencing of *ANKRD11*, one familial case and three sporadic patients were diagnosed through whole exome sequencing and one patient was identified through genomewide array analysis. All patients were evaluated by a clinical geneticist. Detailed orofacial phenotyping including orthodontic evaluation, intraoral photographs and orthopantomograms was performed in 10 patients and revealed besides the hallmark feature macrodontia of the central upper incisors, several additional dental anomalies as oligodontia, talon cusps and macrodontia of other teeth. 3D Imaging in 14 patients showed consistent and objectively analysed facial dysmorphisms comprising a bulbous nasal tip, upturned nose with a broad base and a round or triangular face. Almost all patients exhibited neurobehavioural problems such as autism spectrum disorder or hyperactivity. One third of patients presented with (conductive) hearing loss. Congenital heart defects, velopharyngeal insufficiency and hip anomalies were less frequent. Based upon our observations, we recommend cardiac assessment and regular hearing tests in all individuals with a molecular diagnosis of KBG syndrome. As the gene is one of the most frequently mutated genes in our center upon testing of neurodevelopmental disorders, it seems an important contributor to the aetiology of both sporadic and familial cases.

DE NOVO WNT5A-ASSOCIATED AUTOSOMAL DOMINANT ROBINOW SYNDROME SUGGESTS SPECIFICITY OF GENOTYPE AND PHENHOTYPE

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Robinow Syndrome (RS), a rare skeletal dysplasia syndrome, is characterized by dysmorphic features resembling a fetal face, mesomelic limb shortening, hypoplastic external genitalia in males, and renal and vertebral anomalies. Both autosomal dominant and autosomal recessive patterns of inheritance have been reported. Since the description of
autosomal dominant Robinow Syndrome (ADRS; OMIM 180700) in 1969 by Meinhard Robinow and colleagues, the molecular etiology remained elusive until only recently. WNT5A was proposed to be the candidate gene for ADRS, as mutations were found in two affected families, one of those being the originally described family. We report three families with RS caused by novel heterozygous WNT5A mutations, which were confirmed in the first family by whole exome sequencing, and in all by Sanger sequencing. To our knowledge, this is the largest number of published families with ADRS in whom a WNT5A mutation was identified. Families 1 and 2 are the first cases showing de novo inheritance in the affected family members and thus strengthen the evidence for WNT5A as the causative gene in ADRS. Finally, we propose WNT5A mutation specificity in ADRS, which may affect interactions with other proteins in the Wnt pathway.

A NOVEL *HOXA1* MUTATION IN A MOROCCAN PATIENT WITH ATHABASKAN BRAINSTEM DYSGENESIS SYNDROME AND REVIEW OF THE LITERATURE

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Athabaskan brainstem dysgenesis syndrome (ABDS) and Bosley-Salih-Alorainy syndrome (BSAS) (OMIM 601536) are rare autosomal recessive disorders, with overlapping features, caused by mutations in the *HOXA1* gene. To our knowledge, ABDS has been described in fifteen patients of Navajo and Apache American Indian descent and BSAS in sixteen patients of Saudi Arabian and Turkish consanguineous families. Only one homozygous *HOXA1* mutation has been described in Navajo and Apache American Indian patients (c.76C>T) and only two mutations in BSAS (c.84C>G and c.175-176insG).

We report a female patient, born of Moroccan consanguineous parents, with a clinical picture highly suggestive of ABDS, comprising: horizontal gaze palsy, right facial paresis, dysplastic ears, sensorineural deafness with severe inner ear abnormalities, pulmonary atresia and ventricular septal defect with multiple aortopulmonary collaterals, abnormal left carotid artery, and central hypoventilation. Array-CGH analysis and sequencing of *CHD7* were normal. Direct sequencing of the *HOXA1* gene identified a novel homozygous frameshift mutation in exon 2, c.743dupT (p.His249Profs*40), which was present in a heterozygote state in both parents.

This report contributes to the description of the clinical spectrum of *HOXA1* related disorders. The main features of ABDS and of BSAS are congenital horizontal gaze palsy, sensorineural deafness with inner ear malformation, congenital heart defects, and global developmental delay. ABDS and BSAS were considered as distinct entities as central hypoventilation is a major feature of ABDS and is not part of BSAS. Although this difference may be related to specific *HOXA1* mutations, central hypoventilation may be insufficient to differentiate both disorders as it is not constant in ABDS. We therefore suggest that ABDS and BSAS correspond to a variable clinical expression of the same entity caused by *HOXA1* mutations.

VAN MALDERGEM SYNDROME WITH A FAT4 MUTATION IN SIBS

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Van Maldergem syndrome (VMS) is an autosomal recessive disorder characterized by intellectual disability, periventricular heterotopia, an unusual face, hearing loss, camptodactyly and syndactyly, renal hypoplasia osteoporosis and tracheal anomalies sometimes necessitating tracheostomy. VMS is caused by homozygous or compound heterozygous mutation in *FAT4* located at chromosome 4q28.1 or in *DCHS1* located at chromosome 11p15.4. We present a brother and sister, born to first cousin parents from Morocco, in whom we clinically diagnosed VMS which subsequently was proven molecularly.

The firstborn child was born at 41 weeks of gestation after a pregnancy complicated by polyhydramnios and foetal ascites. At birth, his weight was 2760g (<P3), length was 49cm, head circumference 35cm. He had severe obstruction of the airways, due to a small jaw, necessitating a tracheostomy. He showed dolicocephaly, long face, hypertelorism, proptosis, down-slanting palpebral fissures, small ears, and overlapping fingers, camptodactyly of one finger, and syndactyly of 2-3 toes bilaterally. He followed a delayed development, both in motor skills and cognition. Conductive hearing loss was detected. Brain MRI showed atretic external auditory canals, periventricular heterotopias, a thin corpus callosum, small olfactory bulbs, partial malrotation of the hippocampus and general reduction of white matter. Extensive additional studies included metabolic screening, classical karyotype, array-CGH and molecular analysis for Meier-Gorlin syndrome yielded normal results. At tfollow, at 4.2 years, his height was 106cm (P25), weight 18 kg (P25) and head circumference 50.5 cm (P25-50), and clinically the diagnosis Van Maldergem syndrome was suspected.

he second child was born at 38 weeks, weighing 2250g (<P3), length 46cm (P10), and head circumference 30cm (<P3). She had also a small jaw, but less than her brother. Furthermore she demonstrated small, low-set, deformed ears, with atretic external auditory canals, hypertelorism, epicanthal folds, slight proptosis, down-slanting palpebral fissures, short columella, full lips, high arched palate, thick gums, overlapping fingers and syndactyly of toes 2-3 bilaterally. Brain MRI showed dysplasia of anterior corpus callosum and malrotation of the hippocampus. She showed an only mild developmental delay (walking at 17 months, first words at 20 months). At 1.8 years her height was 80cm (P25), weight 7870g (<P3), and head circumference 46cm (P10).

The clinical diagnosis Van Maldergem syndrome was subsequently confirmed molecularly by detection of a homozygous mutation p.Ile2234Asn in *FAT4* in both patients. We demonstrate the phenotype and discuss the resemblance to Hennekam syndrome which has been reported to be sometimes allelic to Van Maldergem syndrome.

THE DIAGNOSIS OF MOWAT WILSON SYNDROME IN TWO CASES WITH SEVERE EYE ANOMALIES

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Mowat Wilson syndrome (OMIM 235730) is a genetic disease caused by heterozygous mutations or deletions of the ZEB2 gene (OMIM 605802) located at chromosome 2q21-q23.
It is a condition characterized by distinct facial features, changing with age, moderate to severe intellectual disability, epilepsy and congenital malformations such as Hirschsprung disease, genitourinary anomalies, congenital heart defects, agenesis of the corpus callosum and eye anomalies.
We present two cases with severe eye anomalies and a diagnosis of Mowat Wilson syndrome.
The first case is a boy born at term after an uneventfull pregnancy with severe congenital eye anomalies, hypospadias, persistent foramen ovale and dysmorphic facial features. Ophthalmological investigation revealed bilateral microphthalmia with suspicion of hypoplasia/ dysplasia of the optic nerves. Absence of the optic chiasma was suspected at magnetic resonance of the brain. Array comparative genomic hybridization (aCGH) analysis was performed with the 44 K Agilent array and a 1.1 Mb deletion of the 2q23 band encompassing the ZEB 2 gene was detected.
The second case is a boy born at term after a uneventfull pregnancy. He presented at birth with bilateral microphtalmia and with complete aniridia of the right eye.
A bilateral absence of the optic nerve with absence of optic chiasma was confirmed at the magnetic resonance. Since the age of 6 years he is treated for epilepsy. At the age of 8 years he has a severe intellectual disability and a distinctive facial phenotype. Array comparative genomic hybridization (aCGH) analysis was performed with the 44 K Agilent array and was normal. Molecular analysis of the ZEB2 gene showed a frame shift mutation c.1850dup.(p.(His617fs)).
Although a variety of ocular manifestations has been described, they are less frequently associated with Mowat Wilson syndrome. More severe anomalies as microphtalmia with optic nerve anomalies are unusual presentations of this rare syndrome. This report stresses that the presence of severe eye anomalies should alert the clinician to look for the distinctive facial features of Mowat Wilson syndrome in order to make an early diagnosis which advantages an adapted therapeutical and rehabilitation management.

DISORDERS CAUSED BY *B3GALT6* MUTATIONS: THE SEVERE END OF THE SPECTRUM

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Mutations in *B3GALT6*, a gene encoding an enzyme involved in the glycosaminoglycan synthesis, cause a broad phenotypic spectrum with variable features of a skeletal dysplasia and a connective tissue disorder. The skeletal changes are consistent with spondyloepiphyseal dysplasia with joint laxity, Beighton type[1]. The connective tissue features overlap with a range of several recessive Ehlers-Danlos variants[2].
We present a one-year-old girl with compound heterozygous mutations in *B3GALT6* and severe features of both a skeletal dysplasia and a connective tissue disorder. Prenatal ultrasound examination showed contractures of the wrists and ankles, and short long bones (<p5). Because of breech position a caesarean section was performed. The girl presented with congenital joint dislocations, club feet, severe hypotonia, lung hypoplasia with respiratory distress, a short stature with a relatively large head circumference, and a hemodynamically significant atrial septal defect. She has facial dysmorphisms, blue sclerae, spatulate fingers, a progressive kyphoscoliosis, and a soft, doughy skin. She has myopia (S -5.0 dpt), and congenital hearing loss on brainstem audiometry. She was very painful in her first months. She sustained several spontaneous fractures. Radiologic examination showed signs of osteoporosis for which bisphosphonate treatment is started. At the age of 11 months, an atlanto-occipital subluxation occurred.
Given the combination of joint luxations and spatulate fingers, Larsen syndrome was considered first. However, *FLNB* analysis didn't show any mutations. Analysis of *B3GALT6* showed compound heterozygous mutations: a frame shift mutation and an unknown missense variant concerning a highly conserved nucleotide in the *B3GALT6* gene and amino acid residue in the B3GALT6 protein.
In children with congenital dislocations, joint laxity, skeletal abnormalities and variable signs of a connective tissue disorder, enzymatic defects in the glycosaminoglycan synthesis should be considered.

1. Nakajima *et al* (2013). Mutations in *B3GALT6*, which encodes a glycosaminoglycan linker region enzyme, cause a spectrum of skeletal and connective tissue disorders. Am J Hum Genet 92, 927-934.
2. Malfait *et al* (2013). Defective initiation of glycosaminoglycan synthesis due to *B3GALT6* mutations causes a pleiotropic Ehlers-Danlos-syndrome-like connective tissue disorder. Am J Hum Genet 92, 935-945.

NAIL PATELLA SYNDROME: TWO PATIENTS WITH THE SAME MUTATION AND DIFFERENT CLINICAL MANIFESTATION

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Nail-patella syndrome (NPS) is a rare autosomal dominant disorder characterized by hypoplastic or absent patellae, dystrophic nails, dysplasia of the elbows, and iliac horn. The features of nail-patella syndrome vary in severity between affected individuals, even among members of the same family. Most NPS cases are associated with heterozygous mutation in the LIM homeobox transcription factor 1 beta gene (LMX1B, OMIM 602575).
We report two unrelated patients with c.798G>A (p.Trp266Ter) mutation, in exon 5 of the LMX1B gene in a heterozygous state. The mutation leads to a frameshift with premature termination of translation, which would likely result in a truncated protein or nonsense-mediated decay of the mutant mRNR.
Case 1: a 25 year old woman. She has hypoplastic thumbnails, triangular lunulae of the II-V fingernails, small patellae. No elbow and pelvis abnormalities detected.
Case 2: a 4 year old boy, referred to Genetic Centre due to dysmorphic features and elbow webbing. He has high forehead, thin upper lip, hypoplastic nails, especially thumbnails, aplasia m.tricepitis, elbow webbing, limited elbow extension, small dislocated patellae, talipes.

EXOME SEQUENCING IN PATIENTS WITH CIRCUMFERENTIAL SKIN CREASES KUNZE TYPE: EVIDENCE FOR LOCUS HETEROGENEITY

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Congenital circumferential skin creases are extremely rare and children born with this feature are referred to as 'Michelin tyre babies' based on the similarity with the mascot of the French tyre manufacturer. Some of these children have additional abnormalities including typical facial dysmorphism, cleft palate, short stature and intellectual disability. For this syndrome, our group proposed the term 'Circumferential skin creases Kunze type' (Wouters *et al.*, 2011). So far, less than 10 cases have been described in the literature and all occurrences are sporadic. In an international collaboration we collected DNA samples from 8 patients with Circumferential skin creases Kunze type. Exome sequencing was performed on the HiSeq2000 platform for two case-parent trios as well as two additional patients with this syndrome. Data analysis revealed the presence of pathogenic mutations in either one of two interacting genes, providing evidence for genetic heterogeneity. Three additional patients with the same phenotype have also been found to carry a mutation in one of these genes. While some patients carry a heterozygous *de novo* mutation, others present with homozygous mutations. Accurate genotype-phenotype correlations are being investigated. In addition, we are performing functional analyses at the protein level to elucidate the pathogenic mechanism of the mutations.

SACRAL AGENESIS, ABNORMAL VERTEB RAL OSSIFICATION AND PERSISTENT NOTOCHORDAL CANAL CAUSED BY A MUTATION IN THE T (BRACHYURY) GENE

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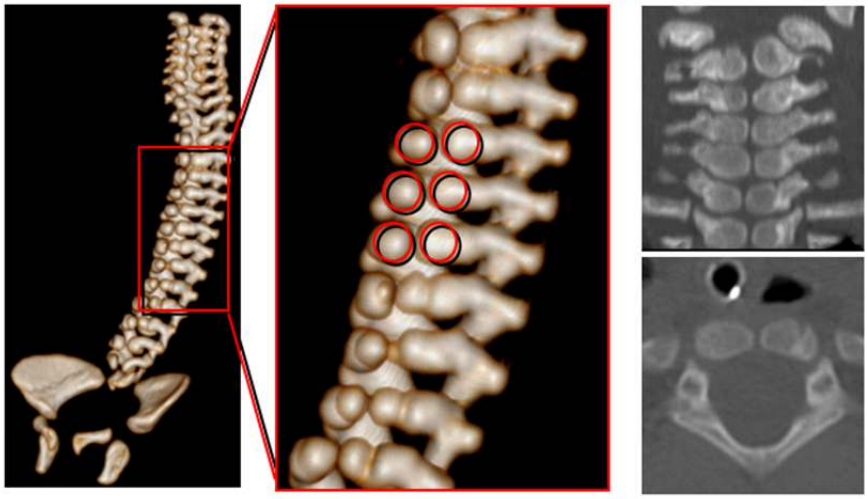
The T gene (brachyury gene) is the founding member of the T-box family of transcription factors and is vital for the formation and differentiation of the mesoderm and the axial development of all vertebrates. We here present four patients from three consanguineous families exhibiting sacral agenesis, a persistent notochordal canal and abnormal ossification of the vertebral bodies (see below) in addition to various other anomalies.



Given the consanguineous nature and the similarity of the phenotypes between the 3 families, we performed homozygosity mapping and identified a common 4.1Mb homozygous region on chromosome 6q27, containing the T gene. Sequencing of T in the affected individuals led to the identification of a shared homozygous missense mutation, p.H171R, in the highly conserved T-box. The homozygous mutation results in diminished DNA binding, increased cell growth, and interferes with the normal expression of genes involved in ossification, notochord maintenance and axial mesoderm development. We suggest that screening for the ossification of the vertebrae is warranted in patients with sacral agenesis to evaluate the possible causal involvement of the T gene.

EXOME SEQUENCING AND LINKAGE ANALYSIS AS TOOLS IN SOLVING UNCOMMON CARDIOMYOPATHIES IN SMALL FAMILIES

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Introduction: Two distinct families, both with two children affected by different lethal cardiomyopathies were analyzed using linkage analysis and exome sequencing. The first family has two siblings from consanguineous parents of Turkish descent and presented with isolated dilated cardiomyopathy, leading to early death in infancy. The diagnosis of an extremely rare and lethal disorder, mitogenic cardiomyopathy (MCMP), was made histologically. The second family has two siblings from non-consanguineous parents of Caucasian descent and presented with a unique lethal congenital cardiopathy, i.e. non-compaction of the right ventricle(RVNC).
Methods: Genomewide parametric linkage analysis was performed, SNP typing platform was used in a recessive model. Genotyping was done in parents and both the unaffected and affected siblings. Exome sequencing analysis was performed. Data analysis was done using commercial and in-house developed software. Only variants in genes from the linkage regions were retained. In both families, all homozygous calls were excluded in the parents and the unaffected siblings, reference calls were excluded in the affected siblings. Only exonic and splicing variants were included, synonymous variants were excluded. Variants occurring with a frequency of <1% in the 1000 genomes project or with an unknown frequency were included.
Results: Linkage analysis was performed. In the first family, after variant filtering of the exome sequences, 6 candidate genes were identified in the linkage region with homozygous mutations in the patient, inherited from both parents, and for which the unaffected sibling is heterozygous or reference. In the second family one candidate gene was identified using the same criteria. This gene list was manually curated using functional data and genotype-phenotype correlations. All results were confirmed by Sanger sequencing.
We identified a deleterious mutation in the *ALMS1* gene as the most likely cause op MCMP. The two affected siblings are homozygous for a frameshift deletion of one basepair in the *ALMS1* gene. This is predicted to cause a premature stop at position 5 downstream. The unaffected sister and parents are heterozygotes. In the second family, we identified two compound heterozygous variants in the *KIF20A* as the most likely cause for RVNC. Further functional studies were performed in the RVNC family showing increased multiploidy segregation patterns and demonstrating delayed cell growth with lowered transcription and protein steady-state levels.
Conclusions: Linkage analysis combined with exome sequencing identified a homozygous deleterious mutation in the *ALMS1* gene as the cause of the first phenotype. Alström syndrome is characterized by a typically transient dilating cardiomyopathy in infancy, suggesting that mitogenic cardiomyopathy represents the extreme phenotype, resulting in demise before the other clinical symptoms become evident. Two compound heterozygous variants in *KIF20A* are described, for the first time in literature, as the cause of the second phenotype. These observations further illustrates the role of *ALMS1* in cell cycle regulation and *KIF20A* in cytokinesis. Reaching a genetic diagnosis in rare disorders remains a challenge. We illustrate that even in small families with only two affected individuals, the identification of the underlying defect is feasible, using a combination of the sophisticated genetic tools.

TWO SIBLINGS WITH A CONGENITAL NEUTROPHIL DEFECT SYNDROME CAUSED BY HOMOZYGOUS VPS45 MUTATIONS

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We report on two siblings from consanguineous parents that presented with severe neurological and immunological deficits. They both suffered from neutropenia and neutrophil dysfunction with bone marrow fibrosis and frequent invasive infections and developed hemolytic trombocytopenia and anemia. They had severe failure to thrive and diarrhea. There was neurological involvement with severe psychomotor retardation, cortical blindness, hearing loss, thin corpus callosum on MRI and dysrythmia on EEG. There was hepatosplenomegaly and nephromegaly and hypertension. Both children died of infections at the age of 8 and 7 months respectively. DNA samples were included in an international collaboration and through homozygosity mapping with SNP arrays and whole exome sequencing a homozygous VPS45 mutation (p.Glu238Lys) was identified in both siblings. In five other children with comparable immunological deficits a p.Thr224Asn mutation in the same gene was identified. VPS45 encodes a protein that regulates membrane trafficking through the endosomal system. The VPS45 mutations were shown to be causal on the basis of the following findings: they fully segregated with the phenotype, were absent from 250 alleles of normal controls with the same genetic background and from published databases, caused structural alterations in VPS45 and were located in residues highly conserved among species. Furthermore, in both neutrophils and fibroblasts the Thr224Asn mutation led to decreased VPS45 levels, affected proteins that interact with VPS45, impaired cell migration and increased apoptosis. In addition, a zebrafish model with reduced VPS45 protein had severe neutropenia, resembling that in the patients. VPS45 deficiency should be considered in patients with neutropenia, nephromegaly and severe bacterial and fungal infections. The cellular defects in this disease suggest that other immunodeficiency syndromes may also result from impaired vesicle trafficking.

NEU-LAXOVA SYNDROME IS A HETEROGENEOUS METABOLIC DISORDER CAUSED BY DEFECTS IN ENZYMES OF THE L-SERINE BIOSYNTHESIS PATHWAY

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Neu-Laxova syndrome (NLS) is a rare autosomal recessive disorder, which presents with a recognizable pattern of severe malformations leading to prenatal or early postnatal lethality. Homozygous mutations in PHGDH, a gene involved in the first and limiting step in L-serine biosynthesis, were recently identified as the cause of the disease in three families. By studying a cohort of 12 unrelated families affected by NLS, we provide evidence that NLS is genetically heterogeneous and can be caused by mutations in all three genes encoding enzymes of the L-serine biosynthesis pathway. Consistent with recently reported findings, we could identify PHGDH missense mutations in three unrelated families of our cohort. Furthermore, we mapped an overlapping homozygous region on chromosome 9 containing PSAT1 in four consanguineous families. This gene encodes phosphoserine aminotransferase, the enzyme for the second step in L-serine biosynthesis. We identified six families with three different missense and frameshift PSAT1 mutations fully segregating with the disease. In another family, we discovered a homozygous frameshift mutation in PSPH, the gene encoding phosphoserine phosphatase which catalyzes the last step of L-serine biosynthesis. Interestingly, all three identified genes had been previously implicated in serine deficiency disorders, characterized by variable neurological manifestations. Our findings expand our understanding of NLS as a disorder of the L-serine biosynthesis pathway and suggest that NLS represents the severe end of serine deficiency disorders, demonstrating that certain complex syndromes characterized by early lethality may indeed be the extreme end of the phenotypic spectrum of already known disorders.

GAIN-OF-FUNCTION MUTATION IN STIM1 (P.R304W) IS ASSOCIATED WITH STORMORKEN SYNDROME

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Stormorken syndrome is a rare autosomal dominant disorder characterized by a phenotype that includes miosis, thrombocytopenia/thrombocytopathy with bleeding time diathesis, intellectual disability, mild hypocalcaemia, muscle fatigue, asplenia and ichthyosis. Using targeted sequencing and whole exome sequencing, we identified the c.910C>T transition in a STIM1 allele (p.R304W) only in patients and not in their unaffected family members. STIM1encodes Stromal interaction molecule 1 protein (STIM1) which is a finely tuned endoplasmic reticulum (ER) Ca2+ sensor. The effect of the mutation on the structure of STIM1 was investigated by molecular modeling, and its effect on function was explored by calcium imaging experiments. Results obtained from calcium imaging experiments using transfected cells together with fibroblasts from one patient are in agreement with impairment of calcium homeostasis. We show that the STIM1 p.R304W variant may affect the conformation of the inhibitory helix and unlock the inhibitory state of STIM1. The p.R304W mutation causes a gain of function effect associated with increase of both resting Ca2+ levels and store operated calcium entry. Our study provides evidence that Stormorken syndrome may result from a single-gene defect which is consistent with Mendelian dominant inheritance.

PRENATAL PRESENTATION OF MORE COMMON AND RARE SKELETAL DYSPLASIAS

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Skeletal dysplasias are rare and clinically and genetically heterogeneous. As a consequence making a diagnosis and establishing the recurrence risk for the parents requires a multidisciplinary approach. We present some cases of prenatal presentation of skeletal dysplasias, and show ultrasound abnormalities, clinical pictures, radiological features and molecular data. Also, the clinical work up is described. Case 1 is a case of de novo achondroplasia, diagnosed in the 32th week of pregnancy. The mother suffered from severe polyhydramnios. Symmetrical shortening of long bones was diagnosed. The baby died intrauterine some weeks later. Case 2 and 3 comprise children with decreased mineralisation of the skeleton, one child with lethal osteogenesis imperfecta on the basis of a mutation in one of the COL1 genes, another child with hypophosphatasia and a mutation in the ALPL gene. The fourth case is campomelic dysplasia with typical bowing of the tibia, the diagnosis was confirmed by finding a mutation in the SOX9 gene. Case 5 is a girl with diastrophic dysplasia, presenting with symmetrical limb shortening and an abnormal position of the feet and a mutation a the DTDST gene. The sixth case presented with microcephaly, severe short stature, and brain anomalies on the prenatal ultrasound scan. The clinical diagnosis MOPD (microcephalic osteodysplastic primordial dwarfism) type 1 was made and confirmed by compound heterozygosity for mutations in the RNU4ATAC gene. Case 7 and 8 are sibs with short limbs are contractures of hands and feet. NGS revealed compound heterozygosity for mutations in the B3GALT6 gene, which is compatible with the clinical diagnosis of SpondylEpiMetaphysealDysplasia with Joint Laxity (SEMD-JL).

LINES OF BLASCHKO AS A MANIFESTATION OF FUNCTIONAL MOSAICISM

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Patterned pigmentary disturbances are seen in a large variety of human genetic disorders. Cytogenetic studies have provided evidence that such skin lesions often reflect chromosomal mosaicism.
In women X-inactivation results in functional mosaicism, and in X-linked skin disorders this can manifest itself by the appearance of pigmented skin striations following Blaschko`s lines. This has been reported for several X-linked diseases, like Incontinentia Pigmenti, caused by mutations in the NEMO gene, Focal Dermal Hypoplasia, caused by PORCN mutations, Christ-Siemens-Touraine syndrome etc. In these conditions heterozygous females often show a Blaschko-linear pattern of Lyonization.
With techniques like SNP array copy number variations can be detected containing genes on the X-chromosome, that lead to severe diseases in males, but in females can also lead to the typical skin changes.
Also mosaics of other (cryptic) chromosome abnormalities can lead to the same skin lesions.
We show four female patients with streaky hyperpigmentation following the lines of Blaschko, with or without accompanying symptoms; one with a de novo deletion on Xq26.2-26.3, containing the PHF6 gene, responsible for the Börjeson-Forssman-Lehmann syndrome in males, and the HPRT1 gene, responsible for the Lesch-Nyhan syndrome in males. The second two patients shows a hypomorphic mutation in the NEMO gen, giving rise to Hypohydrotic Ectodermal Dysplasia with Immune-deficiency in males. The third patient is a girl with a mosaic trisomy 14.

CONGENITAL ANTEROLATERAL BOWING OF THE TIBIA WITH IPSILATERAL POLYDACTYLY OF THE HALLUX ASSOCIATED WITH CEREBRAL CYST: A NEW ENTITY?

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Congenital anterolateral bowing of the tibia combined with ipsilateral polydactyly of the hallux (CABTP) is a rare entity that resembles the anterolateral tibial bowing which is associated with neurofibromatosis type 1 (NF1). NF1-related tibial bowing has a poor prognosis, as it usually progresses to pathologic fracture and therapy-resistant pseudarthrosis. Adversely, CABTP is associated with relatively favorable prognosis with spontaneous resolution of bowing and absence of neurocutaneous signs. Therefore, CABTP is considered a distinct entity in the field of tibial bowing and has no association with NF1. About 23 cases of CABTP have been reported thus far: all cases are unilateral and sporadic. There is no parental consanguinity and there is a preponderance of males, with a sex ratio of 4/1.

Here we report on 4 patients with CABTP in association with corpus callosum agenesis and a large interhemispheric cyst (table 1). The male/female ratio is 3/1. Associated anomalies include minor hand anomalies, epilepsy and learning difficulties or developmental delay. The association of polydactyly and agenesis of the corpus callosum is described in acrocallosal syndrome (ACS). In this condition, polydactyly is seen both in hands and feet, and can be bilateral. The condition is associated with severe mental retardation. Interestingly, in approximately 25% of cases, intracranial cysts were observed. There is also a preponderance of males. Given the skewed sex ratio in both ACS and CABTP, and their marked clinical overlap, we suggest that the two conditions are manifestations of a single disorder with variable expression.

Finally, the foot anomalies in CABTP strikingly resemble those seen in oro–facial–digital syndrome type 1 (OFD1), where typically unilateral partial duplication of the big toe is seen, with varus position. Interestingly, an intragenic *CXORF5* deletion was detected in a female foetus who presented bilateral CABTP, corpus callosum agenesis and an interhemispheric cyst on prenatal ultrasound. We investigated whether the present entity of CABTP with a cerebral cyst is pathogenetically related to OFD by means of exome sequencing in our patient cohort. The results of these genetic analyses will be discussed here.

Table 1. Patient characteristics

	gender	CABTP	brain	development	hand
Case 1	M	right	CCA, interhemispheric cyst	mild delay	syndactyly III-IV
Case 2	M	right	CCA, interhemispheric cyst aqueduct stenosis, cerebellar hypoplasia	severe DD, epilepsy	syndactyly I-II hypoplasia distal phalanx II
Case 3	F	bilateral	CCA, interhemispheric cyst	mild delay	syndactyly right IV-V
Case 4	M	right	CCA, interhemispheric cyst neuronal migration defects	mild delay, epilepsy	none

CCA: corpus callosum agenesis, DD: developmental delay, F: female, M: male

PHACE SYNDROME IN A GIRL WITH SEGMENTAL FACIAL HEMANGIOMA AND POSTERIOR FOSSA BRAIN MALFORMATION

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Infantile hemangiomas are common benign vascular tumours which primarily involve the skin. They affect approximately 5-10% of children less than 1 year of age. Hemangiomas are composed of endothelial precursor cells which rapidly proliferate but eventually regress and involve. The majority of hemangiomas is localized and solitary. A subgroup of patients with infantile hemangiomas, most commonly of the face, exhibits additional structural anomalies known as PHACE(S) association or syndrome. PHACE(S) is an acronym encompassing the following features: P = posterior fossa brain malformation, H = hemangioma of the face, A = arterial anomalies, C = cardiac anomalies, E = eye anomalies and S = sternal defects (MIM #606519).
Here, we report on a 13year old girl who was referred with the tentative diagnosis of Sturge-Weber syndrome. Thorough clinical and radiological assessment showed characteristic findings of PHACE syndrome including an infantile left-sided facial hemangioma with progressive involution, a posterior fossa brain malformation with hypoplasia of the cerebellar vermis and the left cerebellar hemisphere, and left-sided visual impairment due to astigmatism. She has learning difficulties, recurrent headaches and focal epileptic seizures which started at the age of 11. Echocardiography and MR angiography of the brain were unremarkable. There is no sternal clefting.
PHACE(S) syndrome is a probably underdiagnosed disorder which may be confused with Sturge-Weber syndrome. In contrast to PHACE(S) syndrome patients with Sturge-Weber syndrome have no hemangiomas but vascular malformations of the skin (port-wine stains) which increase in colour intensity over time, and vascular malformations of the leptomeninges. Cardiac anomalies and structural brain malformations are usually not part of the spectrum.
As PHACE(S) may be complicated by severe vascular and cardiac events a timely diagnosis is important for appropriate therapy.

KEY-NOTE LECTURE

UNDERSTANDING CORTICAL DEVELOPMENT: INSIGHTS FROM GENETICS OF NEURONAL MIGRATION DISORDERS AND MALFORMATIONS OF CORTICAL DEVELOPMENT (MCD)

J. CHELLY

COPY NUMBER VARIATIONS IN CONGOLESE PATIENTS WITH ID

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1. Introduction

Chromosomal Microarray (CMA) has become the first-tiers diagnostic tests for patients with Intellectual Disability (ID) (Schaefer and Mendelsohn, 2013). With High Resolution CMA (HRCMA) the detection rate of chromosomal aberrations has increased up to 13 - 31 % among patients with idiopathic ID (Wincent et al 2012; Lundvall et al., 2012). CMA allowed identification of novel CNVs and refinement of known chromosomal aberrations. Using such technology in understudied population such as Congolese may reveal novel CNVs and refine known aberrations. We applied the CMA to Congolese patients with idiopathic ID. The first aim of this study is to determine the frequency and nature of pathogenic variations among the study population. This is an ongoing study and we hereby report the preliminary results.

2. Material and Methods

2.1. Study population:

We recruited 128 indexes (34 Females and 94 Males) from 6 specialized institutions across Kinshasa Clinical classification:

A. Recognizable syndromes with known etiology: 19 (14.84 %) (17 Down Syndrome, 1 Williams Syndrome and 1 Partington Syndrome)
B. Syndromic without recognizable etiological diagnosis (≥3 minor dysmorphic features or at least 1 major feature + Minor(s)): 50 (39.06 %)
C. Non-Syndromic: 54 (42.18 %)
D. Probably Environmental / Non-genetic: 5 (3.90 %)

IQ was available only for 35 patients: 2 Borderline, 22 Mild, 9 Moderate, 2 Severe, 0 Profound.

2.2. Methods

We used 8x60k Agilent Microarray slides previously used once. These slides were washed on an Agilent Robot for 30 minutes in bath 1 at 35°C (mix of 350 ml of wash buffer 1 and 350 ml of MilliQ water, stirring at speed 7) and 1 minute in bath 2 at room temperature. The experiment followed the manufacturer's procedure except that we extended the labeling period to 22 hours to reach the best QCmetrics. We validated our protocol against the Illumina 8v1 and 4x180 Agilent Microarray slides. Reused slides reported additional false positives calls and all of them were removed when we raised the threshold for report to 350 kb.

3. Results

At current stage 74 patients have been tested with reused 8x60k Agilent Microarrays out of the 109 with idiopathic ID (67.89 % of the cohort). Among the 74 tested patients, pathogenic copy number changes have been detected in 11 (14.86 %).

Table 1. Detection rate of pathogenic CNV for each clinical group.

Idiopathic ID (109 indexes)				
Categories	Definition	n	Tested	Pathogenic CNV (%/74 tested)
B	Syndromic without recognizable etiological diagnosis	50	38	7 (9.46 %)
C	Non Syndromic	54	34	4 (5.40 %)
D	Probably Environmental / Non genetic	5	2	0
Total		109	74	11 (14.86 %)

4. Discussion

Trisomy 21 is the major chromosomal cause for ID in Kinshasa. The detection rate for CMA thus far (14.86 %) in our study is similar to other populations (Wincent et al 2012; Lundvall et al., 2012, Rauch et al., 2006, Devriendt et al., 2003). Majority of detected aberrations are recurrent. Reused slides have shown a reliable output in our study. This is great opportunity to implementing CMA in limited resources setting.

MACROCEPHALY AND OVERWEIGHT IN TWO PATIENTS WITH 1q21.1 TRIPLICATION

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Rearrangements of chromosome 1q21.1 have shown considerable variability in phenotypic expression. Chromosome 1q21.1 duplications (OMIM 612475) have been associated with macrocephaly, learning difficulties, developmental delay, intellectual disability and mild dysmorphic features. Half of these patients have autistic behaviors. Phenotypic features of 1q21.1 deletion patients (OMIM 612474) include microcephaly, intellectual disability, autism, schizophrenia, cardiac abnormalities and cataracts.
Neither the duplication nor the deletion patients have a recognizable phenotype. For other genomic disorders, such as the Somerville-Van der Aa syndrome, the description of rare triplications has helped to define the clinical hallmarks of the disorder. Here we describe two male patients with a 1q21.1 triplication, de novo in the first patient and inherited from the father in the second patient.
The first patient is a 19-month-old boy who was referred to the geneticist because of dysmorphic facial features. He is the first child of non-consanguineous Tunisian parents. He was born with normal parameters, after an uneventful pregnancy. His developmental milestones were not delayed (sitting at 6 months, walking at 15 months). His weight and head circumference are above 97th centile, his height is normal (P50). His active speech is limited to a few separate words in a trilingual situation. Communication skills and language comprehension seems to be normal. There are no oromotor difficulties, feeding problems or behavioral problems. Clinical features include hypertelorism, epicanthal folds, long, mildly downslanted palpebral fissures, a broad, flattened nasal bridge, a short philtrum, and small ears with uplifted lobes. His hands and feet are relatively small. He has short thumbs bilateral but no clear brachydactyly. His skull is normocephalic with bitemporal indentation. He has a low posterior hairline.
The second patient is a 7-year-old boy, born by cesarean section after an uncomplicated pregnancy. His birth weight and head circumference were situated on P25, his length on P5. Because of mild gross motor delay (sitting at 6 months, walking at 18 months) and increasing head circumference (above P95 at age of 14 months) he was referred to a developmental-behavioral pediatrician. The neurological examination is remarkable for hypotonia and hyperflexible joints. There is no developmental regression. MRI of the brain shows some nonspecific abnormality of white matter. Cardiac echogram is normal. He has a history of torticollis, ENT problems (mild subglottic stenosis, submucous cleft palate and laryngomalacia), upper airway obstruction, sleep apnea, autism, gastroesophageal reflux, difficulty eating and a picky appetite. He has an alternating esotropia with lazy right eye. He had bilateral inguinal hernia repair and unilateral undescended testicle surgery. At the age of 18 months his development was normalized, demonstrating good response to physical therapy. Clinical features at age of 7 years include a low anterior hairline with anterior upsweep, generous forehead, cupped ears with uplifted lobes, downturned corners of the mouth and a slightly tented upper lip. He has no hand or feet abnormalities. His weight is above the 96th centile and his height is on the 85th centile.
In conclusion, both patients are macrocephalic and overweight. The diversity of other symptoms observed in these triplication carriers confirms the variable phenotypic presentation of 1q21.1 rearrangements.

DUP (1) (q43–q44) & DEL (21) (q22.2–q22.3) CHARACTERIZED BY FACIAL DYSMORPHISM, CONGENITAL HEART DEFECT AND MENTAL RETARDATION

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We report on the patient with distinctive facial features, congenital heart defect (CHD), brain anomalies, bilateral hearing failure, cognitive and language development delay, emotional instability and carrying a unique chromosomal rearrangement, partial trisomy 1q43–q44 and partial monosomy 21q22.2–q22.3, due to unbalanced segregation of a paternal balanced reciprocal translocation t(1;21)(q43;q22). Both chromosome 1q and 21q imbalances were previously associated with recognizable phenotypes. To our knowledge, combined trisomy 1q and monosomy 21q has not been previously reported.

Our patient is 8-year-old first-born female child of nonconsanguineous parents with complicated family genealogy (her cousin's cognitive and motor development is delayed, paternal grandparent's siblings died during the first year of their lives, paternal grandparent's cousin with congenital cleft lip and palate (CLP)). Her birth weight, length, and occipitofrontal circumference were 3550 g (50^{th} percentile), 53 cm (50^{th} percentile) and 37cm (97^{th} percentile), respectively. Apgar scores were 8 at 1 and 5 minutes. Macrocephaly, bilateral CLP, CHD (atrial septal defect, bicuspid aortic valve), talipes and joint hypermobility were identified in neonatal period. Bilateral cleft lip was operated only at 6 months of age due to the recurrent respiratory infections, cleft palate was operated at the age of 2 years. The patient's development milestones were delayed and she expressed poor motor skills, coordination, emotional instability. The primary imunodeficiency, aortic root and ascending aorta enlargement were diagnosed at the age of 6 years. Narrowing external auditory canal, bilateral hearing failure and rhinolalia were also diagnosed. At 7 years of age, strabismus, astigmatism, anisocoria and congenital nuclear and posterior subcapsular cataract were identified. Brain magnetic resonance imaging (MRI) revealed expressed internal and external hydrocephaly, mega cisterna magna and stenosis of aqueductus cerebri. Patient's current phenotype expresses macrocephaly, triangular face, hypertelorism, downslanted palpebral fissure, especially of the left, scar after bilateral CLP repair, hemangioma in the medium of the lower lip, nipples position asymmetry, joint hypermobility. Chromosome analysis of peripheral blood lymphocytes revealed normal karyotype. Subtelomeric multiplex ligation-dependent probe amplification (MLPA) screening revealed the duplication in 1q44 and deletion in 21q22.3. Whole genome genotyping analysis of the patient showed a duplication in the region 1q43–44 and a deletion in the region 21q22.2–22.3 with sizes 8.4 Mb and 6.8 Mb respectively. Due to the second pregnancy and complicated family history, FISH analysis of amniocytes was performed and revealed identical balanced reciprocal translocation in the fetus as in the father.

The combined effect of deleted and duplicated chromosome segments may produce such combination of phenotypes. The deletion observed in our patient in the distal 21q22.2–q22.3 region involves the genes associated with some of her clinical findings, such as facial clefts, chronic sinopulmonary disease, cataract, strabismus, hearing loss and intellectual deficiency. The partial duplication of the above mentioned region of the long arm of chromosome 1 is a relatively rare chromosomal anomaly, including *RGS7, FH, SDCCAG8, AKT3, COX20, HNRNPU, NLRP3* genes. Additional testing of other members from this family is ongoing.

CARNEY COMPLEX: CLINICAL HYSTORY OF A PATIENT WITH GAIN OF FUNCTION OF *PRKACB*

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Carney complex is mostly due to inactivating mutations of the PKA regulatory subunit RIα (encoded by *PRKAR1A*).
We report the clinical history of a patient with Carney Complex owing to a different genetic etiology.
The patient was the first child of non-consanguineous Italian parents. She was born at 38 weeks of gestation. Her birth weight was 3,360 g. Psychomotor development was normal: she could sit at 6 months, walk and start talking at 15 months. She was operated on for inguinal hernia. She was "shy" with attention deficit disorder, hyperactivity and learning difficulties. We have seen her first at the age of 12 years: she was sent to us with the suspected diagnosis of Peutz-Jeghers syndrome.
At 12 years of age her head circumference was 53.5 cm (50-75th centile), her height 153 cm (50-75th centile) and weight 41.8 kg (50th centile). A lot of pigmented lesions of the skin and mucosae were mainly located in the oral, perioral, periorbital, perianal and genital regions; multiple myxomata were detected in the external ear canals bilaterally and were surgically removed. At that time the diagnosis of Carney Complex was suspected, but the molecular analysis of the gene *PRKAR1A* did not find any mutation.
At 19 years of age, mammary ultrasound showed bilateral myxomata and multiple blue nevi were noted in the vulva. Her head circumference was 57 cm (50-75th centile), height 175 cm (>97th centile), weight 73 Kg (90th-97th centile). Echocardiography, thyroid and renal ultrasound were all normal. Due to the presence of clinical signs of acromegaly, an MRI was carried out and revealed a pituitary adenoma of 8x6 mm. Her corticotropin, cortisol, thyroid hormone and prolactin levels were normal. The growth hormone (GH) level increased (14.9 ng/ml); the levels of IGF-1 and its binding protein IGF-BP3 were also elevated. Somatostatin analogue treatment was started in preparation for transsphenoidal surgery without any significant reduction of the pituitary adenoma. She was operated on at the age of 20 years. The tumor histology was in line with a GH secreting adenoma.
We examined the patient again at the age of 24 years when an adrenal MRI did not show hyperplasia. A CGH-Array showed a *de novo* 1.6-Mb triplication of chromosome 1p31.1, including *PRKACB,* which codes for catalytic subunit beta (Cβ), the second most important catalytic subunit of PKA. The anomaly was confirmed by FISH, which showed the additional genomic material in a de novo supernumerary marker chromosome. Levels of Cβ, but not of Cα, were elevated in the patient's lymphocytes and fibroblasts and in a myxoma of the breast. In her lymphocytes, cAMP increased kinase activity to levels like those in patients with Carney complex caused by *PRKAR1A* mutations. We did not detect *PRKACB* mutations/amplifications in other cases with Carney complex negative for the common loss of function mutation of *PRKAR1A*, but mice carrying a transgene for human *PRKACB* showed increased growth hormone levels.
We suggested that gain of function of *PRKACB,* resulting from the presence of four copies of the gene (instead of the normal two), led to the patient's Carney complex phenotype, given the role of Cβ in PKA function [Forlino et al NEJM, 2014]. The discovery that gain of function mutations in Cα subunit *of PRKA* causes adrenal tumors and Cushing's syndrome only [Beuschlein et al, NEJM, 2014; Cao et al, Science, 2014, Goh et al, NG, 2014;; Sato et al, Sciene 2014], a condition absent in our patient who suffered instead from a pituitary adenoma, makes likely that gain of function of the two main catalytic subunits of PKA, Cα and Cβ, causes distinct, tissue-specific abnormalities with the amplification of Cβ connected to (at least in our patient) with other, nonadrenal features of Carney complex, like skin pigmentation, acromegaly, and myxomas. On the contrary, loss of function mutations RIα leads to the full Carney complex phenotype, including both pituitary and adrenal adenomas.
Our observations demonstrate how the follow-up and clinical evaluation of all the clinical signs in a patient which appear over time are extremely important in leading reason to suspect genetic mechanisms unlike classical ones.

DEFINITION OF 5q11.2 MICRODELETION SYNDROME REVEALS OVERLAP WITH CHARGE SYNDROME AND 22q11 DELETION SYNDROME PHENOTYPES

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Microdeletions of the 5q11.2 region are rare; in literature only two patients with a deletion in this region have been reported so far. In this study we describe four additional patients and further define this new 5q11.2 microdeletion syndrome. A comparison of the features observed in all six patients with overlapping 5q11.2 deletions showed a phenotypic spectrum that overlaps with CHARGE syndrome and 22q11.2 deletion syndrome including choanal atresia, developmental delay, heart defects, external ear abnormalities and short stature. No colobomas or abnormalities of semicircular canals and olfactory nerves were reported. Two male patients had genital abnormalities. We estimated a 2.0 Mb (53.0 – 55.0 Mb) Shortest Region of Overlap (SRO) for the main clinical characteristics of the syndrome. This region contains nine genes and two non-coding microRNAs. In this region DHX29 serves as the candidate gene as it encodes an ATP-dependent RNA-helicase that is involved in the initiation of RNA translation. Screening a small cohort of 14 patients who presented the main features however did not reveal any pathogenic abnormalities of DHX29.

MIXED PHENOTYPE LANGER-GIEDION/CORNELIA DE LANGE IN MICRODELETION 8q23.3-q24.1

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Langer-Giedion syndrome, or tricho-rhino-phalangeal syndrome type II, (TRPS II; MIM:150230) is a contiguous gene syndrome with disruption of genes *TRPS1* and *EXT1* as the more directly related with the phenotype. Cornelia de Lange is a well known dysmorphic syndrome (CdLS) with almost five genes described. Heterozigous mutations of *RAD21* gene are associated with a mild CdLS (CDLS4; MIM: 614701). We present a patient with an interstitial deletion at 8q23.3-q24.1 encompassing *EXT1* and *RAD21* genes, but not *TRPS1*.

The proband is the first gestation from a young, healthy parents. Pregnancy was complicated by fetal growth retardation. Delivery was at 34 weeks gestation. The newborn was a female with weight: 1300 gr (p<3), heigth: 37 cm (p<P3), OFC: 27 cm (p<3), Apgar 6/7. She presented thick eyebrows, bulbous tip of the nose, long philtrum, thin upper lip, large and prominent ears. In the study by a-CGH an interstitial deletion of 2,3 Mb at the chromosomal region 8q23.3-24.1 (Chr8: 116,915,114-119,171,074) was found. The deletion involved, among others, *EXT1* and *RAD21* genes, but not *TRPS1*. Genetic study of both parents was normal and we assumed de novo mutation.

The baby is now 2 year old, and she presents sparse and thin scalp hair, two exostoses (in right 6th rib, right distal tibia) cone-shaped epiphyses, short stature, developmental delay and premature adrenarche. This clinical findings are in fact correlated with a mixed phenotype of TRPS II and CdLS type 4. We have found four similar cases published in the literature. All have a craniofacial with mixed features of TRPSII and CLD4, exostosis, and mild, or border line, developmental delay. In two cases normal height. Premature adrenarche, similar to our patient, was also found in one case.

9q33.3q34.11 MICRODELETION: DELINEATION OF A NEW CONTIGUOUS GENE SYNDROME INVOLVING THE *STXBP1, LMX1B* AND *ENG* GENES ASSESSED USING REVERSE PHENOTYPING

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Five patients, 3 females and 2 males aged 5 to 18 years, carrying a *de novo* overlapping 1.5, 2.7, 2.8, 3.1 and 4.1 Mb deletion of chromosome 9q33.3q34.11 made it possible to define a new contiguous gene syndrome. The patients display common clinical features including facial dysmorphism, epilepsy, intellectual deficiency of varying degrees and multiple congenital abnormalities. Analysis of the genes comprised in the deletions prompted us to use reverse phenotyping. The *STXBP1* gene, in which *de novo* heterozygous mutations or deletions have been reported in patients with Ohtahara syndrome, was the best candidate to explain the cognitive and epileptic phenotype. The *LMX1B* gene, in which heterozygous mutations or deletions have been reported with Nail-patella syndrome, explained the presence of nail dysplasia and bone malformations, in particular patellar abnormalities. The *ENG* gene, in which autosomal dominant mutations or deletions have been reported in patients with Hereditary haemorrhagic telangiectasia type 1, was probably responsible for the epistaxis and cutaneo-mucous telangiectasias described in the oldest patients. The *NR5A1* gene, deleted in one patient only, was probably responsible for his genital malformations. A high genotype-phenotype correlation was found in these 5 patients, except for the remarkable facial dysmorphism, including a prominent metopic ridge, large forehead, high arched eyebrows, strabismus, bulbous nose and small mouth. This systematic analysis of the genes comprised in the deletion allowed us to identify genes whose haploinsufficiency is expected to lead to disease manifestations and complications that require personalized follow-up, in particular for renal, eye, ears, vascular and neurological manifestations.

A NEW CASE OF 9q34.3 MICRODUPLICATION SYNDROME: FURTHER DELINEATION OF THE CLINICAL SPECTRUM

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Chromosome 9q subtelomeric region shows genomic instability, as both 9q subtelomeric region copy number losses and gains have been reported. The 9q34.3 microdeletion syndrome is also known as Kleefstra syndrome, whose core features include moderate to severe developmental delay/intellectual disability, childhood hypotonia and distinct facial features. The syndrome can also be caused by an intragenic mutation in the euchromatin histone methyltransferase 1 (EHMT1) gene causing haploinsufficiency of *EHMT1*. Increased dosage of the same *EHMT1* has been hypothesized as responsible for neurodevelopmental impairment, speech delay and autism spectrum disorders which configure the 9q34.3 microduplication syndrome, so far described in only 20 patients.
We report on a 10 years 10 month-old boy at last follow-up in the autism spectrum (ASD) affected by mild intellectual disability, fine-motor dyspraxia and showing mild facial dysmorphisms (wide forehead, flat nasal bridge, anteverted nares), who recently underwent to surgery for bilateral pes cavus deformity. Neurological examination as well as brain and spinal cord MRI showed no abnormalities.
High-resolution array CGH analysis revealed a *de novo* heterozygous duplication of approximately 527 kb at 9q34.3, encompassing the EHMT1 and CACNA1B (calcium channel, voltage-dependent, N type, alpha-1B subunit) genes, as well as two rare gains, a 400 kb duplication including the full *SYF2* gene at 1p36.11, inherited from the father, and an intragenic 24 kb duplication affecting *IL1RAPL2* at Xq22.3, inherited from the mother. While SYF2 has been implicated in regulation of neuronal apoptosis during neuro-inflammation, IL1RAPL2 encodes an interleukin-receptor with a role in modulating neurotransmitter release from pre-synaptic membrane.
EHMT1 expression assays performed by RT-qPCR on the patient's peripheral blood cells showed a statistically significant increase of the gene expression levels compared to those of ten controls. *CACNA1B* expression assays could not be performed on the patient's peripheral blood, as the gene, which encodes an N-type calcium channel, was found to be specifically expressed in the central nervous system, where it controls neurotransmitter release from neurons.
Trough the molecular characterization of the present patient the correlation between *EHMT1* increased copy numbers and quantitative transcript anomalies, to date only suspected, has been assessed for the first time. Although a possible contribution to ASD of a few CNVs could not be excluded, the autism spectrum disorder has been characterized over time, better delineating the 9q34.3 microduplication syndrome. The feet deformity, already reported in some *EHMT1* haploinsufficient followed-up patients, allows to expand the clinical spectrum of the 9q34.3 microduplication syndrome as well.

OVERGROWTH AND DEVELOPMENTAL DELAY ASSOCIATED WITH A 200 KB DELETION IN 16p11.2 IN TWO FAMILIES

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Due to a high density of segmental duplications, the short arm of chromosome 16 is prone to a number of recurrent rearrangements. A common 600 kb microdeletion or –duplication in 16p11.2 has been associated with autism, intellectual disability, schizophrenia, and mirrored weight and head circumference phenotypes. An adjacent, but separate distal 200 kb region in 16p11.2, which contains the *SH2B1* gene, has been associated with isolated obesity as well as with developmental delay. Both aberrations are associated with high variability and incomplete penetrance.
We now report on two families harbouring the 200 kb microdeletion in 16p11.2. A 5 years 9 months old girl was referred to our clinics with suspected Sotos syndrome due to tall stature and developmental delay. Birth measurements were unsuspicious but at time of consultation her height and weight were above the 97th centile, and bone age was advanced by 18 months. She could walk with 18 months, started to speak with 20 months and attended special school due to learning disabilities at the age of 7 years. Whereas *NSD1* testing revealed normal results, molecular karyotyping showed the 200 kb deletion in 16p11.2, which was inherited from the healthy mother.
The second family consisted of a 12 year old boy with unspecific mild to moderate intellectual disability and mild obesity and his 4 year old half-sister with severe obesity, tall stature, macrocephaly and mild motor delay. Due to suspected Sotos syndrome in the girl, *NSD1* testing was performed in her and was normal. Molecular karyotyping revealed the 200 kb deletion in 16p11.2 in both siblings. Interestingly, the girl, but not the cognitively more severely affected boy, additionally harboured a microduplication 1q21.1, which has been recurrently associated with variable and incompletely penetrant developmental delay, ID, behavioural anomalies and large head circumference. Both aberrations were inherited from the mother, who was obese but otherwise healthy and without cognitive problems.
These two families further characterize the variable spectrum of phenotypes associated with the 200 kb microdeletion in 16p11.2. Our findings in family 2 also show that not even the co-occurrence of two ID-associated microaberrations necessarily leads to cognitive impairment.

EVALUATION OF DISTAL 22q11 DELETION AND DUPLICATIONS. A HIGHLY VARIABLE PHENOTYPE

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Chromosome 22 is rich in segmental duplications that mediate recurrent genomic rearrangements, notably the 22q11 deletion associated with velocardiofacial syndrome (diGeorge syndrome). Over the last few years, a number of patients with recurrent atypical distal deletions and duplications have been described. These genomic aberrations are located distally to the common recurrent ~3Mb region implicated in the velocardiofacial syndrome.
However, the observed phenotypes within the atypical distal deletion and duplication regions do not seem to be consistent. The copy number changes have been observed in phenotypically normal individuals. The inconsistencies in clinical presentation and the presence of the copy number change in unaffected family members could be due to factors such as incomplete penetrance, variable expressivity or a failure to recognie more subtle manifestations of a phenotype. Therefore, this region poses a challenge for diagnostic interpretation
Due to the diversity of published clinical features for these recurrent rearrangements and reports of asymptomatic parental inheritance, we present a retrospective evaluation of a case series of patients with 22q11 distal deletion syndrome with additional prenatal cases to identify the common clinical features and to discuss the difficulties of genetic counseling the 22q11 distal deletion syndrome.

X-LINKED AGAMMAGLOBULINEMIA AND MOHR-TRANEBJAERG SYNDROME (XLA-MTS): A RARE CONTIGUOUS GENE SYNDROME CAUSED BY A DELETION OF THE GENES *BTK* AND *TIMM8A*

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X-linked agammaglobulinemia (XLA) is a genetic disorder characterized by early-onset and recurrent bacterial infections with marked reduction in all classes of serum immunoglobulins, and absent B cells in affected males. XLA is caused by mutations in the gene *BTK* located at Xq21.1. Mutations consist of point mutations in around 92% of cases, and partial- or whole-gene rearrangements, mainly deletions, in 8% of cases. Mohr-Tranebjaerg syndrome (MTS) is a much rarer X-linked condition with around fifty cases in the literature. It is a neurodegenerative disorder characterized by sensorineural deafness, progressive dystonia and optic atrophy, and is therefore also called deafness-dystonia-optic neuronopathy (DDON) syndrome. It is caused by mutations in the gene *TIMM8A* which is located close to the 3' end of *BTK*.

We report a patient in whom the diagnosis of XLA was made at the age of 6 months, and confirmed by MLPA which identified a deletion of the last 9 exons of *BTK*. The mother and maternal grand-mother were shown to carry the deletion, and these results allowed genetic counselling in the maternal family. The patient had then language delay and severe progressive bilateral deafness was diagnosed at 5 years and required cochlear implant at 9. He further developed motor difficulties in daily life and in writing, which lead to the diagnosis of left upper limb dystonia. The patient was referred to the genetics department where the diagnosis of the contiguous gene deletion syndrome XLA-MTS was suggested. This hypothesis was confirmed by array-CGH (Agilent 180K) analysis which showed a 9.96 kb deletion encompassing the 3' end of *BTK* including exons 11-19 and *TIMM8A*.

The XLA-MTS deletion syndrome has already been reported in the literature in 16 patients from 13 families. It is caused by deletions of the Xq22 region, probably involving Alu sequences, which are responsible for a disruption of *BTK*. The deletions reported vary from 20 to 196 kb and remove the 3' end of *BTK*, *TIMM8A* and in some cases two other genes located downstream, *DRP2* et *TAF7L*.

This observation illustrates that, in case of XLA caused by a mono- or multi-exonic deletion involving at least the last exon of *BTK*, it is important to think about the possibility of this contiguous gene deletion syndrome which changes the prognosis, and to look for a larger deletion with an appropriate method. More generally, it shows that one should be cautious in all situations of genetic diseases due to deletions involving the first and/or last exons of a particular gene which are detected by targeted analysis. Indeed, usual technics used for detection of gene rearrangements (such as quantitative PCR, MLPA, QMPSF, …) do not determine the precise breakpoints when they are located outside the gene. Thorough analysis of the literature and of genome data, and additional molecular investigations, particularly for genes which are known to be involved in contiguous gene deletion syndromes, are necessary in order to provide an appropriate care to the patient and accurate genetic counselling to the whole family.

Xq26.2q26.3 MICRODUPLICATION IN A BOY WITH DEVELOPMENTAL DELAY, DISTINCT FACIAL APPEARANCE AND GENITOURINARY ABNORMALITIES

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The phenotypic consequences of functional disomy of X-chromosome genes in men remain mostly unknown. We here report on a 5-year-old boy with a a 0.77 Mb Xq26.2q26.3 microduplication, encompassing the whole coding sequence of the *PHF6, HPRT1, PLAC1* genes and the first exon of the *GPC3* gene. The duplication was inherited from the phenotypically normal mother and not detected in two healthy maternal brothers. The boy presented with global developmental delay with no speech, stereotypic movements, autoagression, facial dysmorphic features, clinodactyly of toes, micropenis and hypoplastic scrotum. The phenotype of the reported patient shares some features with recently reported microduplication syndrome of Xq25q26 (Møller et al., 2014), like prenatal growth retardation, genital abnormalities, digital malformations and intellectual disability, but not the short stature, microcephaly, and facial features. The smaller size of duplication with only partial duplication of the *GPC3* gene is a possible cause of phenotypic discrepancies. The genotype – phenotype correlation of the present and the reported individuals will be presented.

CONGENITAL NEPHROTIC SYNDROME: NOT ALWAYS THE FINNISH TYPE!

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Congenital nephrotic syndrome (CNS) is associated with alterations in podocyte associated genes, which usually are mutations in the NPHS1 or NPHS gene. We report a case of a newborn girl autopsied with a CNS in 1993. Twenty years later, on request of her sister, the case was revised and further molecular analysis was performed in the framework of genetic counselling. We detected an uncommon mutation in the WT1 gene, which is a seldom cause of CNS and responsible for Denys-Drash Syndrome - a clinically variable disorder of the urogenital system with the triad of CNS, structural urogenital anomalies and risk of Wilms tumor development.

Methods:
Use of long-term stored formalin-fixed paraffin embedded tissue detecting a WT1 mutation and XY-genotype with sophisticated molecular techniques (FISH, PCR and genome-sequencing).

Results:
Focal segmental and global glomerulosclerosis, with extensive foot process effacement at electron microscopy, confirmed the previous diagnosis of CNS. Molecular study of isolated DNA showed, to our surprise, a XY-genotype. As the phenotypic female newborn had a uterus didelphys we concluded it was an intersex child, which occurs in 30% of cases of DDS. Therefore, WT1 mutation analysis was performed on the long-term stored formalin-fixed paraffin embedded tissue, detecting a missense 1097G-A (Arg366His) mutation in the WT1 gene, which was not found in the parents or the sister.

Conclusion:
This is the first case of CNS caused by Denys-Drash syndrome, where the uncommon missense 1097G-A (Arg366His) mutation in the WT1 gene, was diagnosed on long-term stored formalin-fixed paraffin embedded tissue.

MOLECULAR GENETICS OF PATIENTS WITH OCULOCUTANEOUS ALBINISM

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Oculocutaneous albinism (OCA) is an autosomal recessive disease affecting 1/17000 person in the general population. It is characterized by hypopigmentation of the skin, hair and eyes. The main handicap in patients is at the ophthalmologic level (nystagmus, reduced visual acuity, photophobia, foveal hypoplasia). There are nowadays 6 known OCA genes (TYR, OCA2, TYRP1, SLC45A2, SLC24A5, C10ORF11) (OCA1,2,3,4,6,7 respectively). An OCA5 locus has been localized, but the gene is not known yet. Apart from the OCA types, an X-linked ocular albinism gene (OA1, GPR143) as well as 10 genes involved in syndromic forms (Hermansky-Pudlak Syndrome, Chediak-Higashi Syndrome) of albinism have been identified. It should be noted that recently mutations were identified in the SLC38A8 gene in patients with FHONDA (on autosomal recessive form of ocular albinism).
We routinely search for mutations in the OCA1, 2, 3, 4, 6, 7, OA1 and HPS1 genes. Analysis involves the search for both point mutations and gene rearrangements (very high-resolution array-CGH). The study of over 400 patients showed the following representation of the different types of albinism: OCA1 (36%), OCA2 (25%), OCA3 (2%), OCA4 (11%), OCA6 (1.25%), OCA7 (0%), OA1 (6%), HPS1 (1%). 17.75% of patients remain without a molecular diagnostic either because they present only one mutation (6%) in one gene or because they do not have any mutation at all in the genes analyzed (11.75).
This suggests three main alternative hypotheses. First of all the patient may have a hitherto clinically undiagnosed form of syndromic albinism. For this reason, we are now analyzing all 18 known albinism genes (plus 9 genes for Waardendurg and Griscelli Syndromes) by next generation sequencing in the diagnostic laboratory (PGM, Ion Torrent, Life Technologies). Secondly, mutations may reside in unexplored regions of the genes (regulatory sequences, introns). We have sequenced the whole of the OCA1-4 genes (exons, intron, flanking regions); preliminary data will be presented. Finally, it is likely that additional OCA genes remain to be identified. Exome sequencing has been undertaken to find new OCA genes.
Following the original example of colleagues in Milan (Italy), we have started in Bordeaux an Albino Day. In one day patients have all evaluations performed, at the genetic (counselling, genetic test), dermatological (evaluation of phototype, naevus and photo protection) and ophthalmological (visual acuity measurement, refraction study, optical coherence tomography of the retina and visual evoked potential) levels during one day include dermatological examination with.
This precise evaluation is necessary to improve the management of the albino patients, thus allowing a better delineation of the phenotype and helping for the evaluation of phenotype -genotype correlations, although this is be rendered difficult by the high number of genes involved in the pigmentation process, and that may act as modifiers of the phenotype.

A PATIENT WITH A PATERNAL UPD-14 LIKE PHENOTYPE DUE TO MATERNAL 14q MICRODELETION

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We describe a 14q32 microdeletion detected in a patient with severe developmental delay, feeding difficulties, growth retardation, progressive scoliosis and dysmorphisms and his normal mother.
He was a male, second child of non consanguineous Indian parents. A sister born preterm was dead due to cerebral hemorrhage. The pregnancy had a normal course until the 33th week, when sudden rupture of membranes happened and caesarean operation was organized. At birth, he showed breech presentation and respiratory distress, so ventilation and resuscitation were necessary. His birth parameters were: weight 1.970 kg (25-50th centile), length 43 cm (25th centile), head circumference 33 cm (90th centile), Apgar score 2(1 min)-4(5 min)-6(10 min). He had chronic breathing difficulties, with relapsing lung atelectasis. He had also severe feeding problems, he was alimented via PEG and at 4 months of age he underwent surgery for pyloric hypertrophic stenosis. He had severe developmental delay and hypotonia (not able to control his head at the age of 5 months). Physical examination at age of 5 months showed: hyposomia (weight, length and head circumference below 5th centile), frontal hypertrichosis, horizontal palpebral fissures, mild synophrys, thick eyebrows, bulbous nose with anteverted nostrils, full cheeks, thick gums, large ears with overfolded helix and hypoplastic lobes. He had long fingers and slight 3rd left finger campodactyly, raised 2nd toe, bilateral inguino-scrotal hernia, hypotrophic muscle mass and severe hypotonia. He also showed very severe cervico-thoracic scoliosis with an important torsional component and gibbosity. The baby died suddenly at home at 6 months of age.
Cerebral ultrasound showed “ventricolomegaly and poor gyrations”. Brain MRI showed “simple cortical circumvolutions in frontal regions, point lesions of periventricular malacica suffering, slight corpus callosum”. “More distal origin of sovraortic vessels” was noted at thoracic CT. Fundus oculi noted “pale papilla”. Echocardiography showed “persistent fetal circulation, endocardial hyperechogenicity in right papillar muscles”. Orthopedic and physiatric evaluations noted “progressive scoliosis in cervicodorsal region, with important torsional components, right gibbosity”. The following analyses were normal: abdominal ultrasound, tracheobroncoscopy, plasmatic dosage of acylcarnitines, aminoacids, mucopolysaccharides, 7-dehydrocholesterol, urinary CMV and standard karyotype.
Array-CGH analysis revealed in the proband a 14q microdeletion (del(14)(q32.2q32.31)) of about 130Kb and a 2q microduplication (dup(2)(q14.3)) of about 72.4Kb. The microdeletion on chromosome 14 was inherited from the healthy mother, while the microduplication on chromosome 2 was inherited from the healthy father.
Though little knowledge is present in literature about this rare condition, we know that the deleted region on chromosome 14 contains several imprinted genes. In particular three of them, MEG3, MEG8 and RTL1as are expressed only by the maternal allele (Ogata T et al 2008, Kagami M et al 2010). Till now about 7 patients are described with a 14q32 maternal deletion and clinical features similar to those of paternal UPD14 (polyhydramnios, small bell-shaped thorax, dysmorphic facial features, skeletal anomalies, diastasis recti, hypotonia, developmental delay, poor prognosis) (Sutton VR et al 2000, Kagami M et al 2008, Kagami M et al 2010).
According to current knowledge, we can speculate that the healthy mother has inherited the deletion from her father and that the clinical effects generated by the del(14)(q32.2q32.31) are causative of the phenotype, similar to that generated by another mechanism, UPD14. The diagnosis was important for the recurrence risk of the family and for the possibility of prenatal diagnosis in successive pregnancies of the family.

DESCRIPTION OF SEVEN NOVEL PATIENTS WITH SCHINZEL-GIEDION SYNDROME AND MUTATION IN SETBP1 GENE. FURTHER DELINEATION OF THE NEURORADIOLOGICAL PHENOTYPE

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Schinzel-Giedion syndrome was first described in 1979, and is characterized by typical facial gestalt, severe developmental delay, visceral malformations (heart, urinary tract, genitalia and skeletal). Patients usually have short lifespan. Facial characteristics are coarse face, large forehead, hypertelorism, midface hypoplasia, protruding eyes, anteverted nares, dysplastic ears, hirsutism. Hydronephrosis is frequent, as are genitalia anomalies. Congenital heart defect are often minor. Skeletal anomalies comprise occipital synchondrosis, hypoplastic pubic bone or ossification delay. Certain patients developed embryonic tumors (mainly Primitive NeuroEndocrine Tumor). As for neurological characteristics, patients display severe developmental delay, and microcephaly is sometimes present. Epilepsy is frequent. Different cerebral malformations are described such as ventriculomegaly, hypoplastic or absent corpus callosum, cortical atrophy.
In 2010, *SETBP1* gene (located in 18q12.3) was identified as responsible for Schinzel-Giedion syndrome, by exome approach. Reported molecular anomalies are *de novo* missense mutations, some recurrent, all localized in the same protein domain, homologous to SKI oncogene.
We present 7 novel patients with Schinzel-Giedion syndrome (4 girls and 3 boys) with mutation in *SETBP1*. Previously reported mutations were identified in 4 patients (p.Asp868Asn, p.Gly870Ser, p.Ile871Thr) and the 3 others were novel (p.Ser869Thr, p.Ser869Arg, p.Gly870Cys). The novel mutations are, as all the previously described mutations, localized in the known mutational hotspot.
All patients had typical facial gestalt, severe developmental delay, epilepsy and genitourinary anomalies. All but one had hydronephrosis, the remaining patient developed coralliform lithiasis and has developed no hydronephrosis to date. We confirm the frequent previously reported neuroradiological features such as ventricular dilation, abnormal corpus callosum and/or septum and cortical atrophy. Abnormal gyration was also seen in several patients as already described. However, patients in our series seem to display similar posterior fossa anomalies such as hypoplastic pons, enlarged medulla oblongata, sometimes associated to cerebellar hemisphere dysplasia. Also, most of our patients had small caudate nuclei.
These seven novel cases further delineate the clinical and molecular spectrum of Schinzel Giedion syndrome, in particular the neuroradiological phenotype.

IS EXOME SEQUENCING OF SINGLE PATIENTS WITH INTELLECTUAL DISABILITY AN EFFECTIVE DIAGNOSTIC STRATEGY?

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Trio-sequencing can be used in all disorders, and has particularly proven its value in finding causes of intellectual disability (ID) or multiple congenital anomalies. In contrast, we investigated whether sequencing only the affected patient without parents is sufficient to find the causative mutation, leading to a considerable reduce in costs. In this study, we enrolled 36 patients with unexplained ID or multiple congenital anomalies, and sequenced the exome. The exome sequences were analysed with a stringent post-sequencing annotation pipeline including an ID gene panel of ~500 genes for filtering of the data. All remaining variants with a potential clinical consequence were validated by Sanger sequencing and tested in the parents for inheritance.
After variant filtering we noticed an average of 13 variants per patient (range 2 to 27) requiring further clinical interpretation. The majority of these variants were inherited from one of the parents. Hitherto, we identified 5 *de novo* mutations and 1 homozygous mutation in 36 patients (17%).
These results can be roughly divided in 3 categories, with a mutation in:
- a well-known gene, however the associated syndrome was not recognized in the patient,
- a known gene, but the clinical course of the patient is not accordance with the documented phenotype,
- a gene that is not yet linked to a phenotype and consequently little information can be found.

Our series contains examples in all 3 categories, they will be presented and discussed.
In our approach, without exome sequencing the parents, a relatively high amount of potentially pathogenic variants remain. All these variants require clinical interpretation which is very time-consuming, while most of these variants were likely benign because they turned out to be inherited from one of the parents. With trio-analysis inherited variants can be filtered out suggesting that this strategy, at this moment, is more efficient in identifying the causative variant.
In the future when databases are filled with more and more exome data and consequently with more rare benign variants, exome sequencing single patients will become a more realistic diagnostic approach.
Currently, we are trio-sequencing this series to determine whether that approach will result in more mutations explaining the phenotype.

NEW CASE OF BIALLELIC TRMT10A DEFICIENCY IDENTIFIED BY EXOME SEQUENCING CONFIRMS THE ASSOCIATED PHENOTYPE OF PRIMARY MICROCEPHALY WITH INTELLECTUAL DISABILITY AND SHORT STATURE

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Recently a mutation in the *TRMT10A* gene was identified in a large consanguineous family of Moroccan origin defining a new syndrome of young onset diabetes, short stature and microcephaly with intellectual disability. By linkage analysis and exome sequencing a homozygous nonsense mutation was identified in all three affected siblings. The protein encoded by *TRMT10A* (also *RG9MTD2*), which was proposed to have tRNA methyltransferase activity, was shown to be ubiquitously expressed with enriched levels in the affected tissues brain and pancreatic islets and to be absent in lymphoblasts from the affected siblings. We now report a new case of biallelic *TRMT10A* deficiency in a girl born to apparently non-consanguineous parents of Kosovo origin. By exome sequencing in our patient we identified a homozygous nonsense mutation (c.379C>T) in the *TRMT10A* gene. Of note, this is the same mutation as recently reported, introducing a premature stop codon at position 127 of the protein. Our patient presented with primary microcephaly, intrauterine onset borderline growth, mild intellectual disability and fine motor problems, a high palate with uvula bifida and minor facial features such as long narrow face with narrow palpebral fissures, long thin nose and small mouth. At age 4 years a seizure disorder started. Notably, at age 8 years, our patient did not yet manifest diabetes, which was of adolescent onset in the previously described family. In conclusion, our report of a novel patient confirms the phenotype of the novel syndrome associated with biallelic *TRMT10A* deficiency including short stature and microcephaly with intellectual disability.

PIGA MUTATION IDENTIFIED BY WES IN A BOY WITH OVERGROWTH, EPILEPTIC ENCEPHALOPATHY AND DYSMORPHIC FEATURES

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Short formal case report:
We present a boy with prenatal overgrowth (BW: 5276 g, GA 38+&), hypotonia, early onset severe epilepsy with apnoea, and dysmorphic features. He deceased 1 11/12 years old.
Whole exome sequencing, as part of a trio analysis, was performed and a splice site mutation (c.13+1G>C) was found in PIGA (in Xp22). His healthy mother carried the mutation and it was found to be de novo in her.

Only few patients with mutations in PIGA at Xp22 have been published yet. The case will be presented as a short formal case report, and will add to the emerging clinical picture.

CTNNB1 RELATED NEURODEVELOPMENTAL DISORDER, A RECOGNIZABLE SYNDROME

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We present a toddler girl with developmental delay and distinct morphological and neurological symptoms that was diagnosed after exome sequencing as related to a mutation in the gene encoding β-catenin (CTNNB1).
Recent research in the mutant mouse (Tucci et al., 2014) demonstrated the consequences of β-catenin dysfunction throughout development as the result of decreased cadherin interaction, decreased interhemispheric connections, with deficits in dendritic branching, long-term potentiation and cognitive function. In childhood developmental delay associated with a complicated neurodevelopment CTNNB1 mutations represent a distinct syndrome with intellectual disability, childhood hypotonia, progressive spasticity of lower limbs, and abnormal craniofacial features in adults.

A NOVEL KAT6B MUTATION; EXPANDING THE PHENOTYPE?

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Introduction: *KAT6B* mutations have been identified in individuals affected by Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS or Ohdo syndrome, OMIM #603736) and the more severe GenitoPatellar Syndrome (GPS, OMIM #606170). We present a case with a novel *KAT6B* mutation.
Case description: The boy was the first and only child of healthy non-related parents. Family history was unremarkable. Pregnancy and delivery at term were normal. Birthweight 2840 g (3^{rd}-10^{th} centile) In the first week he presented with feeding problems, flexion contractures at hips, clenched fingers, overlapping toes, small mouth, long philtrum and short palpebral fissures. Chromosome analysis and array-CGH were normal. At the age of 3 months he had surgery because of a sigmoid volvulus. He developed severe feeding difficulties with failure to thrive, a laryngo- and pharyngomalacie, short stature, mild contractures in elbows and knees, a mask-like facies, nocturnal hypoxia, hepatic fibrosis and had unexplained fever, leukocytosis and thrombocytosis. His motor development was delayed and he could only communicate by sign language. He died at the age of 3.5 years due to respiratory insufficiency.
Methods and results: Whole exome sequencing was performed. A novel de novo variant was detected in intron 9 of the *KAT6B* gene affecting a splice donor site (c.2115+2T>A).
Discussion and conclusion: We found a novel *KAT6B* mutation in a boy in whom no diagnosis could be made during life, despite extensive (metabolic and genetic) investigations. The splice site variant in this highly conserved amino-acid is predicted to be deleterious and may lead to exon skipping and disruption of the open reading frame. Mutations leading to SBBYSS occur throughout the gene (proximal to the last exon or more distally in the last exon) and lead to nonsense mediated decay resulting in reduced protein levels (haploinsufficiency). Mutations seen in GPS lead to expression of a truncated protein and are considered gain of function mutations. Our patient showed several features seen in SBBYSS, although hepatic fibrosis, leukocytosis and thrombocytosis have not been described before. We expect that next generation sequencing techniques lead to a broader phenotype of *KAT6B* mutation carriers.

BROADENING THE PHENOTYPE OF *SOX2* MUTATIONS AND MICRODELETIONS BY ARRAY ANALYSES AND EXOME SEQUENCING

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We report on two German patients with intellectual disability but no anophthalmia/microphthalmia. Both patients were identified by a German cooperative study on patients with intellectual disability (www.german-mrnet.de) and a follow-up study.
The first patient is the second child of healthy, non-consanguineous German parents. He was born at term after a pregnancy complicated by vaginal bleeding. Birth measurements were normal. Cerebral and vitreous bleeding and a persistent bilateral arteria hyaloidea were diagnosed. The patient has a broad forehead and a mild ptosis of his left eye. The right ear is small, dysplastic and low set, the left earlobe protruding and the patient is deaf. He has psychomotor delay (sitting with 2 years, no waking with 2 ½ years, first words with 2 ½ years). Body measurements were normal until the age of 2 ½ years. Microarray, *CHD7* and *EFTUD2* analyses gave normal results. Exome sequencing revealed a de novo C>T transition in the protein coding region of *SOX2*, c.335C>T (chr3:g.181,430,483C>T). This substitution causes an amino acid exchange p.(Pro112Leu) which is predicted to be deleterious by the three prediction algorithms PolyPhen-2 (score 1.0), MutationTaster (score 0.999) and SIFT (score 0.00).
The second patient is the first child of healthy, unrelated German parents. After a pregnancy complicated by bleeding the girl was born at term by cesarean section with normal birth measurements. She had a high forehead, a flat midface, a broad nasal bridge and a small mouth. Body measurements were normal throughout her life. Motor and speech delay were noted (IQ 40 WISC at age 14 years). At the age of 2 years epilepsy was diagnosed and a treatment with valproic acid was started. Comparative genome hybridisation analysis revealed a de novo 235 kb deletion within chromosome band 3q26.33 (chr3:g.181,225,746_181,460,587del) containing only *SOX2* and parts of *SOX2-OT*.
Both patients present with intellectual disability but without the characteristic ophthalmological manifestations expected in patients with point mutations in *SOX2*. This is in accordance with the description of patients with larger microdeletions of the region that do not show microphthalmia /anophthalmia and leads to the recommendation to include *SOX2* gene in intellectual disability gene panel investigations.

FEATURES OF A PATIENT WITH ARID1B MUTATION

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We present a boy with ARID1B-mutation detected by trio sequencing. Corpus callosum agenesis was detected in utero. After birth the patients showed psychomotor retardation, hypotonia, and a range of dysmorphic features: broad nasal bridge, large eyes, thin upperlip, broad philtrum, uplifted earlobes, adducted thumbs, long fingers, and fetal pads on fingers and toes, Investigations were performed for L1 syndrome, Pitt Hopkins syndrome, and Mowat Wilson Syndrome, all with normal results. Finally a trio-analysis showed a de novo 2 bp deletion in the ARID1B-gene. The patient is presented and related to the current literature on ARID1B mutations.

MODERN DILEMMAS; IMPACT OF UNCERTAIN FINDINGS ON A SECOND GENERATION

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With the advent of whole genome approaches to diagnosis either using array CGH or exome/whole genome sequencing the underlying causes of problems in our patients are being identified in unprecedented numbers. However, whilst for many families we are providing the information they want, for others we are giving them further worries by identifying significant but unanticipated diagnoses unrelated to the presenting problem. Individual departments and international initiatives are examining how best to deal with these issues in terms of consent and disclosure. A further category of results stemming from whole genome approaches are findings where the relevance to the presenting problem is uncertain. In general these will be clarified in time as more data accumulates, but when they are found in patients of reproductive age the anxieties raised for the whole family in a pregnancy can be considerable. I will give two interesting examples of this type of dilemma in families I have known for many years.

Family 1

RP, first seen in 1999 as an 11 year old girl with mild intellectual disability, a large head and facial dysmorphic features. No cause was identified. Mother made many diagnostic suggestions over the years. Reviewed at age 20 years at request of parents, further investigations done but no cause found. Presented (with her parents) at 25 years old when she was 21 weeks pregnant. Array studies revealed a small de novo deletion of 9p (9p23p22.3(13,974,415-14,286,259)) which included one OMIM gene, *NFIB.* The relevance of this finding was uncertain and we did not do tests in pregnancy or in the newborn baby (who looks just like her mother with a weight and length on 50th centiles but OFC on 90th centile but is making normal progress). *NFIB* is of course related to *NFIX* which depending on the type of mutation can cause a Soto-like syndrome or Marshall-Smith syndrome.

Family 2

SJ was born in 1991 with split hand and foot syndrome involving all four limbs; I saw her soon after birth and found no evidence of other syndromic features, her parents were normal and there was no family history. At 13 years she developed epilepsy and responded to Tegretol, she also had depression and extremely low self-esteem and was prescribed fluoxetine. She presented again aged 20 years (accompanied by her parents) when she was 22 weeks pregnant, a scan having revealed that her baby had split hands and feet. Array studies revealed a duplication at 10q24.32 (arr10q24.32(102,959,324-103,443,018)x3dn) which has been described in SHFS but she also had a duplication at 22q13.33(49,436,136-49,525,079)x3dn containing two OMIM genes ACR and SHANK3. We decided not to test the baby after birth since he clearly has the 10q duplication associated with SHFS but if he has the other duplication we were concerned the family would link this to SJ's epilepsy when there is no evidence for such a link.

In neither family has there been a demand for testing the babies, and the new grandparents have been exceptionally supportive to their vulnerable daughters. Was non-testing the right approach?

DIFFICULTIES IN INTERPRETING MOLECULAR FINDINGS IN FNLB GENE AND PREDICTING THEIR CONSEQUENCES IN TWO FAMILIES WITH LARSEN SYNDROME

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We report two families where the index patients had rather mild but typical findings of Larsen syndrome but there were other mutation carriers in the family with very mild or absent clinical picture. The index patient in Family 1 had anterior subluxation of both knee joint (elongated anterior and medial collateral ligaments in MRI); these were corrected at the age of 7 years. In addition, he had slight ulnar deviation of wrists, drum-stick fingers and dysmorphic (broad and medially curved) feet needing special shoes. His father had similar joint problems. The younger sister also showed abnormal shape of feet but no other features suggesting Larsen syndrome. The father is tall (188 cm), the children are of average height. The father and both children carried in FBLN gene the mutation c.4718T>C (p.Ile1573Thr) in exon 27. This has not been described before but can be predicted to be damaging and thus pathogenic.
In family 2, the index child had features suggesting Larsen syndrome, including bilateral luxation of the knees and hyper-extensible joints. A variant in FLBN gene was found, c.3522G>A p.(Ser1174Ser) in exon 21 but the same mutation was seen also in the mother's DNA. The variant exists in 1000Genomes and ESP databases, the frequency is < 0.01. The variant can create a new splice acceptor site and thus it can be pathogenic. The mother has not (yet) been investigated by us but she considers herself healthy.
Similar to a majority of syndromes, when molecular diagnostics become widely used, the segregation of the mutations in the families reveals also milder cases, as in our Family 1. On the other hand, in case of some variants it may be difficult to interpret whether the healthy carrier in the family suggests

MULTIFACTORIAL FAMILIAL INTELLECTUAL DISABILITY: A CLINICAL STUDY IN SCHOOLS FOR SPECIAL EDUCATION

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Children attending special schools often have one or more siblings also attending this school, especially when one or both parents also followed special education. To gain more insight in this type of 'familial' intellectual disability (ID), we retrospectively analyzed the clinical and genetic data from 151 children examined in a standardized way in 4 different Flemish schools during the years 2011-2013. These nursery and primary education schools accept children from 3-12 years with mild to severe ID.

We included 151 children, 102 boys and 49 girls. 19 children had one (n=18) or two (n=1) siblings attending the same school. From these 131 separate families, the oldest child was included as index.

The study group consists of the 43 index cases having at least one parent with "ID". We used a clinical, operational definition of ID, i.e. having followed special education and/or sheltered workshop employment. ID was present in the two parents in 23 children, in the mother in 14 and in 6 in the father. The control group were the 88 children with both parents having a normal intelligence.

A much higher rate of etiological diagnoses was made in the cases with normal parents (21/88, 24%) versus the study group (3/43; 7% - one inherited HUWE1 duplication, one de novo 2.37Mb duplication including ARID1B and one XYY). There was no difference in percentage of susceptibility CNV's detected by array-CGH (4/43 in cases; 7/88 in the controls).

Of the 19 families where two (n=18) or 3 (n=1) children attended the same school, we were able to study the concordance in phenotype and results of genetic testing. In the 3 families with normal parents, there were three brother pairs who presented the same phenotype but unknown diagnosis and normal microarray. There was one monozygotic twin, two brothers were suspected to have the same autosomal recessive condition (parental consanguinity), and two brothers presented macrocephaly. Of the 16 families with parental ID, the phenotype (i.e. dysmorphism, macro- or microcephaly, major malformations, neurological manifestations, …) was concordant normal in 8, concordant abnormal in 4. In 4 sib-ships the phenotype was discordant. Of interest, discordant microarray results were observed in 5 sib-ships, despite the fact that they all had a concordant phenotype (abnormal in 4, normal in one) (i.e. 5 causal variants – del15q11.2, dup ARID1B, dup HUWE1 & del GRIA3- and one unclassified variant class 3 of 4Mb). This illustrates the complex etiology of ID in these families, the difficulty in interpreting genetic studies and the need for empiric recurrence risks.

The empiric recurrence risk for ID was calculated from the proportion of siblings that also followed special education. We thus excluded the index case, 2 sets of MZ twins, and in each of the two groups one outlier family, each having 14 children. The size of the families was the same in the study and control group, with an mean of resp. 2.95 and 2.91, median of 3 in both. In the study group, the 43 cases had 82 siblings, of whom 48 (58.5%) also followed special education. The risk for full sibs (32/57; 56%) was similar to that of half-sibs (16/25; 64%). The risk for needing special education appeared to be higher when both parents had ID (25/37; 67.5%) and when father had ID (9/13; 69%) than when only the mother had ID (14/32; 43%). For the children with normal parents, 10/187 (5.4%) followed also special education, and all were full siblings (10/162). In both groups, few children were too young to be evaluated adequately (respectively 5 and 4 siblings).

These results may guide diagnostic genetic investigations and counselling of families where one or more parents did follow special education or has an ID.

IS A COMPUTER-BASED FACIAL DYSMORPHOLOGY NOVEL ANALYSIS READY FOR THE CLINIC?

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Introduction: Previously, we were able to demonstrate that the *facial dysmorphology novel analysis* technology was successful in recognizing the facial dysmorphology associated with targeted selected syndromes by processing 2D facial images. The computer-generated analyses were able to produce results comparable with those of human experts. In this study we investigated the performance of the system by analyzing a random set of images of dysmorphic individuals affected with a random variety of syndromes.
Methods: The images were submitted by more than a hundred clinical geneticists using the Face2Gene mobile application. For quality assurance purposes, 350 images were chosen randomly to be reviewed (without any personal information included) independently by a single human geneticist experienced in dysmorphology (LBV) and compared to matches found by the facial recognition software. Images of individuals being affected with rare chromosomal imbalances were excluded from this study. A Match was considered positive where the syndrome determined by the human geneticist was also listed among the ten best matches suggested by facial analysis software (either by using FDNA's facial gestalt analysis component or FDNA's textual search engine, based on a list of HPO terms representing facial features automatically detected by the system as the search criteria).
Results: In 52/350 cases (15%), the human expert was able to clearly recognize and determine the presence of a specific genetic syndrome, based on gestalt only. In 44 of these cases (85%), there was a positive match between the system and the human expert; of which 38 cases were suggested by the gestalt analysis and 13 cases were suggested by the feature-based search engine (7 cases were suggested by both modalities). Only 8/52 (15%) cases were recognized by the human expert, but not by the system. It is unknown in how many cases the system recognized the "true" syndrome when the human expert did not, since the vast majority of the cases are submitted without molecular confirmation, other than 2 cases in which a molecular confirmation was indicated, and the system was able to suggest the correct syndrome, while the expert could not.
Conclusions: We conclude that computer-based facial recognition system can successfully assist medical professionals in the research and investigation of genetic syndromes characterized by dysmorphic features. Possible future applications may include usage of facial analysis software to complement molecular studies, such as whole exome sequencing.

A CONTEMPORARY APPROACH TO EXHIBIT A COLLECTION OF TERATOLOGICAL FETUSES OF THE MUSEUM FOR ANATOMY AND PATHOLOGY IN NIJMEGEN

THE USE OF COMPUTED TOMOGRAPHY, MAGNETIC RESONANCE IMAGING AND 3D RECONSTRUCTIONS TO VISUALIZE, DESCRIBE AND EDUCATE

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The Museum for Anatomy and Pathology, part of the Department of Anatomy of the Radboud university medical center in Nijmegen, the Netherlands, houses a pathological collection consisting of almost 900 specimens. This collection gives an almost complete overview of the most common macroscopically pathological diseases from the 20th century. This collection also comprises 70 teratological specimens. Based on external dysmorphological features, these 70 specimens are categorized into 7 subgroups:

1. skeletal dysplasias
2. conjoined and acardiac twins
3. syndromes with multiple congenital anomalies
4. sirenomelia
5. holoprosencephaly
6. neural tube defects and
7. unknown diagnose

At present the pathological collection is poorly described and is in desperate need for modernization to fully exploit its scientific and educational value. Recently, efforts have been made to expand and modernize the Museum. A grant from the 'Reinier Post foundation' was assigned for 'The Anatomical Museum of the Future'. A large new teratological exposition is part of the future vision of the Museum and is partially funded by this grant.

Three Tesla Magnetic Resonance Imaging and Computed Tomography of the teratologic fetuses are made to produce high-resolution images. These images will contribute to complete the diagnoses and to create 3D visceral and osteological reconstructions and prints of internal dysmorphological features for both scientific and educational purposes. In this way, we believe the collection can be helpful in the understanding of normal and abnormal embryonic and fetal development and it can play a significant role in the (bio)medical curricula.

We will present the first preliminary results of the high resolution Magnetic Resonance Imaging in this extensive dysmorphological project. The images seem very promising and useful to create three-dimensional prints. Suggestions and ideas regarding the educational value of the specimens are welcomed.

IMAGING THE COLLECTION OF FETUSES WITH SIRENOMELIA FROM THE TERATOLOGICAL COLLECTION OF THE MUSEUM FOR ANATOMY AND PATHOLOGY IN NIJMEGEN

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The Museum for Anatomy and Pathology is part of the Department of Anatomy of the Radboud university medical center in Nijmegen, The Netherlands. It displays a collection of anatomical preparations and a collection of pathological specimen and is open for medical students as well as other visitors. A small part of the pathological collection consists of fetuses with malformations, the 'teratological collection'.
Six of the teratological fetuses were initially categerorized as 'mermaids'. They display a 'fusion' of the lower limbs, which is the characteristic external dysmorphology of a condition called 'sirenomelia'. Sirenomelia is a rare congenital anomaly characterized by a specific malformation of the lower extremities and commonly associated with severe gastrointestinal and urogenital malformations.
We have scanned these fetuses with high resolution 3 Tesla Magnetic Resonance Imaging and Computed Tomography to have more information about the internal anatomy and (dys)morphology. Most fetuses display, as expected, severe internal dysmorphology of the gastrointestinal and urogenital system, but also malformations of cardiac, cerebral and other systems are found.
In the presentation we will give an overview of the available information of our sirenomelia collection. We hope our investigations will shed more light on the pathogenesis of sirenomelia and its overlap with other congenital anomalies, including caudal dysgenesis and VACTERL association.