28th EUROPEAN MEETING ON DYSMORPHOLOGY

GENERAL PROGRAM

WEDNESDAY 6th 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 7th SEPTEMBER

8.45 a.m.			Opening address
9.00 a.m. to 1.00 p.m.			First and second sessions
	1.00 p.m.	Lunch	
2.30 p.m. to 6.00 p.m.			Third and fourth sessions
	7.30 p.m.	Dinner	
9.00 p.m. to 11.00 p.m.			Unknown

FRIDAY 8th SEPTEMBER

9.00 a.m. to 1.00 p.m.			Fifth and sixth sessions
	1.00 p.m.	Lunch	
2.30 p.m. to 6.00 p.m.			Seventh and eighth sessions
	7.30 p.m.	Dinner	

SATURDAY 9th SEPTEMBER

Breakfast - Departure

SCIENTIFIC PROGRAM

Note: This program is tentative and may be modified.

WEDNESDAY 6th SEPTEMBER

9.30 UNKNOWN SESSION
Chair: VERLOES A.

THURSDAY 7th SEPTEMBER

08.45 Opening address: STUMPEL C.

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

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

09.15 M. POLLAZZON, H. FODSTAD, S. ROSATO, I. IVANOIVSKI, G. COMITINI, G. GARGANO, S. UNGER, A. SUPERTI-FURGA AND L. GARAVELLI
Our experience in multiple congenital contractures: amyoplasia and distal arthrogryposis

09.30 A. MATULEVIČIENĖ, N. KRASOVSKAJA, B. BURNYTĖ, L. AMBROZAITYTĖ, R. MEŠKIENĖ, R. MATULEVIČIŪTĖ, I. KAVALIAUSKIENĖ , A. MORKŪNIENĖ, A. UTKUS AND V. KUČINSKAS
Spectrum of syndromes associated with craniosynostosis in lithuanian cohort

09.45 N. DIKOW, M. GRANZOW, S. KARCH, K. HINDERHOFER, N. PARAMASIVAM, L.-J. BEHL, L. KAUFMANN, C. FISCHER, C. EVERS, M. SCHLESNER, R. EILS, C.R. BARTRAM AND U. MOOG
Severe autism and craniosynostosis in a boy with a *PTCH1* frameshift-variant: cause or coincidence?

10.00 C. FAUTH, B. KRABICHLER, E. STEICHEN, U. SCHATZ, J. ZSCHOCKE AND S. SCHOLL-BÜRGI
Cloverleaf skull in a boy with a homozygous frameshift mutation in *MASP1* - expanding the clinical spectrum of 3MC syndrome

10.15 S. PASSSEMARD, S. DRUNAT AND A. VERLOES
An old syndrome that mimics autosomal recessive microcephaly

10.30 A. TRIMOUILLE, E. LASSEAUX, P. BARAT, C. DEILLER, S. DRUNAT, C. ROORYCK, B. ARVEILER AND D. LACOMBE
Further delineation of the phenotype caused by biallelic variants in the *WDR4* gene

10.45 K STEINDL, D. KRAEMER, S. AZZARELLO-BURRI, R. BACHMANN, L. GOGOLL, A. BAUMER, B. ONEDA AND A. RAUCH
Clinical spectrum in a series of 10 patients with PTEN defects and pediatric onset of symptoms

11.00-11.30 *Coffee Break*

11.30-12.00 FIRST SESSION: Syndrome delineation part 1
Chair: MIDRO A. - RAUCH A.

11.30 K. KEYMOLEN, L. DE RAEVE, M. DE RADEMAEKER, K. STOUFFS AND G. LEEMANS
Genodermatoses can be bitter things: they can be like splits in the skin that won't heal...(adapted from F Scott Fitzgerald)

11.45 E. BIJLSMA, S. LANGEZAAL, N. JELLUMA, N. DEN HOLLANDER, Y. HILHORST, M. HOFFER, A. GIJSBERS, G. SANTEN, C. RUIVENKAMP, C. VAN RAVENSWAAIJ-ARTS AND S. KANT
Follow-up study after reaching a diagnosis in 85 elderly patients, living in sheltered homes

12.00-13.00 SECOND SESSION: Novel syndrome

12.00 M. JEANNE, M.-L. VUILLAUME, D. UNG, S. VONWILL, D. HAYE, N. CHELLOUG, M.-P. MOIZARD, S. MAROUILLAT, F. LAUMONNIER AND A.TOUTAIN
HIRA, a candidate gene for the neurodevelopmental phenotype of 22q11 deletion syndrome

12.15 G. D'AMOURS, F. LOPES, J. GAUTHIER, V. SAILLOUR, C. NASSIF, V.-A. PELLETIER, Y. PASTORE, S. NIZARD, E. LEMYRE, J.-F. SOUCY AND J.L. MICHAUD
DNAJC21 founder mutation in four patients: confirmation of the link with bone marrow failure and expansion of the phenotype

12.30 C. WINDPASSINGER, J. PIARD, C. BONNARD, M. ALFADHEL, S. LIM, X. BISTEAU, S. BLOUIN, N'A.B. ALI, A.Y.T. NG, H. LU, S. TOHARI, S.Z.A. TALIB, N. VAN HUL, M.J. CALDEZ, L. VAN MALDERGEM, S. YOUSSEF, V. COPPOLA, A. DE BRUIN, L. TESSAROLLO, H. CHOI, V. RUPP, K. RÖTZER, P. ROSCHGER, K. KLAUSHOFER, S. ROY, B. VENKATESH, R. GANGER, F. BEN CHEHIDA, U. ALTUNOGLU, A. AL KAISSI, B. REVERSADE AND P. KALDIS
Mutations in *CDK10* in humans and mice cause severe growth retardation, spine malformation, and intellectual disability

12.45 L. RUAUD, G. RICE, C. CABROL, J. PIARD, M. RODERO, L. VAN EYK, E. BOUCHER-BRISCHOUX, A. MARDENS DE NOORDHOUT, E. SCALAIS, F.G. DEBRAY, W. DOBYNS, Y.K CROW AND L. VAN MALDERGEM
Autosomal dominant early-onset spastic paraplegia with brain calcifications: a further example of an IFIH1-related interferonopathy

AFTERNOON

14.30-16.00 THIRD SESSION: Epileptic encephalopathy
Chair: STUMPEL C. - KOHLHASE J.

14.30 S.M. PAPUC, A. BEGEMANN, M. ZWEIER, K. STEINDL, L. ABELA, P. JOSET, B. PLECKO AND A. RAUCH
Two novel European cases of SPATA5 mutations causing epileptic encephalopathy

14.45 S. REDLER, T.M. STROM, T. WIELAND, K. CREMER, H. ENGELS, F. DISTELMAIER, S. JESCHKE, M. KOCH, A. KUECHLER, J.R. LEMKE, J. SCHAPER, N. SCHREYER, H. STICHT, H.-J. LÜDECKE AND D. WIECZOREK
Mutations in *CPLX1* in two families with autosomal-recessive severe infantile myoclonic epilepsy and ID

15.00 I. BROSSARD, G. MIRZAA, E. BRISCHOUX-BOUCHER, C. ALTUZARRA, W.B. DOBYNS AND L VAN MALDERGEM
Congenital macrocephaly and progressive encephalopathy in two siblings with compound heterozygosity for *ASNS* mutations

15.15 W. SAMKARI, A. ILEA, D. GRAS, S. PASSEMARD, L. PERRIN, N. ELENGA, B. GERARD, P. FERGELOT AND A. VERLOES
β-propeller protein associated neurodegeneration (BPAN): three male patients from two families with mutation in *WDR45*

15.30 A.T. MIDRO, F. HANEFELD, D. RYMEN, B. OLCHOWIK, B. PANASIUK, J. FRYC, B. STASIEWICZ JAROCKA, M. ADAMOWICZ, G. MATTHIJS AND J. JAEKEN
ALG1-CDG in siblings with rett syndrome spectrum like phenotype

15.45 D. LEDERER, V. BENOIT, A. DESTRÉE, S. MOORTGAT, U. ULLMAN, J. DÉSIR, K. DAHAN, B. GRISART, C. VERELLEN-DUMOULIN, S. MARY, O. FROMENT AND I. MAYSTADT
Targeted resequencing in intellectual disability and epilepsy in routine diagnosis, 3 years experience

16.00-16.30 *Coffee Break*

16.30-17.30 FOURTH SESSION: Syndrome delineation part 2
Chair: GARAVELLI L.- BOTTANI A.

16.30 A. LUMAKA, P. LUKUSA AND K. DEVRIENDT
Insight into the clinical presentation of Down syndrome in Kinshasa

16.45 S. MOORTGAT, S. BERLAND, I. AUKRUST, I. MAYSTADT, L. BAKER, V. BENOIT, A. CARO-LLOPIS, N.S. COOPER, F.-G. DEBRAY, L. FAIVRE, T. GARDEITCHIK, B.I. HAUKANES, G. HOUGE, E. KIVUVA, F. MARTINEZ, S.G. MEHTA, M.-C. NASSOGNE, N. POWELL-HAMILTON, R. PFUNDT, M. ROSELLO, T. PRESCOTT, P. VASUDEVAN, B. VAN LOON, C. VERELLEN-DUMOULIN, A. VERLOES, C. VON DER LIPPE, E. WAKELING, A.O.M. WILKIE, L. WILSON, A. YUEN, DDD STUDY, K.J. LOW AND R.A. NEWBURY-ECOB
HUWE1 variants cause dominant X-linked intellectual disability: a clinical study of 21 patients

17.00 M.-L. VUILLAUME, M. J., S. BLESSON, A.-S. DENOMME-PICHON, S. ALIROL, C. BRULARD, E. COLIN, B. ISIDOR, B. GILBERT-DUSSARDIER, S. ODENT, P. PARENT, A. DONNART, R. REDON, S. BEZIEAU, F. LAUMONNIER AND A. TOUTAIN
A novel *GABBR2* mutation identified by whole exome sequencing highlights the involvement of GABAB receptors in severe intellectual disability

17.15 H. JOURNEL, A. GUICHET, W. CARRE, L. LEPAGE, M. TARTAGLIA, B. LE MAREC, V. DAVID, D. BONNEAU, S. ODENT AND C. DUBOURG
3 families with Blepharophimosis-Ptosis-Intellectual-Disability Syndrome

17.30 GenIDA: Florent COLIN

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

FRIDAY 8th SEPTEMBER

09.00 KEYNOTE LECTURE
H. DOLLFUS: Linking developmental syndromes and rare retinal degenerations

10.15-11.00 FIFTH SESSION: Recognizable facial phenotype: by the human eye or by the computer
Chair: BIJLSMA E. - PEETERS H.

10.15 J.T. PANTEL, M.A. MENSAH, N. HAJJIR, M. SCHUBACH, T.-C. HSIEH, M. ZHAO, J. HERTZBERG, N. EHMKE, R. FLÖTTMANN, M. COUTELIER, A. KNAUS, L. GRAUL-NEUMANN, D. HORN, P. M. KRAWITZ AND PEDIA Study Consortium
PEDIA study phase 2: prioritizing exomes of undiagnosed dysmorphic patients with image analysis

10.30 P.M. KRAWITZ, A. KNAUS, M. RODRIGUEZ DE LOS SANTOS, M.A. MENSAH, M. ZHAO, J.T. PANTEL, S. MUNDLOS AND D. HORN
Characterization of glycosylphosphatidylinositol biosynthesis defects on biomarkers, phenotypic data and automated image analysis

10.45 A. BOTTANI
Really always so typical and recognizable as published in (even) good journals ? Or when phenotypic descriptions of new syndromes can sometimes be very subjective !

11.00-11.30 *Coffee Break*

11.30-12.30 SIXTH SESSION: When the eye and computer do not yield an answer
Chair: TOUTAIN A. - VAN MALDERGEM L.

11.30 P. TSHILOBO LUKUSA, V. RACE, A. CORVELEYN, L. DE CATTE, M. RAYYAN, P. MOERMAN, W. DEVELTER, J. BRECKPOT AND K. DEVRIENDT
Mendeliome studies in fetal pathology : solving the unknowns?

11.45 B. POPP, A.B. EKICI, C. THIEL, J. HOYER, A. WIESENER, C. KRAUS, A. REIS AND C. ZWEIER
Exome pool-SEQ: large-scale and cost-efficient mutation detection in neurodevelopmental disorders

12.00 Y. JIA, J. LOUW, M. GEWILLIG, B. CALLEWAERT, Y. SZNAJER, P. BOUVAGET, L. LARSEN, J. BRECKPOT, A. CORVELEYN AND K. DEVRIENDT
Genetic testing in isolated familial and sporadic congenital heart defects

12.15 B. POPP, A.B. EKICI, C. THIEL, M. KRUMBIEGEL, A. WIESENER, M.S. REUTER, R. ABOU JAMRA, C. KRAUS, C. ZWEIER AND A. REIS
The emerging field of multiple molecular diagnoses - the Erlangen experience

AFTERNOON

14.30-16.00 SEVENTH SESSION: Syndrome delineation part 3
Chair: KEYMOLEN K. - VERLOES A.

14.30 S. WHALEN, M. MAYER, D. STERNBERG, D. RODRIGUEZ, M.F. PORTNOI, S. CHANTOT-BASTARAUD, P.L. LEGER, D. BRETON, G. PATERNOSTER, C. NAVA AND B. KEREN
A novel case of mosaic variegated aneuploidy syndrome with CEP57 mutation in a boy who was previously diagnosed with congenital myasthenia syndrome with CHAT mutation

14.45 B. RINALDI, V. PALAZZO, FEDERICA NATACCI, T. RIZZUTI, S. BOITO, S. GIGLIO AND F. LALATTA
A prenatal diagnosis of Fraser syndrome due to triallelic pattern of inheritance

15.00 M. ELGIZOULI, J. BEYGO, J. KÖTTING, T. HAACK, K. SCHÄFERHOF, S. BECK-WÖDL AND B. HORSTHEMKE
Shaaf-Yang syndrome in an adult patient with a Prader-Willi 8pws9-like phenotype and autistic features: a long road to diagnosis

15.15 A. BAYAT, M. BAYAT, R. LOZOYA,AND C.P. SCHAAF
Chronic intestinal pseudo-obstruction syndrome and gastrointestinal malrotation in a Morrocan boy with Schaaf-Yang syndrome - Expanding the phenotypic spectrum

15.30 N. COSEMANS, L. VANDENHOVE, I. NOENS, J. MALJAARS, K. DEVRIENDT, J.-P. FRIJNS, A. BALDWIN, H. PEETERS
ZNF462 mutations cause syndromic intellectual disability with ptosis and distinct craniofacial anomalies

15.45 X. LEGUILLOU, M. RODRIGUEZ-BALLESTEROS, G. LE GUYADER, Q. RICHE-PIOTAIX, F. BILAN AND B. GILBERT-DUSSARDIER
Monoamine oxidase A (MAOA) deficiency: a rare cause of mild ID with paroxysmal behavioural symptoms being improved by a therapy

16.00-16.30 *Coffee Break*

16.45-18.00 EIGHTH SESSION: Syndrome delination part 4
Chair: DEVRIENDT K. - BAYAT A.

16.30 J. KOHLHASE, D. MESCHEDE AND I. VERMA
The role of *WNT3* and *WNT7A* in Tetra-Amelia and Fuhrmann syndromes. novel mutations and review of the literature

16.45 C. FAGERBERG, K. BRUUSGAARD, C. STUMPEL, P. SUWANNARAT, C. CARLSTON, J.C. CAREY, M. LEES, V. KALSCHEUER, G.H. BRUUN AND B. STORSTEIN ANDRESEN
Do missense variants in RBM10 cause a distinct phenotype?

17.00 C. STUMPEL, C. VAN ROOZENDAAL, S. STEVENS, K. OBERNDORFF, B. PANIS, C. DE DIE-SMULDERS AND S. STEGMANN
PUF60 mutations in 4 individuals: expanding the phenotype

17.15 M. DE RADEMAEKER, B. DIMITROV, A. LAUMEN AND K. KEYMOLEN
Two cases of a "skeletal" syndrome: the illustration of a variable, broad clinical spectrum

17.30 C. KERKHOFS, K. VAN KAAM, S. VAN TEEFFELEN, R. VAN GOLDE, T. RINNE AND C. DE DIE-SMULDERS
Stillbirth of a male fetus with severe cleft/lip palate and a FGFR1 mutation causing kallmann syndrome in his mother

17.45 Deletions and mutations in MEIS2 are a common cause of syndromic cleft palate
R. VERHEIJE, G.L KUPCHIK, B. ISIDOR, H. CROES, S. LYNCH, U. KINI, M. HEMPEL, J. GHOUMID, J. CLAYTON-SMITH, S. LODDO, Z. TÜMER, C. SHAW-SMITH, E. VAN HOOF, K. ANYANE-YEBOA, A. CORVELEYN, L. HAWKES, F. KORTÜM, C. LE CAIGNEC, A. NOVELLI, N. STONG, F. PETIT, A. REVAH-POLITI, K. DEVRIENDT AND J. BRECKPOT

ASSOCIATED ANOMALIES IN CASES WITH ESOPHAGEAL ATRESIA

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Esophageal atresia (EA) is a common type of congenital anomaly. The etiology of esophageal atresia is unclear and its pathogenesis is controversial. Infants with esophageal atresia often have other non-EA associated congenital anomalies. The purpose of this investigation was to assess the prevalence and the types of these associated anomalies in a defined population. The associated anomalies in cases with EA were collected in all livebirths, stillbirths and terminations of pregnancy during 29 years in 387,067 consecutive births in the area covered by our population-based registry of congenital malformations. Of the 116 cases with esophageal atresia, representing a prevalence of 2.99 per 10,000, 54 (46.6%) had associated anomalies. There were 9 (7.8%) cases with chromosomal abnormalities including 6 trisomies 18, and 20 (17.2%) nonchromosomal recognized dysmorphic conditions including 12 cases with VACTERL association and 2 cases with CHARGE syndrome. Twenty five (21.6%) of the cases had multiple congenital anomalies (MCA). Anomalies in the cardiovascular, the digestive, the urogenital, the musculoskeletal, and the central nervous systems were the most common other anomalies. The anomalies associated with esophageal atresia could be classified into a recognizable malformation syndrome or pattern in 29 out of 54 cases (54 %). This study included special strengths: each affected child was examined by a geneticist, all elective terminations were ascertained, and the surveillance for anomalies was continued until 2 years of age. In conclusion the overall prevalence of associated anomalies, which was close to one in two cases, emphasizes the need for a thorough investigation of cases with EA. A routine screening for other anomalies may be considered in infants and in fetuses with EA.

OUR EXPERIENCE IN MULTIPLE CONGENITAL CONTRACTURES: AMYOPLASIA AND DISTAL ARTHROGRYPOSIS

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Congenital contractures can be divided into two groups: isolated contractures and multiple contractures. Isolated congenital contractures affect only a single area of the body. Multiple congenital contractures include amyoplasia, distal arthrogryposis (DA) and syndromic forms, and are characterized by the involvement of two or more different areas of the body. Amyoplasia shows characteristic clinical features and is almost exclusively sporadic. DAs involve the distal parts of the limbs and represent a group of autosomal dominant disorders. Syndromic forms may have an etiology on the Central Nervous System or can be neurological progressive. We discuss here 3 cases of amyoplasia and 10 cases of DA. Since no specific genetic basis of amyoplasia is known, diagnosis in our 3 patients was clinical. Among the cases of DA, 3 patients of a family present a known heterozygous mutation in the *TNNT3* gene, more compatible in our family with phenotype of DA2B. One girl has the molecular confirmation of diagnosis of multiple pterygium syndrome, Escobar variant, due to a homozygous mutation in the *CHRNG* gene. Molecular analysis of the *CHRNG* gene and an NGS Panel for DA is ongoing in a boy, with the clinical suspicion of multiple pterygium syndrome, Escobar variant. Molecular analysis through a NGS Panel for DA is ongoing in 2 boys, with major clinical suspicion of DA1 in 1 patient and DA2B in the other. In 3 cases we have the clinical suspicion of multiple pterigium syndrome, Escobar variant, DA5D and DA1/DA2B respectively, but molecular analyses were refused by the parents. In conclusion, in the broad spectrum of multiple congenital contractures, we could make a clinical, and sometimes, molecular diagnosis, in 10 out of 13 cases.

Keywords: distal arthogryposis, amyoplasia, molecular analysis

SPECTRUM OF SYNDROMES ASSOCIATED WITH CRANIOSYNOSTOSIS IN LITHUANIAN COHORT

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Craniosynostosis is defined as a partial or complete premature fusion of one or more of the cranial sutures, which leads to abnormal skull shape and complications of different organ systems in some cases. It as a very heterogeneous group in terms of the inheritance patterns, which range from sporadic mutations to autosomal dominant inheritance, and clinical presentation. Here we present 11 Lithuanian patients with conditions involving craniosynostosis, confirmed by molecular genetic testing methods: Apert syndrome (OMIM#101200; 2 patients), Muenke syndrome (OMIM#602849; 7 patients), and craniofrontonasal syndrome (OMIM#304110; 1 patient). Thanatophoric dysplasia (OMIM#187600; 1 patient) was diagnosed prenatally at 15 weeks' gestation.

Apert syndrome is characterized primarily by craniosynostosis, midface hypoplasia, and syndactyly of hands and feet. In both patients with Apert syndrome, heterozygous c.[755C>G];[755C=] (p.[(Ser252Trp)];[(Ser252=)]) mutation in exon 7 of *FGFR2* gene was identified. Muenke syndrome is an autosomal dominant disorder, characterized mainly by uni- or bicoronal synostosis, midfacial hypoplasia, hearing impairment, and intellectual disability. The diagnosis of Muenke syndrome was confirmed by identifying c.[749C>G];[749C=] (p.[(Pro250Arg)];[(Pro250=)]) in exon 7 of *FGFR3* gene in 7 Lithuanian patients. Reduced penetrance and variable expression contribute to a wide spectrum of clinical findings in Lithuanian patients with this condition. Thanatophoric dysplasia is a severe short-limb dwarfism syndrome with the majority of cases being lethal in the perinatal period. In prenatal case of thanatophoric dysplasia, c. [1954A>G];[1954A=], (p.[(Lys652Glu)];[(Lys652=)]) mutation in *FGFR3* gene was detected in the fetus. Craniofrontonasal syndrome is characterised by frontonasal dysplasia, craniofacial asymmetry, craniosynostosis, severe ocular hypertelorism, bifid nasal tip, and grooved nails. Diagnosis was confirmed by detection of heterozygous genotype c.[-95T>C];[-95T=] in *EFNB1*.

Surgical interventions can be applied to manage craniosynostosis, especially for cases with limited involvement of other organs.

SEVERE AUTISM AND CRANIOSYNOSTOSIS IN A BOY WITH A *PTCH1* FRAMESHIFT-VARIANT: CAUSE OR COINCIDENCE?

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PATCHED-1, encoded by *PTCH1,* is a receptor for SONIC HEDGEHOG (SHH). Unligated PATCHED-1 acts as repressor of the SHH signaling pathway. Loss of function sequence variants in *PTCH1* have been associated with Nevoid Basal Cell Carcinoma Syndrome (NBCCS) or Gorlin Syndrome, whereas gain of function variants can lead to holoprosencephaly (HPE7). NBCCS presents with a variable clinical picture including basal cell carcinomas and jaw keratocysts, appearing with puberty or in young adult age. Macrocephaly, facial dysmorphism, skelettal abnormalities especially of the ribs and vertebrae, calcification in falx cerebri, malignancies such as medulloblastoma, and mild development delay can be associated. We report on the identification of the *PTCH1* (NM_000264.3) frameshift variant c.2979dupA; p.(Val994Serfs*151) by exome sequencing (ES) in a 9 year old boy with unusual clinical presentation, consisting of severe craniosynostosis, severe autism with intellectual disability (ID), hypotonia, as well as macrocephaly, hydrocephalus and Chiari I malformation. The variant is located in the second extracellular protein domain. Variants in two other genes considered after filtering were evaluated as not contributing to the phenotype. Macrocephaly and brain malformations are in line with the published phenotype of *PTCH1* sequence variants, however craniosynostosis and severe autism/ID have not been reported in this context so far. The question, whether these symptoms are coincidental, partly secondary or represent the so far unknown severe picture of the *PTCH1*-associated clinical spectrum, will be discussed.

CLOVERLEAF SKULL IN A BOY WITH A HOMOZYGOUS FRAMESHIFT MUTATION IN *MASP1* – EXPANDING THE CLINICAL SPECTRUM OF 3MC SYNDROME

Christine FAUTH[1], Birgit KRABICHLER[1], Elisabeth STEICHEN[2], Ulrich SCHATZ[1], Johannes ZSCHOCKE[1], Sabine SCHOLL-Bürgi[2]

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Cloverleaf skull is a rare skull deformity caused by premature synostosis of multiple cranial sutures. It is characterized by a trilobar skull shape with towering and bossing of the forehead, temporal bulging and occipital flattening. The etiology is heterogeneous and the majority of cases occur as part of a syndrome such as thanatophoric dysplasia, Pfeiffer syndrome, Crouzon syndrome, Apert syndrome, and Carpenter syndrome.

Here, we report on a 5-month-old boy with cloverleaf skull who was born to consanguineous Turkish parents. Clinical findings in this patient include dextroversio cordis with bicuspid aortic valve and aortic stenosis, facial dysmorphism (sparse eyebrows, hypertelorism, short and downslanted palpebral fissures, flat nasal bridge, short nose, tented upper lip, narrow palate, low-set ears), shortening of the 5th fingers, a sacral dimple, a skin tag over the xiphisternum, and a small umbilical hernia.

No mutation was detected in *FGFR1*, *FGFR2*, and *FGFR3*. As the clinical findings were not characteristic of any of the above mentioned disorders associated with cloverleaf skull we decided to perform exome analysis which revealed a homozygous frameshift mutation c.518del, p.(Ile173Thrfs*24), in the *MASP1* gene leading to the diagnosis of 3MC syndrome. Major clinical findings of this rare autosomal recessive disorder are facial dysmorphism, cleft lip/palate, growth deficiency, developmental delay, and hearing loss. 20-30% of patients have craniosynostosis which mainly manifests as plagiocephaly, dolichocephaly, trigonocephaly, or, rarely, turricephaly. However, cloverleaf skull has not been described before.

The present case illustrates that the phenotypic spectrum of 3MC syndrome includes severe multisuture craniosynostosis and that this disorder should be considered in the differential diagnosis of cloverleaf skull.

An old syndrome that mimics autosomal recessive microcephaly

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We report here two siblings with a typical form of autosomal recessive primary microcephaly. Intrauterine growth retardation was observed at birth for the index case and less obvious for the second girl, born from consanguineous parents (2.200kg/height: 46cm/OFC: 31.5cm and 2.9kg/47cm/32cm respectively). However, the OFC was 2 SD below the normal range for both girls. Growth stabilized on the mean after 6 months of age for the first girl but remained below -2SD the mean for weight and height curves for the second one until adolescence. However, the OFC growth kinetics decreased after 6 months and stabilized at -4 SD for both girls after age 1 year old. Walking without support was slightly delayed for both (2 years old). Language was also delayed: both were able to make sentences at 5 years of age. Neuropsychological assessment showed a moderate intellectual deficiency with a developmental quotient corresponding to a 4 years old child for the language abilities and to a 7 years old child for the motor skills. Both girls had synophris, short forehead, atrophic thenar eminence, thin fingers. The visual acuity decreased in the index case and ocular fundus showed a retinal dystrophy at adolescence. WES revealed a classical homozygous and well described mutation in the *VPS13B* gene, causing Cohen syndrome. Except retinal dystrophy, no features were in favor of Cohen syndrome in these siblings. Specifically, no obesity, no neutropenia was reported. This case report suggests that Cohen syndrome can mimics primary microcephaly.

FURTHER DELINEATION OF THE PHENOTYPE CAUSED BY BIALLELIC VARIANTS IN THE *WDR4* GENE.

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Microcephalic primordial dwarfisms are a group of rare Mendelian disorders characterized by severe growth retardation and microcephaly. The molecular basis is heterogeneous, with disease-causing genes implicated in different cellular functions. Recently, 2 patients were reported with the same homozygous variant in the *WDR4* gene, coding for an enzyme responsible for the m^7G_{46} post transcriptional modification of tRNA. We report here the third and fourth patients affected by this disease: two sisters harboring compound heterozygous variants of *WDR4*. Their phenotype differs from that of the first two described patients: they both have a severe microcephaly but only one of the two sisters had a head circumference at birth below -2 SD, their intellectual deficiency is less severe, and they have a GH deficiency and a partial hypogonadotropic hypogonadotropism. One of the two variants is a frameshift mutation, and the other one is a missense occurring in the same nucleotide affected by the first reported pathogenic variant, which could therefore be a mutational hot spot. The description of these two sisters allow us to confirm that biallelic variants in the *WDR4* gene can lead to a specific phenotype, characterized by severe growth retardation and microcephaly.

CLINICAL SPECTRUM IN A SERIES OF 10 PATIENTS WITH PTEN DEFECTS AND PEDIATRIC ONSET OF SYMPTOMS

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The PTEN-Hamartoma-Tumor-Syndrome (PHTS) comprises the clinical subentities of Cowden-Syndrome (CS), Bannayan-Riley-Ruvalcaba-Syndrome (BRRS), PTEN-associated Proteus-(like-) Syndrome. Classical features of the BRRS are usually of pediatric onset and include macrocephaly, Hashimoto thyroiditis, lipomatosis, hemangiomas and café-au-lait spots. PHTS is associated with susceptibility for breast, thyroid, kidney, endometrium and colorectal cancer, classically attributed to the third decade.
We evaluated the clinical spectrum of 10 pediatric patients with PTEN germline defects seen in our center between 2009–2017. While 9 patients had sequence variants or exon deletions restricted to PTEN, one patient had a 6.3 Mb deletion in 10q23. One of the mutated patients additionally harbored a paternally inherited balanced translocation. Notably, we found a surprising early onset of PHTS-related symptoms.

Genodermatoses can be bitter things: they can be like splits in the skin that won't heal...(adapted from F Scott Fitzgerald)

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The skin is the largest organ in humans and it plays an important role as a protection against dehydration and infections as well as in thermoregulation and as a sense organ.

Defects in this skin barrier can have tremendous health consequences and even lead to early demise.

We report a non-consanguineous family who lost two boys with a severe genodermatosis, presenting as a collodion baby in the neonatal period.

The evolution was characterized by neurological involvement and recurrent infections, leading to death between one and two years of age.

Genetic investigations could identify an autosomal recessive monogenic condition explaining the phenotype of the children.

FOLLOW-UP STUDY AFTER REACHING A DIAGNOSIS IN 85 ELDERLY PATIENTS, LIVING IN SHELTERED HOMES

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There are many reasons for genetic testing in patients with intellectual disability: etiology, recurrence risk, prognosis, health watch, and research may all apply. With recent developments in diagnostic techniques, it is possible to label more patients with a diagnosis. Reaching a genetic diagnosis in young children may indeed be crucial for patient management and future family planning. But is this also the case in older patients with intellectual disability?

We run a consultation service in several centres for patients with intellectual disability. For this study, we collected all patients in these centres with a diagnosis made between 2008-2016, either via SNP array or Whole Exome Sequencing. Our medical files were checked for reason for referral and advices for health checks. Medical files in the sheltered homes were checked to see whether advises were adhered to and whether patient management was influenced by the diagnosis.

In > 90% of patients suggestions for health surveillance were followed-up. Patient management was unchanged in most cases. Several case histories will be presented.
Among the cases in which a diagnosis altered patient management are a series of 5 patients with Phelan-McDermid syndrome (PMS, formerly known as the 22q13.3 deletion syndrome). Patients with PMS present with developmental delay and (severely) delayed speech, without major dysmorphic features, while they have a high risk of developing behavioural and psychiatric disturbances during life.
In those 5 patients intellectual disability ranged from mild to severe. Four of them had a deletion ranging from 59.6 kb tot 1.8 Mb in size, and one had a mutation in the SHANK3 gene. This last patient and one of the deletion patients had the so called atypical bipolar disorder earlier mentioned in other PMS patients.
PMS is an example of a disorder in which an etiological diagnosis in adults can still be of importance, especially for an adequate mood-stabilizing treatment strategy.

HIRA, A CANDIDATE GENE FOR THE NEURODEVELOPMENTAL PHENOTYPE OF 22q11 DELETION SYNDROME

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The 22q11.2 deletion syndrome (22q11DS) is a neurocristopathy associated with a wide phenotypic spectrum. Until now, none of the genes located in the 3 Mb typically deleted region (TDR) explains the entire phenotype and the cause of the neurodevelopmental problems remains speculative. At the 26th European Dysmorphology Meeting, we reported an intragenic deletion of the *HIRA* gene, which is located in the TDR, in a 5-year-old female patient with intellectual disability and facial features highly suggestive of 22q11DS. We postulated that this gene could be responsible for the neurodevelopmental phenotype of this syndrome and could induce a global deregulation of gene expression.

Here, we bring more evidence of the implication of *HIRA* in the neurodevelopmental phenotype of 22q11DS. Indeed, using RT-qPCR we demonstrated both in vitro and in vivo in mice that *HIRA* is highly expressed during neuritogenesis. Furthermore, using shRNA, we demonstrated that a 56% repression of *HIRA* expression in murine primary neuronal cultures induced major alterations of neuronal branching. We also studied the expression of two genes, *MRPL40*, located in the TDR and *MYH9* located farther on the chromosome 22, in 3 healthy controls, 4 patients with classical 22q11 deletion and in our patient. The intragenic deletion of *HIRA* induced a deregulation of the expression of this two genes compared to controls and patients with classical 22q11 deletion.

Our data strongly support that *HIRA* is responsible for the neurodevelopmental phenotype of the 22q11DS and could induce a deregulation of gene expression leading to the phenotypic variability of this syndrome.

DNAJC21 FOUNDER MUTATION IN FOUR PATIENTS: CONFIRMATION OF THE LINK WITH BONE MARROW FAILURE AND EXPANSION OF THE PHENOTYPE

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We studied two siblings and two double cousins from a First Nation community, who presented postnatal growth retardation, global developmental delay, skin, teeth and hair abnormalities, hyperlaxity, and bone marrow failure. In addition, all patients had short telomeres, and two of them eventually developed skeletal abnormalities consistent with spondyloepimetaphyseal dysplasia. These features strongly suggested an inherited bone marrow failure syndrome, such as Dyskeratosis congenita (DC), Shwachman-Diamond syndrome (SDS), Rothmund-Thomson syndrome, or Poikiloderma with neutropenia. However, they all lacked many classical features found in these conditions and single gene sequencing failed to identify a mutation in any of the associated genes.

Considering the common ethnic origin and similar clinical features, we hypothesized that the same homozygous mutation was likely responsible for this condition in all patients, and performed exome sequencing on the proband's blood. We identified a homozygous variant in *DNAJC21*, a gene recently linked with Bone marrow failure syndrome 3 (OMIM 617052)[1]. This variant was predicted damaging by all *in silico* prediction algorithms. All affected individuals were confirmed to be homozygous for this variant by Sanger sequencing and available parents were all found to be heterozygous.

The identification of this new variant in *DNAJC21* supports the association with bone marrow failure. The transmission pattern observed in the studied families suggests a founder mutation in this First Nation population. This is supported by the recent report of the same variant in two other patients from a Canadian First Nation population[2]. We describe in detail the characteristics of our patients, and expand the phenotype associated with this new syndrome. Our findings also suggest that *DNAJC21*, in addition to its role in ribosome biogenesis, may be involved in telomere maintenance, making it the latest gene associated with telomeropathies.

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MUTATIONS IN *CDK10* IN HUMANS AND MICE CAUSE SEVERE GROWTH RETARDATION, SPINE MALFORMATION, AND INTELLECTUAL DISABILITY

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We identified eight affected individuals from four separate families with a novel syndrome characterized by growth retardation, spine malformation, facial dysmorphism, and intellectual disability. By homozygosity mapping, array-CGH and whole-exome sequencing, we uncovered bi-allelic loss-of-function mutations in the *CDK10* gene segregating with the disease. CDK10 is a protein kinase that partners with Cyclin M to phosphorylate substrates such as ETS2 and PKN2 to modulate cellular growth. To validate and model the pathogenicity of these *CDK10* germline mutations in mice, we generated a conditional null allele. Homozygous knockout Cdk10 mice die postnatally with severe growth retardation, skeletal defects, kidney and lung abnormalities which partly phenocopy the human disease. Patient-derived fibroblasts and Cdk10 knockout mouse embryonic fibroblasts proliferate normally but developed longer cilia. Transcriptomic analysis of Cdk10 null mouse organs revealed metabolic changes consistent with growth impairment and altered ciliogenesis. Our results document the first loss-of-function phenotype in humans for a member of the CDK family in which CDK10 appears to transduce signals received at the primary cilia to sustain embryonic and post-natal development.

Autosomal dominant early-onset spastic paraplegia with brain calcifications: a further example of an *IFIH1*-related interferonopathy

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We describe a complicated form of progressive spastic paraplegia observed in three individuals over two generations. This native Portuguese family includes two affected brothers and an affected daughter to the eldest brother. Onset of disease occurred within the first decade of life with stiff and waddling gait. On clinical examination, brisk deep tendon reflexes and extensor plantar reflexes were noted. A slow degradation was observed, still compatible with walking without a stick until the fourth decade. Cerebrospinal fluid, slit lamp examination and inflammatory routine chemistry was normal. No involvement of the upper limbs was observed and intellect was preserved, although cognitive deficits with memory loss and behavioral disturbances became manifest during the fourth decade in one individual. T2* brain MRI and CT scan identified extensive intracranial calcifications, both cortical and subcortical, with either a patchy distribution in the temporal and frontal regions alone or associated with thalamic involvement in all three affected family members. A provisional diagnosis of Fahr syndrome was made. Interestingly, an interferon signature was strongly positive in all three affected individuals - with scores ranging from 10 to 53 (NR<2.44), but also in asymptomatic family members, namely theunaffected brother of the 12 year old girl and the 66 year-old paternal grandfather with scores of 10 and 17. The phenotype observed was demonstrated to result from a heterozygous *IFIH1* c.2544 T>G sequence alteration determining a missense p.Asp848Glu change

The type I autosomal dominant interferonopathy hereby described thus represents in our family the molecular basis of a non-complicated form of spastic paraplegia, adding a new aetiology to this very heterogeneous condition.

Two novel European cases of SPATA5 mutations causing epileptic encephalopathy

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Recently, autosomal recessive inherited mutations in SPATA5 have been recently described to cause a phenotype characterized by microcephaly, intellectual disability, generalized intractable epilepsy, hypotonia, spasticity, sensorineural hearing loss and cortical visual defects (Tanaka et al. 2015, Buchert et al. 2016, Kurata et al 2016, and Szczaluba et al 2017). By combining high resolution chromosomal microarray analysis and exome sequencing in a cohort of 63 patients with epileptic encephalopathy, we identified two novel patients with causative biallelic SPATA5 mutations. In both cases, compound-heterozygosity in this autosomal recessive disease gene was difficult to establish, because respectively, either one allele was a copy number variant or a de novo mutation. We present the phenotype of our patients which is in line with published cases.

Mutations in *CPLX1* in two families with autosomal-recessive severe infantile myoclonic epilepsy and ID

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For a large number of individuals with intellectual disability (ID), the molecular basis of the disorder is still unknown. However, whole exome sequencing (WES) is providing more and more insights into the genetic landscape of ID. In the present study, we performed trio-based WES in 311 patients with unsolved ID and additional clinical features, and identified homozygous *CPLX1* mutations in three patients with ID from two unrelated families. All displayed marked developmental delay and migrating myoclonic epilepsy, and one showed a cerebellar cleft in addition. The encoded protein, complexin 1, is crucially involved in neuronal synaptic regulation, and homozygous *Cplx1* knockout mice have the earliest known onset of ataxia seen in a mouse model. Recently, a homozygous truncating mutation in *CPLX1* was suggested to be causative for migrating epilepsy and structural brain abnormalities. ID was not reported. The currently limited knowledge on *CPLX1* suggests that complete loss of complexin 1 function may lead to a complex but variable clinical phenotype, and our findings encourage further investigations of *CPLX1* in patients with ID, developmental delay and myoclonic epilepsy to unravel the phenotypic spectrum of carriers of biallelic *CPLX1* mutations.

CONGENITAL MACROCPEPHALY AND PROGRESSIVE ENCEPHALOPATHY IN TWO SIBLINGS WITH COMPOUND HETEROZYGOSITY FOR *ASNS* MUTATIONS

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We report on two siblings who present with asparagine synthetase deficiency. The index case was a girl, born at 39 weeks of gestation to French non-consanguineous parents. Birth weight was 2.6 kg (-2 SD), length 47.5 cm (-1.5 SD) and OFC 30.5 cm (-4 SD). Her head growth plateaued at 7 months of age (37.5 cm; -5 SD). She had severe developmental delay, no eye contact, hypotonia and generalized seizures. She died at 11 months of age. Brain MRI showed severe microcephaly with progressively diffuse cerebral atrophy. EEG indicated slow rhythms with peak waves in both hemispheres mostly on the left one. Her little brother had an OFC of 32.5 cm (-2.5 SD) at birth, and 33 cm (-5 SD) at 2 months of age. He did not have any clinical seizures, but a course similar to his sister. Whole exome sequencing identified compound heterozygous mutations in *ASNS* (c.487+1G>T splice site mutation, and c.173G>A, p.Gly58Glu) of bi-parental origin. *ASNS* encodes asparagine synthetase, an enzyme that catalyzes the transfer of ammonia from glutamine to aspartic acid to form asparagine. It is an autosomal recessive neurometabolic disorder characterized clinically by severe congenital microcephaly, global developmental delay, intractable epilepsy, and motor impairment usually manifesting as spastic quadriparesis. Diagnosis may be suspected by findings of low cerebral spinal fluid concentration of plasma asparagine. More importantly, progressive rapid microcephaly with brain atrophy is characteristic. In 2013, Ruzzo at al first described nine patients from 4 families who present similar phenotype with severe hypotonia and decreased cerebral volume. This is the fifth family reported so far.

β-propeller protein associated neurodegeneration (BPAN): three male patients from two families with mutation in *WDR45*

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WDR45 has been recently identified as the cause for the X-linked type of neurodegeneration with brain iron accumulation (NBIA). NBIA is clinically characterized by childhood onset encephalopathy accompanied by neurodegeneration in adulthood and iron accumulation in the basal ganglia. WDR45 mutations have been found in majority in females: Therefore, the X-linked dominant mode of inheritance lethal for males has been evoked. We report here two families with *WDR45* mutations. The first family has two affected brothers exhibiting severe encephalopathy and seizure in one of them, carrying a pathogenic mutation predicted to abolish the start codon. This mutation in the hemizygous state was inherited from their healthy asymptomatic mother, who was heterozygote for this mutation. The second family has one affected boy with developmental delay, and a de novo pathogenic missense variant. We'll review the literature on WDR45 syndrome : more than 60 affected females have been reported, but only 14 males within 12 pedigrees (5 including carrier females), most of them, as expected, with a severe expression of the disorder that contrasts with the slower evolution of the disease in females.

ALG1-CDG IN SIBLINGS WITH RETT SYNDROME SPECTRUM LIKE PHENOTYPE

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The congenital disorders of glycosylation (CDG) are a group of genetic disorders with mostly multisystem involvement (usually including the brain) .We present morphologic , neurologic and biochemical data of two Polish girls siblings with hand stereotypes , hyperventilation , seizures , developmental disability, hypotonia, poor head control , brisk deep grinding, no speech development, and autistic behaviour as seen in the Rett syndrome spectrum . The specific pattern of dysmorphic features and compilation of 74 dysmorphic features among 927 studied was found in both sisters. In addition. variable level of appearance were found by using the photoanthropometric method of description and measurements of Munich Dysmorphology Data Base (MDDB) according to Stengel - Rutkowski (1985). The phenotype of the older sister was observed above the age of 30 years. The diagnosis of CDG was made at the age of 10 years in the older sister and at 5 years in the younger one by finding a type 1 pattern of serum sialotransferrins. Molecular analysis of the ALG1 gene revealed two heterozygous mutations in both sisters: p.Ser150Arg (c.450C>A) and p.Arg438Trp (c.1312C>T). These mutations have recently been published in a report on 39 ALG1-CDG patients (Ng et al 2016). Next generation sequencing did not identified any mutation in *MECP2* .

Targeted resequencing in intellectual disability and epilepsy in routine diagnosis, 3 years experience

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Epilepsy is a common neurological disorder with a lifetime incidence rate of 3%. Intellectual deficiency affects 1-3% of children. Many conditions associate epilepsy and mental retardation, caused by mutations in hundreds genes, making genetic diagnosis expensive and challenging in the absence of other congenital anomalies.
By targetted resequencing, we have analysed a panel of 150 genes described in intellectual deficiency associated with epilepsy in 1896 patients. The analysis was done on a routine basis in a diagnostic laboratory based on clinician request. So far, we have found a mutation in 210 patients and we expect a mutation yield of 15% (parental testing are still ongoing). SCN1A, CHD2, PCDH19, SCN2A, SYNGAP1, KCNQ2, SCN8A and STXBP1 are the most frequently mutated genes. Some mutation in known syndromic genes were found in atypical patients, expanding the phenotypic presentation of those syndromes. On contrary, some mutations were found thanks to a good clinical description by referring clinician.
In infants below 3 months, the mutation rate was 34%, SCN2A, KCNQ2 and GLDC being the most frequent. An early diagnostic is important in encephalopathy for genetic counselling with more precise genoype phenotype study being published. Specific treatment are also available for some genes depending on the type of mutation, mainly in chanellopathy (gain or loss of function).
Most of the mutations were de novo but we showed that epileptic encephalopathy can be inherited through various mode of inheritance, making genetic counselling important for these families.
Since january 2017, we have a new panel (70 genes) allowing the detection of large exonic CNVs. The first results show CNV detection in approximately 2-3% of patients.

In conclusion, gene panel analysis is an affordable test in patients with intellectual deficiency and epilepsy in view of low cost and good mutation pick up rate. Genetic testing for patients with epilepsy and intellectual disability is now the most efficient test and is used as first line diagnostic analysis.

Insight into the clinical presentation of Down syndrome in Kinshasa

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Downs syndrome is the most common congenital cause of developmental delay / intellectual disability. Long it was thought to be absent from individual of African origin [PMID: 14359776]. Now a day, many publications have reported about this condition in Africa. Previous studies in South Africa reported that, with some exceptions, the clinical presentation in DS in black African patient was globally similar to that of Caucasian patients. Comparing black African DS to Caucasian African DS, Christianson et al [PMID: 7555887] concluded that clinical presentation of DS in either of these group was reminiscent of the normal presentation for the same ethnic group. It can, thus be conclude that African and Caucasian DS have the same presentation but embedded within different ethnic background. This study aimed at gaining insight into the clinical presentation of DS in Kinshasa.

We identified features consistent with Down syndrome in 19 patients, including 7 females and 12 males. Their ages ranged from 1.86 to 17.08 years with mean age of 9.95±4.62. Maternal age at the time of pregnancy was not available for one patient. For the remaining, fourteen (73.68 %) were born to mothers aged above 35 years, maternal age ranged between 24.32 to 43.27 years and the mean for maternal age at the time of pregnancy was 36.59±5.78 years. Microcephaly was present in 16 patients and was other frequent findings were upslant of palpebral fissures and hypertelorism in 14, epicanthus and sandal gap in 13, flat face in 11, fingers brachydactyly and transverse palmar crease in 10, toes brachydactyly of toes in 7 out of 19. None of them presented with heart murmur or another major congenital malformation.

Overall, the clinical presentation of DS in Congolese patients is similar. The role of maternal age seems to be confirmed. Special education programs are needed both for physicians and parents.

HUWE1 variants cause dominant X-linked intellectual disability: a clinical study of 21 patients

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Whole-gene duplications and missense variants in the *HUWE1* gene (NM_031407.6) have been reported in association with intellectual disability (ID). Increased gene dosage has been observed in males with non-syndromic mild to moderate ID with speech delay. Missense variants reported previously appear to be associated with severe ID in males and mild or no ID in obligate carrier females.

Here, we report the largest cohort of patients with *HUWE1* variants, consisting of 14 females and 7 males, with 15 different missense variants and one splice site variant. Clinical assessment identified common clinical features consisting of moderate to profound ID, delayed or absent speech, short stature with small hands and feet and facial dysmorphism consisting of a broad nasal tip, deep set eyes, epicanthic folds, short palpebral fissures, and a short philtrum.

We describe for the first time that females can be severely affected, despite preferential inactivation of the affected X chromosome. Three females with the c.329G>A p.Arg110Gln variant, present with a phenotype of mild ID, specific facial features, scoliosis and craniosynostosis, as reported previously in a single patient. In these females the X inactivation pattern appeared skewed in favour of the affected transcript.

In summary, *HUWE1* missense variants may cause syndromic ID in both males and females.

A novel *GABBR2* mutation identified by whole exome sequencing highlights the involvement of GABAB receptors in severe intellectual disability

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Gamma-aminobutyric acid (GABA), the predominant inhibitory neurotransmitter in the mammalian central nervous system, mediates synaptic inhibition through ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors. The metabotropic $GABA_B$ receptor is a transmembrane heterodimeric G-protein-coupled receptor composed of two subunits $GABA_{B1}$ and $GABA_{B2}$. Recently, three *de novo* missense mutations have been identified in *GABBR2*, the GABA type B receptor subunit 2 gene, in children with infantile epileptic encephalopathy. We present here a novel *de novo* mutation identified in a female patient with severe intellectual disability but no epilepsy.

The proband was the second child of healthy non-consanguineous parents with no particular family history. She had severe global developmental delay with no recognizable speech, sleep disturbance, behavioral abnormalities including self-injuries, hand stereotypies and lack of hand use, agitation and episodes of hyperventilation. Ophthalmological examination showed strabismus, hypermetropia and astigmatism. She had a normal growth. Facial dysmorphic features included prominent forehead, down-slanting almond-shaped palpebral fissures, down-turned mouth with a thin upper lip, midface hypoplasia and mild prognathism. She also had thoracolumbar kyphosis due to hypotonia. Metabolic screening, EEG, brain MRI, chromosome analysis, array-CGH, and FMR1, MECP2 and MEF2C analyses, did not show any abnormalities. Using a trio whole exome sequencing strategy, we identified a novel *de novo GABBR2* heterozygous missense mutation, c.2119G>A, p.(Ala707Thr). This non-conservative mutation is predicted to be pathogenic using *in silico* analyses and is located in a domain crucial for positive allosteric modulation. This finding strengthens the fact that heterozygous mutations in *GABBR2* could be an emerging cause of severe cognitive impairment. The implication of *GABBR2* should therefore be contemplated in non-specific intellectual disability, even without seizures, particularly in interpreting results of exome or whole genome sequencing.

3 families with Blepharophimosis-Ptosis-Intellectual-Disability Syndrome

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We follow three families – both with 2 childs - with the same phenotype (profond mental retardation, dysmorphic features with blepharophimosis, arthrogryposis), and have the opportunity to test a trio with exome. We need help of homozygoty mapping to detect a mutation in UBE3B gene. Next step was a test in the two other families and we detected the same mutation . At the same time, the association of UBE3B and Blépharophymosis, ptosis Intellectual disability was published.

PEDIA STUDY PHASE 2: PRIORITIZING EXOMES OF UNDIAGNOSED DYSMORPHIC PATIENTS WITH IMAGE ANALYSIS

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Combining molecular data with phenotype information has become the key bioinformatics strategy in interpreting exomes of patients with rare Mendelian disorders. With this approach, the correct mutation can be ranked first place in roughly half of patients with known dysmorphic syndromes and a disease-causing sequence variant in the coding part of the genome. As the high information content of dysmorphic human faces is only incompletely describable by the terminology of the human phenotype ontology, we aimed to analyze the gain in performance by including automated image analysis.

We used facial recognition technology from FDNA to detect dysmorphic features in frontal photographs of patients, and derived similarity scores for the comparison of the gestalt to all known syndromes. In a multicenter effort with currently 15 participating institutions, we built a cohort of more than 400 meticulously studied and molecularly confirmed monogenic syndromic cases.

The inclusion of pattern recognition for the human face in the prioritization process increased the ratio of exome cases with the top-ranked disease-causing mutation by more than thirty percent. In the clinical routine, where only a limited number of candidate mutations is evaluated, this also translates into a higher diagnostic yield.

Interestingly, we were also able to delineate classifiers for gene-specific phenotypes of recently identified disease genes and we are therefore advocating to define case groups of yet undiagnosed patients by computer-assisted image analysis.

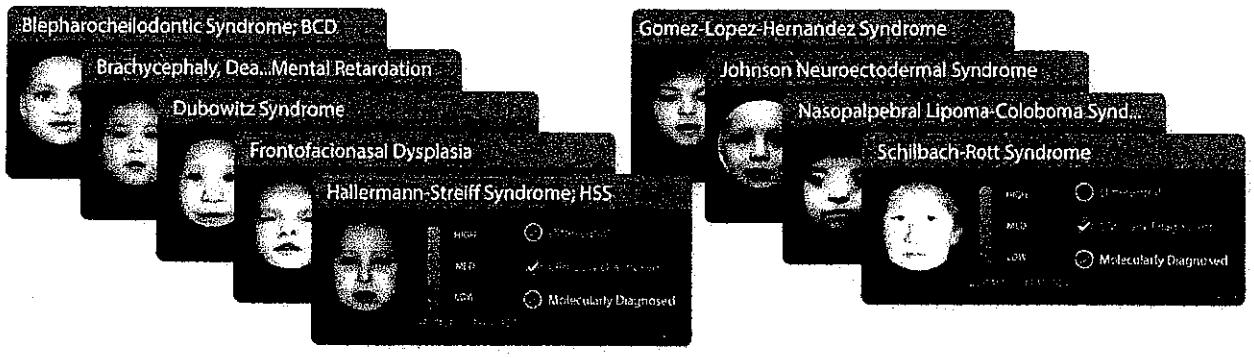

Figure 1: Dysmorphic syndromes with unknown molecular cause included in PEDIA phase 2.

CHARACTERIZATION OF GLYCOSYLPHOSPHATIDYLINOSITOL BIOSYNTHESIS DEFECTS ON BIOMARKERS, PHENOTYPIC DATA AND AUTOMATED IMAGE ANALYSIS

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Glycosylphosphatidylinositol (GPI) biosynthesis defects (GPIBDs) are a group of phenotypically overlapping syndromes with intellectual disabilities that are caused by recessive mutations in currently 14 genes of the molecular pathway. The serum activity of alkaline phosphatase (AP), a GPI-linked enzyme, has been used to divide GPIBD patients into Hyperphosphatasia with Mental Retardation syndrome (HPRMS) and other subtypes, and link these phenotypic series to certain subsets of genes. However, with the increasing number of identified cases we now know that also AP is a variable feature in GPIBDs.

We therefore studied the discriminatory power of flow cytometry that is based on multiple GPI-linked substrates. In addition, we evaluated computer-assisted classification from FDNA that is based on all clinical features and as well as on the facial gestalt of patients with a GPIBD.

We found certain malformations more likely to be associated with particular gene defects. However, especially at the severe end of the clinical spectrum of HPMRS, there is a high phenotypic overlap with another subset of GPIBDs, termed Multiple Congenital Anomalies Hypotonia Seizures syndrome (MCAHS). The cell surface reduction of GPI-linked markers correlates with the severity of the phenotype, but no gene-specific profile could be identified. Interestingly, it was facial recognition software that achieved the highest accuracy in clustering GPIBDs.

The effectiveness of gestalt analysis in the correct gene inference in a GPIBD is remarkable and illustrates how the information contained in human faces is still pivotal in the delineation of genetic entities.

Really always so typical and recognizable as published in (even) good journals ? Or when phenotypic descriptions of new syndromes can sometimes be very subjective !

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A few syndromes (Down, Williams, de Lange,...) are phenotypically *so* typical that any first-year dysmorphologist (or even a plain medical resident) will usually make a spot diagnosis with good confidence.

Many syndromes (Prader-Willi - if due to a 15q11q13 deletion - , Angelman, Fragile X, Rubinstein-Taybi, Mowat-Wilson,...) are said to be *very* typical, especially if there is a highly suggestive history and the one or two key physical findings : with some experience, it should not be too difficult to suspect or diagnose them clinically.

With the recent technological advances, more and more new syndromes are being described at such a pace that it is becoming rather difficult to remember them all and, on top of that, to be able to guess the involved gene or chromosome change by mere observation, *before the molecular result is known*. And this notwithstanding the fact that many authors do claim in their papers that the phenotype of their new syndrome is very characteristic and recognizable ! It is usually true that the described patients, at least based on published photographs, all seem to have two ears and eyes, one nose and one mouth, but I must confess that I do not always see (could be due to my high myopia) the phenotypic gestalt which makes these new entities so "typical" or unique.

A quizz will be done to illustrate the point : those with the least correct answers will get a prize !

My conclusion : even the best of dysmorphologists should learn, with time, to be quite humble and should in many instances better rely on arrayCGH or NGS findings to make a correct diagnosis rather than on their own eyes, ears or...nose !

Mendeliome studies in fetal pathology : solving the unknowns?

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Reaching an etiological diagnosis in fetuses with congenital malformations remains challenging. We will illustrate our experience with Mendeliome analysis to complement the traditional dysmorphological examination.

Case 1 illustrates the value of Mendeliome analysis in aspecific findings. This boy, of consanguineous parents, presented at gestational age of 22 weeks with large subependymal cysts bilaterally with ventriculomegaly but normal gyration. A metabolic condition was suspected. Neonatally, he presented a severe neurological picture with respiratory difficulties. He died at age 7 days. Metabolic testing failed to reach an etiological diagnosis. Mendeliome analysis showed a homozygous mutation c.1513+1G>A in the Pyruvate Carboxylase (PC) gene. In retrospect, the marked lactate aciduria was compatible with this. Enzymatic testing on skin fibroblasts revealed a deficiency of the pyruvate carboxylase enzyme.

Case 2 is the third child of second cousins. He presented at gestational age of 22 weeks with a central nervous system malformations: hypoplastic cerebellum, dysplastic corpus callosum, hypoplasia of the thalami and bilateral ventriculomegaly. There were bilateral club feet and clenched hands and hydronephrosis grade II. No diagnosis was reached and the pregnancy was terminated. Mendeliome revealed a de novo hemizygous mutation in the PDHA1 gene c.498C>T ; p.Ile166Ile), a known mutation affecting splicing. The final diagnosis is thus Pyruvate Dehydrogenase E1-Alpha Deficiency.

In Case 3 the fetus presented with severe IUGR, a small chin and low implanted ears, persistent left superior caval vein and multiple placental lacunae. Furthermore overall fetal movements were severely restricted. Termination of pregnancy at 24 weeks 5 days revealed a weight of 320g (p3 = 500g). At autopsy, there was cutaneous syndactyly of toes 2-3 and a persistent left superior caval vein. Mendeliome analysis revealed compound heterozygosity for two mutations in the RTTN gene, c.289delG (p.Val97Trp fs*45) and a maternal mutation c.2582-9T>A (disrupting splicing on white blood cell mRNA). Mutations in this gene cause a form of microcephalic dwarfism with polymicrogyria with or without seizures (OMIM 614833).

Finally, Case 4 illustrates how major interpretational difficulties exist when the phenotype doesn't match the known postnatal phenotype. This fetus was referred at 25 weeks with bilateral club feet and postaxial polydactyly of the hands. Polyhydramnios developed. In a trio mendeliome analysis a de novo mutation in the EHMT1 gene was detected: (c.736C>T (p.Arg246*). Myotonic dystrophy was excluded. It is difficult to assign with certainty the clinical features to this phenotype.

EXOME POOL-SEQ: LARGE-SCALE AND COST-EFFICIENT MUTATION DETECTION IN NEURODEVELOPMENTAL DISORDERS

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High throughput sequencing has greatly advanced disease gene identification, especially in heterogeneous entities such as neurodevelopmental disorders (NDDs), comprising intellectual disability (ID) and autism spectrum disorders. Despite falling costs this is still an expensive and laborious technique, particularly when studying large cohorts. To address this problem we developed Exome Pool-Seq as an economic and fast screening technology. Sequencing of 96 individuals can be performed in eight pools of 12 equimolar concentrated samples on less than one Illumina sequencer lane. Calling variants using a ploidy of 24 and performing subsequent validation and segregation analysis by Sanger sequencing, we identified 27 (likely) pathogenic mutations in a pilot study of 96 cases. This detection rate achieves comparable results to individual exome analyses but reduces costs by more than 85%.

Twenty-five loss-of function or likely pathogenic (previously reported, deleterious prediction) missense variants were identified in 923 established NDD genes (based on SysID database, status November 2016) (ACTB, AHDC1, ANKRD11, ATP6V1B2, ATRX, CASK, CHD8, GNAS, IFIH1, KCNQ2, KMT2A, KRAS, MAOA, MED12, MED13L, RIT1, SETD5, SIN3A, TCF4, TRAPPC11, TUBA1A, WAC, ZBTB18, ZMYND11), two in 543 (SysID) candidate genes (ZNF292, BPTF), and additionally a de novo loss-of-function variant in LRRC7, not previously implicated in NDDs. Identified mutations included mainly de novo, but also X-linked and autosomal-dominantly or autosomal-recessively inherited variants. Strikingly, in one patient with a severe ID and neurological phenotype we identified a mutation in IFIH1 that was reported to cause Aicardi-Goutieres syndrome type 7 and was also identified in four healthy family members.

In some individuals, the diagnosis had been clinically suspected but the disease associated gene had not been known at time of presentation, other patients presented with a milder or an atypical phenotype. Several examples will be presented.

Genetic testing in isolated familial and sporadic congenital heart defects.

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The genetics of congenital heart defects (CHD) is highly heterogeneous. In individuals with a syndromic (S) CHD, sporadic or familial, the chances of establishing an etiological diagnosis are high, after microarray and exome studies. However, few studies have dealt with genetic testing in non-syndromic (NS) familial and sporadic CHD.

In a first study, targeted sequencing of the coding regions of 57 genes previously implicated in CHD was performed in 36 patients from 13 NS-CHD families with probable autosomal dominant inheritance. We identified six disease causing variants in three genes (*MYH6, NOTCH1,* and *TBX5*), which explain the defects in six families (46%). Variant interpretation is complicated by variability in expression and non-penetrance. In general, the genes implicated corresponded to the previously known genotype-phenotype associations, as in other similar studies. Of interest, TBX5 mutations were found in two families with isolated septal defects and absence of any limb manifestation.

In a second study, we resequenced a panel of 38 genes previously associated with ASD and 47 genes previously associated with other types of CHD (both syndromic and nonsyndromic) in 19 ASD families (Leuven 5, Lyon 11 and Denmark 3). A certain or tentative genetic diagnosis could be made in 7 out of 19 families (37%), with mutations detected in *NKX2.5* ((n = 3), *ACTC1, MYH6, NOTCH1* and *GJA1*.

We participated in a large trio exome study by the Sanger Center (Sifrim et al., Nat Genet, 2016.) In sporadic NS-CHD cases, a small excess was detected of *de novo* protein truncating in CHD genes and of missense mutations in CHD genes and non-DD genes. Also an excess of inherited rare SNV's (minor allele frequency <1%) was observed in known CHD genes in NS-CHD, but not in S-CHD. The questions remains whether trio exome analysis is of clinical diagnostic interest in sporadic NS-CHD as the yield is very low (about 2%). Furthermore, some cases had an inherited mutation in a gene associated with a recognisable cardiac phenotype (e.g. the *ELN* gene) and more than half had a mutation in a gene that typically causes a S-CHD, be it with variable expressivity: *SOS1, FBN2, SALL4* and *COL1A1*. Trio exome analysis in sporadic, NS-CHD is unlikely to change the currently used empiric recurrence risks in the majority of cases.

THE EMERGING FIELD OF MULTIPLE MOLECULAR DIAGNOSES - THE ERLANGEN EXPERIENCE

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The presence of multiple independent genetic disorders in a single patient is a recently emerging pattern, often challenging an accurate clinical diagnosis. Several exome based studies have recently described the identification of two or more monogenic disorders in about 5% of their study cohorts. We now report on five cases with such 'blended phenotypes'.

The first case, a boy previously diagnosed with Williams-Beuren syndrome due to the typical microdeletion 7q11.23, additionally presented with severe, refractory seizures. Exome sequencing identified a de novo frameshifting variant in GABRA1 explaining the epileptic encephalopathy. As a second case we discuss a consanguineous family in which we identified a known pathogenic variant in C12orf57 causing Temtamy syndrome probably accounting for most of the clinical features in both affected individuals. In addition, both are homozygous for a pathogenic variant in CBS, causing pyridoxine-responsive homocystinuria, likely modifying their phenotype.

In the third family molecular genetic testing had identified compound-heterozygosity for two ALDH3A2 variants in a male with developmental delay, blindness, ichthyosis and spastic paraplegia confirming the suspected diagnosis of Sjögren-Larsson syndrome. He deceased at age 28 years. His younger sister, who was also blind and had juvenile chronic kidney disease, did not inherit any of the ALDH3A2 variants. Instead she was diagnosed with Senior-Løken syndrome due to compound-heterozygosity for two IQCB1 variants. Postmortem analysis confirmed the additional diagnosis of Senior-Løken syndrome in her brother, thus explaining his severe phenotype. In a fourth family two siblings with variable degrees of developmental delay, kidney disease and differing additional features were suspected clinically to have a ciliopathy. Exome sequencing identified likely pathogenic, compound heterozygous TMEM67 variants in both. CMA analysis in the girl revealed an additional 795kb de novo duplication in 22q13.2, explaining her more severe intellectual disability. She also was found to have monosomy X mosaicism, explaining her short stature. Furthermore, she was found to be a heterozygous carrier for the typical NPHP1 deletion, likely acting as a modifier and explaining her more severe kidney disease.

In a fifth family a boy presented with moderate intellectual disability and mild obesity and his maternal half-sister with severe obesity, tall stature, macrocephaly and mild motor delay. CMA detected a 200 kb microdeletion in 16p11.2 in both siblings and in the less severely affected girl additionally a microduplication in 1q21.1. The obese but healthy mother is a carrier of both these CNVs which have been associated with incompletely penetrant developmental delay.

Our findings and those in the emerging literature demonstrate the need for in depth molecular investigations in the presence of atypical or variable symptoms to identify possibly overlapping or blended phenotypes.

A novel case of mosaic variegated aneuploidy syndrome with CEP57 mutation in a boy who was previously diagnosed with congenital myasthenia syndrome with CHAT mutation

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We report the case of a 4 $^{1/2}$ year old boy who is the first child of first cousin parents. At birth, he presented with respiratory distress, hypotonia and poor spontaneous movements. During the first months of life he acquired no respiratory autonomy and stayed poorly responsive, with few spontaneous movements, intermittent eye contact and pursuit, ophtalmoplegia and ptosis. Diagnosis of congenital myasthenic syndrome (CMS) was rapidly suggested, but Pyridostygmine treatment did not lead to significant efficacy. However, CMS was confirmed at 8 months as a homozygous mutation was identified in *CHAT* gene. Treatment by Pyridostigmine was started again, which led to slight improvement on the motor level. But despite the treatment he displayed several episodes of cardio-respiratory arrest and required full time mechanical ventilation on a tracheotomy. Psychomotor development was delayed, more than what was expected with CMS. And he presented other atypical signs, with postnatal growth retardation on – 4 SD, small hands and feet, microcephaly at – 4 SD, cryptorchidism. And at 4 years of age, a complex craniosynostosis was diagnosed.

During the 3rd pregnancy of the mother, a genetic evaluation was requested because of the atypical signs. Whole exome sequencing was performed and diagnosed a homozygous mutation in CEP57 gene. Interestingly, this same mutation has been reported in 2 of the 5 patients published up to date with CEP57 mutations. These 2 patients presented typical signs of mosaic variegated aneuploidy syndrome (MVAS), with IUGR and post-natal growth retardation, and typical cytogenetic anomalies. In these 2 patients, mild developmental delay is reported, not reported in the other 3 patients with a different mutation. In one of the 2 patients with the same mutation, craniosynostosis is reported.

In our patient, chromosomal analysis is underway to search for the typical hallmarks of this syndrome. The blood karyotype done at birth was considered normal.

A detailed description of our patient will be presented, with a review of the literature on MVAS.

A prenatal diagnosis of Fraser syndrome due to triallelic pattern of inheritance.

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Biallelic mutations in either *FRAS1* or *FREM2* have been described in subjects with Fraser syndrome, a recessive disease characterized by cryptophthalmos, ear defects, syndactily and renal and genital malformations. Together with one other related genes, *FREM1*, *FRAS1* and *FREM2* constitute a multiprotein ternary complex, the so-called Fraser complex, whose role is crucial for the functional properties of the extracellular matrix in many tissues.

Loss-of-function mutations of the *FREM1* gene cause MOTA syndrome, an autosomal recessive genetic disorder firstly described in 1992. Main clinical manifestations include morphological defects in eyes and nose, genitourinary and gastrointestinal malformations and psychomotor delay. Up to now, biallelic mutations in *FREM1* have been associated to several nosological entities other than MOTA (BNAR syndrome, isolated renal agenesis and congenital diaphragmatic hernia), demonstrating a significant heterogeneity.

Considering both the functional synergy among the three genes and the clinical overlap between the Fraser syndrome and *FREM1*-related disorders, it seems likely that all these nosological entities belong to the same spectrum. However, the haploinsufficiency of any of these genes does not seem to produce the same clinical consequences, as the more severe phenotype observed in Fraser syndrome has never been described in biallelic mutation of *FREM1*.

In this report, we describe a fetus at 20 week of gestation whose pregnancy has been termonated because of a multiple congenital anomalies. From the 18th week of gestation fetal ultrasound identified an anidramnios in association with bilateral renal agenesis and a right encephalocele. Fetal autopsy added facial dysmorphisms, left cryptophthalmos and right anophthalmos, low set and small ears, cutaneous bilateral syndactyly, bilateral talipes with syndactyly of the 5th finger.

A putative diagnosis of Fraser syndrome was suggested. Genetic investigations showed a normal male karyotype whereas a NGS analysis identified an omozigotic missense variant in *FREM1*, inherited from each parent, and a nonsense heterozygous variant in *FRAS1*, of maternal origin.

We speculate that the triallelic combination of these variants could explain the severe fetal phenotype, suggesting that the functional impairment of the Fraser complex might be related also to the mutational load of its genic components.

SHAAF-YANG SYNDROME IN AN ADULT PATIENT WITH A PRADER-WILLI 8pws9-LIKE PHENOTYPE AND AUTISTIC FEATURES: A LONG ROAD TO DIAGNOSIS

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Schaaf-Yang syndrome (OMIM #615547) is a recently characterised disease entity that results from truncating mutations in *MAGEL2*, a maternally imprinted, paternally expressed gene located in the Prader-Willi syndrome critical region on the long arm of chromosome 15 (15q11q13). Patients with Schaaf-Yang syndrome usually satisfy the major diagnostic criteria of Prader-Willi syndrome but are distinguished by additional features, mainly symptoms from the autism disorder spectrum and interphalangeal joint contractures. Here, we describe the development of the clinical features and course of the syndrome in an adult patient over time and the diagnostic work-up involved in identification of the causative mutation in *MAGEL2*. At 28 years of age, this is to our knowledge the oldest reported case of Schaaf-Yang syndrome. In addition, we draw comparisons with the limited number of reported cases (28 in total) of Schaaf-Yang syndrome in the literature and offer conclusions on the necessity of considering a differential diagnosis of Schaaf-Yang syndrome in patients with a PWS-like phenotype where a genetic confirmation of the diagnosis is lacking.

Chronic intestinal pseudo-obstruction syndrome and gastrointestinal malrotation in a Morrocan boy with Schaaf-Yang syndrome - Expanding the phenotypic spectrum.

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Truncating mutations in the maternally imprinted, paternally expressed gene *MAGEL2*, which is located in the Prader-Willi critical region 15q11-13, have recently been reported to cause Schaaf-Yang syndrome, a Prader-Willi-like disease, manifesting developmental delay/intellectual disability, hypotonia, contractures, feeding difficulties, and autism spectrum disorder. Many patients suffer from chronic constipation, feeding difficulties, and gastroesophageal reflux. Here, we report a novel patient with Schaaf-Yang syndrome with severe chronic digestive malfunction, manifesting as intestinal malrotation and intestinal pseudo-obstruction. This case expands the clinical phenotypic spectrum of Schaaf-Yang syndrome.

ZNF462 MUTATIONS CAUSE SYNDROMIC INTELLECTUAL DISABILITY WITH PTOSIS AND DISTINCT CRANIOFACIAL ANOMALIES

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Rare variant analysis methods like translocation breakpoint mapping and whole exome or whole genome sequencing are powerful methods to discover genes for rare Mendelian conditions. Although historically distant, they have in common that causality is established through either extensive functional studies or independent observations in two or more families. Recently, the latter is facilitated by initiatives of families to share phenotypic and genomic information on social media and web-based tools designed to find matches. *ZNF462* was identified as a candidate gene for intellectual disability (ID) and craniofacial anomalies through a unique *de novo* balanced translocation 46,XY,t(9;13)(q31.2;q22.1) in a Belgian patient A. Information from a personal blog on a patient B and a web-based data sharing tool allowed for the identification of a second patient in California with the same genetic condition: patient B has a *de novo* frameshift mutation in *ZNF462*: chr9:109690456 c.4263delA p.(Glu1422Serfs*... (NM_021224.4). However shortly after this finding, the gene and the corresponding phenotype was published by Weiss et al. (ref).

Patient A (24y) has trigonocephaly, a prominent metopic ridge, underdeveloped supraorbital ridges, bilateral ptosis and epicanthus, a large mouth with thin upper lip, retrognatia and low set and posteriorly rotated ears. He has a low posterior hairline and hirsutism on the back and shoulders. His abdominal muscles are hypotrophic with distention and umbilical hernia. He has small hands and feet with proximal implanted thumbs and bilateral simian creases. On X-ray of the skull there was a synostosis of the metopic suture and the anterior part of the sagittal suture. Brain MRI showed hypogenesis of the posterior corpus callosum. He has mild intellectual disability, both in terms of intelligence (Composite Score = 57; Verbal Comprehension Index = 62; Perceptual Reasoning Index = 62; Working Memory Index = 68; Processing Speed Index = 55) and adaptive behavior. At the behavioral level, he meets criteria for autism spectrum disorder with manifestations of active-but-odd social behavior, difficulties in relationships with peers, specific interests, and strong adherence to routines. Patient B (3.5y) has similar clinical features including underdeveloped supraorbital ridges, ptosis and protruding and low set ears. He has a transposition of the great vessels, a dysgenesis of the corpus callosum, tracheomalasia and a lambdoid craniosynostosis. He is delayed in early motor milestones and language development. The specific clinical features allowed for the identification of a possible third patient C (35y). However, no mutation was found by sequencing of the *ZNF462* gene.

We conclude that *ZNF462* is a novel gene for a recognizable form of syndromic ID. Efforts by parents to share phenotypic and genomic information of their child offer opportunities for connections upon which new discoveries depend.

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MONOAMINE OXIDASE A (MAOA) DEFICIENCY: A RARE CAUSE OF MILD ID WITH PAROXYSMAL BEHAVIOURAL SYMPTOMS BEING IMPROVED BY A THERAPY

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MAOA deficiency was first described in 1993 by Brunner in a large recessive X-linked Dutch kindred, and so called Brunner syndrome (OMIM 300615). Linkage analysis led to the disease causing gene, *MAOA*, located on Xp11.21. Since the last 20 years, MAOA deficiency has been reported in only 3 other families, one French and 2 Australian.

The MAOA enzyme have a key role in oxidative deamination of the neurotransmitters serotonin, dopamine, adrenaline and noradrenaline, as well as metabolizing minor amines including tyramine.

We report the case of a young male adult, without any family history, referred to us for paroxysmal behavioural symptoms for which he already had to deal with the justice system, because of aberrant sexual behaviour and pyromania actions. He was very anxious, alterned periods of agressiveness and placidity, had sleeping disturbances, and a mild intellectual deficiency. Clinical analysis revealed a hypotonic face and a very anusual essential tremor, almost constant. Because of hypotonia, we tested the Steinert Myotonia gene and the patient was found with an expansion of 270 CTG. As this could not explain the whole phenotype, we went further and using our self-made panel of 275 genes involved in DI and/or behaviour disorders, we found a frameshift mutation (c.1068delG; p.Ala358fs) in the *MAOA* gene, inherited from his mother. This was confirmed by a very high rate of blood serotonin (4N). A selective serotonin reuptake inhibitor (SSRI) treatment is going on.

All affected patients share a rather specific behavioural phenotype: episodic impulsive behaviour leading at times to physical agression seems to be the most important behavioural clue; they also have autistic features, including lack of friendships, difficulties interpreting female relationship, narrow interests and obsessional collecting. Parasomnias, including night terrors, and subtle neurological symptoms of tremor, stereotypical hand movements or occasional body twitches also appear to be characteristic. Faced with this phenotype, diagnosis could be easily done by the analysis of the blood serotonin level. These symptoms can be improved by SSRI treatment.

Besides the now well demonstrated advantage of NGS analysis in diagnosis of DI and/or behaviour disorders, this case highlights the place of the clinical geneticist in DI diagnosis, when a first molecular anomaly does not fit the phenotype.

THE ROLE OF *WNT3* AND *WNT7A* IN TETRA-AMELIA AND FUHRMANN SYNDROMES NOVEL MUTATIONS AND REVIEW OF THE LITERATURE

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Mutations in the *Wingless* homologous genes *WNT3* and *WNT7A* have been associated with different syndromes mainly characterized by limb malformations. One nonsense mutation in *WNT3* was reported as the cause for tetra-amelia in a single family in 2004, and in 2015 a *WNT3* missense mutation was associated with bladder exstrophy. Apart from these two, no other *WNT3* mutations have been reported. Mutations in *WNT7A* have been published in 2006 to cause Fuhrmann and Al-Awadi-Raas-Rothschild syndromes. Since then, only five other mutations have been reported in patients affected by those syndromes. Here we report a novel mutation in *WNT3* in tetra-amelia syndrome and a novel *WNT7A* mutation causing Fuhrmann syndrome, and give a review of the role of WNT3 and WNT7A in the pathogenesis of these limb malformation syndromes.

Do missense variants in RBM10 cause a distinct phenotype?

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Loss of function mutations in RBM10 are known to cause TARP-syndrome. TARP is an acronym for Talipes, ASD, Robin sequence, and Persistent superior vena cava. The phenotype of TARP syndrome has with time however shown to be more variable than the acronym indicates.
Missense variants have not been reported to cause TARP syndrome, and has not yet been proven to be disease causing. We present the phenotype of 6 patients with missense variants in the RBM10-gene and suggest, that missense variants in the RBM10-gene are indeed disease causing and lead to a recognizable phenotype.
The RBM10 protein functions as a regulator of alternative splicing and we speculate that the missense mutations identified in patients may lead to a dysfunctional protein and that this will be reflected in aberrant splicing of genes involved in disease pathology. To identify RBM10 regulated genes we performed siRNA knock down in HeLa cells followed by RNA-seq analysis. Patient cells are being analyzed for changes in expression of identified candidate genes by QPCR/PCR and will eventually be analyzed also by RNA-seq.

PUF60 MUTATIONS IN 4 INDIVIDUALS: EXPANDING THE PHENOTYPE

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In 2009, Verheij et al, reported 2 individuals with a 8.35 Mb overlapping deletion of chromosome 8q24. These patients showed coloboma,feeding problems, congenital hipdislocation, postaxial polydactyly and intellectual disability.

Mutations in the *PUF60* gene have been reported as causal for Verheij syndrome (Dauber et al, 2013). Over 20 persons with a mutation in *PUF60* have been reported sofar (Dauber et al, 2013; El Chehadah et al, 2017; Low et al, 2017; Graziano et al, 2017).

Mutations in *PUF60* turn out to be not that rare: within a couple of years we were able to make the diagnose in 4 patients. Targeted exome sequencing was the method used. We diagnosed 2 males, aged 5 and 31 years of age, and two females, aged 11 and 31 years respectively.

In the 11 years old girl, CHARGE syndrome was the clinical diagnosis for many years.
In the 31 years old woman we initially made a clinical diagnosis of acrofacial dysostosis Catania type.
The 31 years old male presented with a nonspecific mild intellectual disability.
The youngest male was born with preaxial polydactyly on one hand. Together with a square form of the face Greig syndrome was the first differential diagnosis.
Two patients have an inframe deletion, one patient has a premature stopcodon and protein truncation. The fourth has a splice site modification with exon skipping leading to probable haploinsufficiency.
We show the patients and their mutations and discuss the clinical phenotype reported sofar.

From a clinical perspective, the diagnosis of PUF60 mutation can be suspected especially in the differential diagnosis of CHARGE syndrome. In the other cases it would not be possible to make the diagnosis without exome sequencing.

As far as we are aware, preaxial polydactyly has not been reported before.

Two cases of a "skeletal" syndrome: the illustration of a variable, broad clinical spectrum

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We report on two cases with the same diagnosis of a rare , although well known bone disease in which the presentation and course is different and the diagnosis is often delayed due to a relatively late onset of the clue signs.

First case is a boy prenatally diagnosed with multicystic kidney disease, he was born prematurely with some minor facial dysmorphism , bicuspid aortic valve and a hoarse voice. Subsequently a vascular malformation in the cervicodorsal spine and Chiari 1 malformation was observed. Skeletal symptoms were observed from the age of 1 year on.

The second case is a girl who was referred at the age of two because of hearing loss, recurrent respiratory infections and a coarse face. She had a congenital hip luxation at birth. Growth evolution was retarded in the subsequent years and facial dysmorphism became more prominent. At the age of 7 years the diagnosis was made on the base of dysmorphism and further investigations showed typical skeletal changes and other features.

With this two cases we like to illustrate the importance of recognizing the facial dysmorphism and being aware of some less frequent, but important signs of the syndrome of the disease in order to make a earlier diagnosis or in the era reverse dysmorphology to check for the right subpanel of genes.

STILLBIRTH OF A MALE FETUS WITH SEVERE CLEFT/LIP PALATE AND A FGFR1 MUTATION CAUSING KALLMANN SYNDROME IN HIS MOTHER

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Kallmann syndrome is a rare disorder caused by deficiency of gonadotropin-releasing hormone (GnRH) and associated with an impaired sense of smell. Here, we report on a female patient with Kallmann syndrome who delivered a stillborn male fetus with multiple congenital abnormalities. Genetic testing in this woman revealed a variant of unknown significance (VUS) in a splice site of the FGFR1 gene (c.449-6G>A, p.?). The VUS was also detected in the paternal uncle with Kallmann syndrome.

The patient got pregnant with ovulation induction. At 20+3 weeks AD prenatal ultrasound showed multiple abnormalities: bilateral cleft lip/palate, hypospadias, severe intrauterine growth restriction and possibly an aberrant aortic arch. At 23+6 weeks AD fetal death was concluded. Postnatally we saw a very severe cleft lip/palate, low set ears and a very small penis. The male fetus also had the VUS in the FGFR1 gene. Facial defects like cleft lip/palate have been reported in patients with Kallmann syndrome caused by mutations in the FGFR1 gene.

Further studies were conducted to determine the pathogenicity of the variant in the FGFR1 gene. The c.449-6G>A variant results in the use of an alternative splice acceptor site at position c.449-4. This results in an insertion of 4 nucleotides in the pre-mRNA, frameshift of the open reading frame and a premature stop codon in exon 5. Nonsense mediated decay was not detected. The protein will miss about 673 amino acids.

Based on the results of the family testing and RNA studies we concluded that the c.449-6G>A variant in the FGFR1 gene is underlying the Kallmann syndrome in this family and the severe cleft lip/palate in the male fetus is very likely also caused by the FGFR1 variant.

DELETIONS AND MUTATIONS IN *MEIS2* ARE A COMMON CAUSE OF SYNDROMIC CLEFT PALATE

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Orofacial clefts are the most common craniofacial human birth defect, affecting the lip only (CL), both the lip and the palate (CLP) or the palate alone (CP). Most clefts are isolated (70% of CL or CLP and 50% of CP), sporadic and likely have a multifactorial cause. Orofacial clefts, associated with developmental delay, dysmorphic features or other major congenital anomalies, are defined syndromic. These mostly have a single genetic cause, either chromosomal or monogenic.

Deletions on chromosome 15q14 are a known chromosomal cause of cleft palate, typically co-occurring with intellectual disability (ID), facial dysmorphism and congenital heart defects (CHD). These features are attributed to haploinsufficiency of the gene *MEIS2* on 15q14. De novo loss-of-function mutations in *MEIS2* were previously described in two patients with CP, ID and CHD (Louw *et al.* 2015, Fujita *et al.* 2016). To further delineate the *MEIS2*-related phenotypic spectrum, we describe 8 additional patients with *de novo* mutations (3 frameshift, 1 stop, 3 splice site and 1 missense) in this gene. All but one were identified by whole exome sequencing or clinical exome analysis for unexplained syndromic ID. One mutation was found by targeted sequencing of *MEIS2* in a girl with a clinical suspicion of this syndrome.

Key features of the *MEIS2*-related syndrome include palatal defects (9/10; 90%), ranging from bifid uvula to overt CP, intellectual disability (8/8; 100%) and CHD (5/10; 50%). Development is typically mildly to moderately delayed. No recognizable facial gestalt could be ascribed to this syndrome. However, most patients present with thin, arched and laterally displaced eyebrows, hypoplastic alae nasi and a thin upper lip.

In addition, we gathered clinical and molecular data from patients with 'small' (i.e. <3 Mb) deletions on 15q14, including 8 previously unpublished patients. A genotype-phenotype correlation study was undertaken to identify recurrent features of the 15q14 deletion syndrome, which are not related to *MEIS2*, but rather to some of the neighboring genes.

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