ISDS 2005

MARTIGNY
AUGUST 25-28
2005

7th Meeting of the International Skeletal Dysplasia Society - Martigny, Hôtel du Parc, Aug. 25th to 28th, 2005

Program, Abstracts and Participants

August 23rd - 25th

Nosology Meeting 2005

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Scientific Program

Thursday, August 25

16:00-16:10 ... Superti-Furga: Welcome and Introduction

16:10-18:00 ... MECHANISMS OF DISEASE AND LATE-BREAKING NEWS
Moderators: Stefan Mundlos and Stephen Robertson

16:10-16:30 ... Ikegawa: Osteoarthritis and Lumbar Disc Disease Caused by Dysregulation of TGFβ Signaling

16:30-16:50 ... Nishimura: Camurati-Engelmann dysplasia - with (or without) TGFβ mutations

16:50-17:10 ... Gensure: Familial Caffey Disease and Collagen I Mutations

17:10-17:30 ... Cormier: 3M Syndrome is caused by CUL7 Mutations

17:30-17:50 ... Boyd: Cranio-Lenticulo-Sutural Dysplasia is Caused by COPII Mutations

Friday, August 26

9:00-11:00 ..... CLINICAL DELINEATION OF OLD AND NEW SYNDROMES
Moderators: David Rimoin and Martine LeMerrer

9:00-9:15 ..... Huber: Molecular Analysis of SHOX in 140 Patients with Short Stature

9:15-9:30 ..... Hill: The Arthropathy of NOMID

9:30-9:45 ..... Smithson: Spondylometaphyseal Dysplasia Sutcliffe Type

9:45-10:00 ..... McCann: Two Further Cases of Acrofacial Dysostosis ?

10:00-10:15 ... Costa: Skeletal Dysplasia with Muscle Spasms- a NewDisorder?

10:15-10:30 ... Giovannucci: Novel Syndrome with Peculiar Skeletal andClinical Findings

10.30-10:45 ... Sillence: A Second Family with Czech Dysplasia Metatarsal Type

10:45-11:00 ... Savarirayan: Clinical and Radiographic Findings in Ten Patients with Metatropic Dysplasia

11:00-11:30 Coffee break

11:30-12:30 ... POSTER SESSION: AUTHORS AT POSTERS

12:30-14:00 Lunch

14:00-16:30 ... MICE AND MODELS
Moderators: Shiro Ikegawa and Geert Mortier

14:00-14:15 ... Rossi: Microarray and Proteomic Studies of Phenotypic Variability in BrtlIV Mice

14:15-14:30 ... Mallet: Chondrocytic lines as a model for Achondroplasia and Thanatophoric Dysplasia

14:30-14:50 ... Pirog-Garcia: T583M COMP Knock-in Mouse as a Model of Mild Pseudoachondroplasia

14:50-15:10 ... Leighton: A Knock-in Mouse Model of MED Caused by a MATN3 mutation

15:10-15:30 ... Rossi: Contribution of Amino Acid Sulfur to Proteoglycan Sulfation in a Mouse Model of Diastrophic Dysplasia

15:30-15:50 ... Mundlos: An Inversion Involving the Mouse SHH Locus Results in Brachydactyly Through Dysregulation of SHH Expression

15:50-16:10 ... Lee: CRTAP and 3-Prolyl Hydroxylation of Fibrillar Collagens

16:10-16:30 Coffee Break

16:30-17:30 ... **DISCUSSION OF UNKOWNS**

Moderators: Jürgen Spranger, Andrea Superti-Furga

17:30-18:30 ... Christine Hall: "Signs" in skeletal dysplasias (special semiserious lecture)

Saturday, August 27

8:30-9:30 ..... **ISDS BUSINESS MEETING**

9:45-12:30 ..... **MOLECULAR CHARACTERIZATION**

Moderators: Mike Briggs and Bill Horton

9:45-10:00 ..... Rimoin: How many Classifications are necessary?

10:00-10.15 ... Hellemans: Mutation Analysis of LEMD3 in Osteopoikilosis, B-O Syndrome and Melorheostosis

10:15-10:30 ... Dagoneau: Weill-Marchesani Syndrome: Dominant and Recessive

10:30-10:50 Coffee Break

10:50-11:05 ... Sangiorgi: Mutational Analysis of EXT1/EXT2 in Patients with Multiple Exostoses

11:05-11:20 ... Bonafe: Vertebral Segmentation Defects: Phenotype delineation of Spondylo-Costal Dysostosis type 1 and 2 and search of other candidate genes

11:20-11:35 ... Turnpenny: The Search for Further Causes of Abnormal Vertebral Segmentation

11:35-11:50 ... Mortier: The Phenotypic Spectrum of COL2A1 Arg-to-Cys Mutations

11:50-12:05 ... Mundlos: Mutations in the Receptor Interaction Site of GDF5 Cause Symphalangism and Brachydactyly A2

12:10-13:00 ... **ISDS DIAGNOSTIC COMPETITION**
with Christine Hall and Andrea Superti-Furga

*** afternoon excursions; standing dinner at Hotel ***

20:00-22:00 ... **BEYOND THE DIAGNOSIS**
Moderators: Andres Giedion and Sheila Unger

20:00-20:15 ... Spranger: Classification of the Enchondromatoses

20:15-20:30 ... Renella: Spondyloenchondrodysplasia (SPENCD) With Spasticity, Cerebral Calcifications, and Immune Dysregulation

20:30-20:45 ... Sillence: Bisphosphonate Therapies in Skeletal Dysplasias: New Indications, New Trials, and Widening Precautions

20:45-21:00 ... Zeitlin: Limb Deformity Correction and Bisphosphonate Therapy in Jansen Metaphyseal Dysplasia

21:00-21:15 ... Bacino: Quantification and Analysis of Craniofacial Features in Skeletal Dysplasias by Morphometric Analysis Using 3-D Laser Surface Scans

21:15-21:30 ... Zabel: Autosomal Recessive Schmid Metaphyseal Dysplasia

21:30-21:45 ... LeMerrer: Albright Osteodystrophy and Acroscyphodysplasia could be Due to a GNAS1 Mutation

21:45-22:00 ... Aguirre : Presentation of an Extended Family with Autosomal Dominant Nager Syndrome

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Sunday, August 28

9:00-11:00 ..... **PERSPECTIVE 2005**

9:00-9:15 ..... Taylor: ESDN: A System for Increasing Access to Genetic Testing of Bone Dysplasias

9:15-9:30 ..... Robertson: Genotype-Phenotype Correlations In Frontometaphyseal Dysplasia

9:30-9:45 ..... Mendoza: Candidate Gene Analysis In Four Families With CDAGS Syndrome

9:45-10:00 ..... Bonafe: The Wide Phenotypic Spectrum of RMRP Mutations

10:00-10:15 ... Thiel: Patients With Extreme Short Stature and RMRP Mutations

10:15-10:30 ... Alanay: Phenotypic and Mutational Spectrum of Acromesomelic Dysplasia Maroteaux

10:30-10:50 ... Superti-Furga: Overview of Nosology 2005 and Wrap-Up

10:50-11:00 ... Cormier and LeMerrer: Paris 2007

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End of Scientific Program

POSTERS

(listed by presenting author)

- Alanay: Spondylo-Ocular Syndrome: A New Entity Involving the Eye and Spine
- Cavalcanti: Skeletal dysplasias in a Brazilian Perinatal Genetic Service
- Dimitrov: Unusual clinical features in a Patient with AR form of MED Extending the Phenotype of this Entity
- Eich: Hydrometrocolpos, postaxial polydactyly, and hypothalamic hamartoma in a patient with probable Pallister-Hall syndrome: differential diagnosis with the McKusick-Kaufman syndrome
- Fresquet: Mutations and Polymorphisms in the Single A-Domain of Matrilin-3 Affect the Structure and Function of this Important Cartilage Structural Protein
- Garofalo: Mutation of the SNAPc Binding Site in RNASE MRP Promoter in CHH
- Giovannucci-Uzielli: Peculiar Skeletal Changes Associated with Maternal Uniparental Heterodisomy for Chromosome 14 in a Phenotypically Abnormal t(13;14) Robertsonian Translocation Carrier
- Giovannucci-Uzielli: Desbuquois Dysplasia: Radiological and Clinical Patterns for the Diagnosis of a Rare Autosomal Recessive Condition
- Horn: Clinical and Molecular Characterization of Two Adults with Autosomal Recessive Robinow Syndrome
- Kaitila: Growth Hormone Treatment in 35 Prepubertal Children with Achondroplasia
- Kaitila: Familial Campomelic, Non-Fracturing Osteogenesis Imperfecta
- Mendoza-Londono: SEDC with severe failure to thrive and psychomotor retardation in a Child with a GLY904GLU Substitution in COL2A1
- Mendoza-Londono: Metaphyseal dysplasia with cone shaped epiphyses of the lower limbs (Bellini type): two additional patients with unique extraskeletal manifestations
- McIntosh: Growth charts for weight, height and other anthropometric measurements in children with skeletal dysplasias
- Mornet: Multiple Exon-Skipping of the ALPL Gene in a Patient with Severe Hypophosphatasia
- Mortier: Identification of an Unbalanced X-Autosome Translocation by Array-CGH in a Boy with a Syndromic Form of Brachytelephalangic CDP

- Nikkel: Multiple Epiphyseal Dysplasia with Hernias, Hypermobility, and Dysmorphisms
- Pinto-Basto: Spondyloepimetaphyseal Dysplasia Associated with Joint Laxity and Multiple Dislocations, Mental Retardation, Retinopathy and Deafness
- Rimoin: Skeletal Dysplasia Registry, Los Angeles
- Saha: Desbuquois syndrome: An Antenatal Dilemma
- Santos: Clinical Hypochondroplasia in a Family Caused by HeterozygousDouble Mutation in FGFR3 Encoding GLY380LYS
- Savarirayan: Medial Temporal Lobe Dysgenesis in Hypochondroplasia
- Scarano: Lethal Hypophosphatasia Prenatally Diagnosed: Clinical and Molecular Studies
- Sillence: Novel Malignancies in a Boy with Maffucci Syndrome Treated with Pamidronate
- Smithson: Fetal Growth Parameters Can Overestimate Severity of Hypophosphatasia
- Steichen: DLL3-Mutations in Spondylocostal Dysostosis Type1 (SCDO1)-Report of 2 Patients
- Toiviainen-Salo: Binder Syndrome Associated with Early Onset Primary Osteoporosis
- Unger: Metaphyseal Chondrodysplasia with Cone-Shaped Epiphyses of the Long Bones: Report of a Sixth Patient
- Wang: Decompressive Craniotomy and Barrel-Stave Osteotomies for Increased ICP in a Patient with Camurati-Engelmann Disease and Skull Hyperostosis
- Zabel: Autosomal Dominant Metaphyseal Anadysplasia
- Zabel: Osteoglophonic Dysplasia with Severe Osteolytic Fibrous Mandibular Defects
- Zankl: Preselection of Cases Through Expert Clinical-Radiological Review Significantly Increases Mutation Detection Rate in Autosomal Dominant Multiple Epiphyseal Dysplasia

ABSTRACTS OF ORAL PRESENTATIONS

(in chronological order)

OSTEOARTHRITIS AND LUMBAR DISC DISEASE ARE CAUSED BY DISREGULATION OF TGF-β SIGNALING: COMMON BONE AND JOINT DISEASES ARE ALSO TGF-β-PATHIES.

Shiro Ikegawa

Lab. for Bone and Joint Diseases, SNP Research Center, RIKEN (The Institute of Physical and Chemical Research), Institute of Medical Science, University of Tokyo

Genetic factors play critical roles in the etiology and pathogenesis of common bone and joint diseases. To identify susceptibility genes for common bone and joint diseases, we have been performing systemic large-scale association studies followed by linkage-disequilibrium mapping in various diseases. We have found two genes; ASPN (asporin) for osteoarthritis and CLIP (cartilage intermediate layer protein) for lumbar disc disease. Both genes encode extra-cellular matrix proteins that bind to and negatively regulate TGF- b1 in chondrocyte of the articular cartilage and lumbar disc, respectively. Our results highlight the importance of TGF- b in chondrocyte metabolism and etiology and pathogenesis of bone and joint disease. Relation of growth factors, extra-cellular matrix and disease would be a good target of future research in bone and joint diseases.

CAMURATI-ENGELMANN DISEASE AND TGFβ1 MUTATIONS

Gen Nishimura, Koh-ichiro Yoshiura, Akira Kinoshita, Yoshio Makita, Shiro Ikegawa, Naomichi Matsumoto, Norio Niikawa

Camurati-Engelmann disease (CED) is an autosomal dominant sclerosing bone dysplasia with diaphyseal and craniofacial hyperostosis. Over 90 % of CED patients have been shown to have mutations in TGFB1, which occur almost exclusively in the LAP (latency associated peptide) domain of TGF-beta-1, particularly in exon 4, as in our experiences and other studies. These mutations are thought to cause constitutive activation of the TGF-beta-1 signaling pathway. A working hypothesis for the constitutive activation is instability of the latent form of TGF-beta-1, which is easily transformed into the activity form. Our work showed increas in amount of the active form of TGF-beta-1 in the cultured cell media from CED fibroblasts. CED is often associated with marfanoid habitus, anemia, and muscular weakness. The multi-system affliction is accounted for by functional diversity of TGF-beta-1 signaling. Functional complexity of TGF-beta-1 signaling is further complicated by the fact that loss-of-function mutations of TGFBR1 and 2 create Marfan syndrome and Marfan-like syndrome. During the study, we encountered a few CED-like patients without a TGFB1 mutation, who had diaphyseal hyperostosis, marfanoid habitus, and muscular weakness, but showed, unlike classical CED patients, sclerotic changes in the epiphyses.

A NOVEL COL1A1 MUTATION IN INFANTILE CORTICAL HYPEROSTOSIS (CAFFEY DISEASE) EXPANDS THE SPECTRUM OF COLLAGEN-RELATED DISORDERS

R.C. Gensure1, O. Mäkitie2,3, C. Barclay2, C Chan2, S. DePalmer4, M. Bastepe1, H. Abuzahra1, R. Couper5, S. Mundlos6, D. Sillence7, L. Ala Kokko8, J. Seidman4, W.G. Cole2, and H. Jüppner1

1Endocr and Pediat Endocr Units, Depts of Med and Pediatr, Mass. General Hosp and Harvard Med School, Boston, MA, USA. 2Div of Orthopaedics, Hosp for Sick Children, Toronto, Ontario, CA. 3Dept of Pediatr Endocrinol, Helsinki Univ Hosp, Helsinki, Finland. 4Dept of Genet, Harvard Med School and HHMI, Boston, MA, USA. 5Univ of Adelaide, Dept of Paediat, Women's & Children's Hosp, North Adelaide, Australia. 6Max-Planck Inst for Molec Genet and Inst for Med Genet, Charite, Berlin, Germany. 7Depts of Paediat and Child Health, Children's Hosp at Westmead Clin School, Westmead, Australia. 8Collagen Res Unit, Biocenter and Dept of Med Biochem and Mol Biol, Univ of Oulu, Finland.

Infantile cortical hyperostosis (Caffey disease) is an autosomal dominant disorder characterized by episodes of localized rapid subperiosteal bone formation, which are usually limited to the first 2 years of life. We performed a genome-wide screen for genetic linkage in an affected family and mapped the genetic locus of Caffey disease to chromosome 17q21 (2-point LOD score: 6.78). Candidate genes within the linked region were sequenced after PCR amplification of genomic DNA. Affected individuals and obligate carriers were heterozygous for a missense mutation (3041C>T) in exon 42 of COL1A1, which was predicted to alter the amino acid sequence (R836C) of the triple helical domain of the α1(I) chain of type I collagen. The same mutation was identified in the affected members of an unrelated family with Caffey disease, and it occurred, most likely as a de-novo mutation, in identical twins each affected by this disorder. The mutation was not found in a single sporadic case, and it was not present in >300 chromosomes from healthy individuals. Dermal fibroblast cultures from an affected individual retained abnormal disulfide-bonded dimeric α1(I) chains, designated ß11', within the cell layer. 2D-SDS-PAGE analysis showed that these ß11' dimers dissociated after reduction of disulfide bonds into a1(I)' chain that was likely to contain the R836C mutation. EM analysis of collagen fibrils from individuals with the R836C mutation showed decreased number of fibrils, increased variability of size and shape of fibrils, and increased material interspersed between collagen fibrils. Mutations in COL1A1 have been previously shown to cause Ehlers-Danlos syndrome (EDS) and osteogenesis imperfecta; we therefore re-examined our Caffey patients for features of these disorders. Individuals with R836C mutation showed increased joint laxity, noticeably soft skin, frequent inguinal hernias, similar to EDS type III, while fracture rates were only 1.6 per patient and bone densitometry was normal. Our findings extend the spectrum of COL1A1-related diseases to include a hyperostotic disorder. Further definition of the mechanisms leading to Caffey disease may provide new approaches for treating disorders associated with abnormal bone turnover.

3-M SYNDROME IS CAUSED BY CUL7 MUTATIONS

Céline Huber1, Dora Dias-Santagata2, Anna Glaser3, James O'Sullivan4, Kenneth Wu2, Xinsong Xu2, Kerra Pearce3, Rong Wang6, Graeme C.M. Black4, Peter E. Clayton4, Andrew Read4, Martine Le Merrer1, Peter J. Scambler3, Arnold Munnich1, Zhen-Qiang Pan2, Robin Winter3, Valérie Cormier-Daire1 and the clinical consortium on 3 M syndrome

1Department of Genetics and INSERM U 393, Hôpital Necker Enfants Malades, Paris, France 2 Department of Oncological Sciences and of Human Genetics, The Mount Sinai School of Medicine, New York, USA 3Genes, Development and Disease Theme, Institute of Child Health, London, UK 4Department of Clinical Genetics, St. Mary's Hospital, Manchester,UK

3-M syndrome (OMIM 273750) is an autosomal recessive condition characterized by severe pre- and post-natal growth retardation with normal endocrine function, facial dysmorphism, large head circumference, and normal intelligence. Skeletal changes include long slender tubular bones and tall vertebral bodies. Using an homozygosity mapping strategy in 7 consanguineous families with 3-M syndrome, we first mapped the disease gene to chromosome 6p21.1 (Zmax = 12.4 at θ=0 at the D6S271 locus). After excluding several candidate genes, we considered CUL7 as a good candidate based on the cul7 gene targeted mouse model characterized by intrauterine growth retardation (IUGR) at late gestational age, with a placenta of reduced size and early death of respiratory distress. Studying a series of 29 families with 3-M syndrome, we discovered 25 mutations in the CUL7 gene including 19 non sense and 6 missense mutations. CUL7 assembles an E3 ubiquitin ligase complex containing Skp1, Fbx29/Fbw8, and ROC1 and promotes ubiquitination. Functional studies showed that two tested mutations, i.e. R1445X and H1464P, abrogate CUL7 recruitment of ROC1. These findings provide the first evidence of a cullin gene mutation in a human disease and suggest that impaired ubiquitination may play a role in the pathogenesis of IUGR in humans.

CRANIO-LENTICULO-SUTURAL DYSPLASIA IS CAUSED BY ABNORMAL COPII-MEDIATED INTRACELLULAR TRAFFICKING

Simeon A. Boyadjiev Boyd1, David Hur1, George Zhang1, and Wafaa Eyaid2

1McKusick-Nathans Institute of Genetic Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; 2Department of Pediatrics, King Fahad Hospital, Riyadh, Saudi Arabia.
Correspondence: sboyd@mail.jhmi.edu

We described Cranio-Lenticulo-Sutural Dysplasia (CLSD, OMIM 607812) as a novel autosomal recessive dysmorphic syndrome with mild generalized skeletal dysplasia. Five males and one female in a consanguineous Saudi Arabian family have similar craniofacial features, including wide-open calvarial sutures with large and late-closing anterior fontanels, frontal bossing, hyperpigmentation of the forehead, hypertelorism, a broad and prominent nose, and Y-shaped sutural cataracts. The skeletal features also include vertebral and pelvic anomalies. A genome-wide scan detected linkage to chromosome 14q13-q21. All affected individuals are homozygous for a putative missence mutation in a member of the COPII intracellular trafficking pathway that is not present in 500 control chromosomes. A distinct cellular phenotype of grossly dilated endoplasmic reticulum (ER) was observed in primary fibroblasts of an affected patient and unaffected carrier of CLSD. Mutations in SEDL, another member of the ER-to-Golgi trafficking pathway, have been described in patients with X-linked Spondiloepiphyseal Dysplasia Tarda (SEDT), who have a similar cellular phenotype of dilated ER. We suggest that mutations in other members of the COPII pathway may produce genetic syndromes with skeletal involvement.

MOLECULAR ANALYSIS OF THE SHOX GENE IN A SERIES OF 140 PATIENTS WITH SHORT STATURE : IDENTIFICATION OF PAR1 DELETIONS DOWNSTREAM OF THE SHOX GENE.

Céline Huber1, Myriam Rosilio2 Sara Benito-Sanz3, N. Simon Thomas4 , Arnold Munnich1, Karen E. Heath3 , Valérie Cormier-Daire1.

1Dept of Med Genet and INSERM U393, Hopital Necker, Paris, France; 2Lilly France, Paris, France; 3Dept of Pediat Endocrinol, Hosp Univ Niño Jesús, Madrid, Spain; 4Wessex Regional Genet Lab, Salisbury, UK.

Leri-Weill Dyschondrosteosis (LWD) is an autosomal dominant form of mesomelic dysplasia associated with short stature due to shortening of the lower legs and Madelung deformity. LWD has been ascribed to large scale deletions and point mutations of the SHOX gene on the pseudoautosomal region 1 of the X and Y chromosomes (PAR1). We report here the SHOX molecular analysis of 140 patients (88 F and 52 M) included in GeNeSIS, the International observational study conducted by Eli Lilly and Company. They all presented with short stature (height range between -3.5 and - 2SDS) and Madelung deformity was clinically present in 36 patients. The molecular study included a linkage analysis of PAR1 using 2 extragenic microsatellite DNA markers, CASHOX, DXYS233 and 2 intragenic markers GASHOX, CTSHOX. After exclusion of a deletion of the SHOX gene, direct sequencing of the six SHOX exons was performed. Finallly, for a subset of patients (35) with classical DCS or with non informative microsatellite analysis, a further linkage analysis of PAR1 (using 4 microsatellite DNA markers located between CTSHOX and DXYS233 repeats) was performed.We found SHOX abnormalities in 56/140 patients, including 9 point mutations and 47 deletions of which the entire SHOX gene was deleted in 35, partially present in 1 and excluding the SHOX gene in 11. Among the 57 patients presenting with clinical LWD, SHOX abnormalities were observed in 36 cases (63%) including 5 point mutations, 22 complete deletions of SHOX gene and one partial deletion encompassing only the intragenic GASHOX and CTSHOX repeats. In addition, we identified 8 deletions located downstream of the SHOX gene and encompassing the region located between CTSHOX and DXYS233 repeats suggesting a positional effect. Among the 83 patients with short stature not associated with clinical LWD, SHOX abnormalities were observed in 20 cases (24.1%) including 4 point mutations, 13 complete deletions and 3 partial deletions of the region located downstream of SHOX. We conclude that SHOX anomalies are responsible for more than 60 % of LWD phenotype in our series and for a significant part of short stature. In addition, the identification of deletions of variable size and located downstream of the SHOX gene suggests giving consideration to the systematic use of PAR1 microsatellite markers in the molecular screening of LWD patients.

THE ARTHROPATHY OF NOMID: A DERANGEMENT OF ENCHONDRAL BONE.

Hill S,[1] Dwyer A[1], Poznanski A[2], Yao L,[1] Canna S[3], Goldbach-Mansky R[3]

[1]Warren G. Magnuson Clinical Center, Diagnostic Radiology, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health (NIH), [2]Northwestern University; shill@nih.gov

Neonatal onset multisystem inflammatory disease (NOMID) is an autoinflammatory disease characterized by fever, chronic urticarial rash, aseptic meningitis, uveitis, sensorineural hearing loss, and deforming arthropathy. The deforming arthropathy is a pathognomonic feature of NOMID. Most commonly seen in the knees, it is associated with extremely short stature (72% are in 3rd or less percentile) and overgrowth of the patella and metaphysis/epiphysis. Involvement is asymmetrical, bilateral and non-uniformed resulting in early physeal fusion, leg bowing and leg length discrepancy. Mutations in CIAS1 on the long arm of chromosome 1 have recently been identified in 2/3rds of patients affected with NOMID. The CIAS1 gene encodes a pyrin-like protein associated with upregulation of IL-1 and the modulation of apoptotic pathways and expressed in leucocytes and cartilage. Expression of CIAS1 in cultured chondrocytes has raised the question whether abnormal chondrocyte apoptosis is related to the ossesous abnormalities of NOMID. In this study we assess a larger group of patients on anti-inflammatory therapy with serial radiographs/MRI. Eighteen patients were examined (age range 4-28 yrs, mean 11 yrs) at six month intervals by MRI and radiography for from 12-18 months while on Anakinra (a human recombinant form of IL-1 receptor antagonist that inhibits the inflammation pathway but not apoptosis.) Abnormalities were seen in the knees in 11/18 patients. Two of the 11 patients also had other joints involvement (shoulders, wrists, hips, ankles). Knee findings included enlarged, fragmented patellae (6 patients), and enlarged deformed metaphysis/epiphysis (femora in 9, tibiae in 3) without evidence of synovitis or internal derangement. No consistent association was present between the presence/absence of bony abnormalities and CIAS1 mutations. Metaphyseal/ epiphyseal abnormalities appeared to be the result of a “mass producing process” that originated in the physis and deformed the adjacent metaphysis and epiphysis. This was usually heterogeneous, comprised of areas of disorganized calcification, and separated from the adjacent normal-appearing metaphyseal marrow by a well-defined calcified margin. Treatment with Anakinra showed marked regression in the systemic inflammatory findings; however, in all 11 patients with abnormalities on the initial studies, serial MRI’s and plain radiographs during the treatment period showed dramatic progression of the boney abnormalities and longitudinal growth of the long bones. No bone abnormalities developed in the other 7 patients. These findings confirm that the deforming arthropathy of NOMID is the result of endochondral boney overgrowth. The fact that the mass of abnormal bone appears to originate from within the physes suggests an underlying derangement in the normal sequence of chondral proliferation, development and replacement with osteoid.

SPONDYLOMETAPHYSEAL DYSPLASIA SUTCLIFFE (CORNER FRACTURE) TYPE – LONG TERM OUTCOME

Amirfeyz R[1], Gargan M[1], Grier D[2], Hall CM[3], Smithson SF[4]
Departments of Orthopaedics[1], Radiology[2] and Clinical Genetics[4], Bristol Children's Hospital, UK, Department of Radiology[3], Great Ormond Street Children's Hospital, London, UK.
sarah.smithson@ubht.swest.nhs.uk

Background: SMD Sutcliffe type is a rare dysplasia first described in 1965 and characterised by short stature, developmental coxa vara and triangular ossification centres at the metaphyseal periphery (which can resemble fractures). The hip complications often require early surgical intervention.
Objectives: To observe the natural history and clinical outcome of SMD Sutcliffe type in the original reported case and her 2 affected children.
Methods: A woman who presented in childhood with this form of SMD was followed up after 35 years with 2 of her 4 children.
Results: The 3 affected family members were of short stature and experienced hip pain and walking difficulties from early childhood. The radiological findings included oval vertebral bodies with anterior pointing in the spine, irregular metaphyses of the long bones with adjacent triangular ossification centres or bone fragments, marked coxa vara and slipped capital femoral epiphyses. The mother had hip surgery in childhood and bilateral hip replacements at the age of 18 years, after which she had a good long-term clinical outcome. Two of her sons inherited the SMD and experienced hip problems requiring surgery in childhood.
Discussion: This report describes the long-term outcome of SMD Sutcliffe type in the original patient and confirms autosomal dominant inheritance in this condition. Although complications in the hip were present at a young age and were associated with striking radiological findings, the outcome for growth and joint function after surgery was good.

TWIN FEMALE FETUSES WITH BILATERAL CLEFT LIPS AND PALATES, LIMB ABNORMALITIES AND AGENESIS OF THE CORPUS CALLOSUM. TWO FURTHER CASES OF ACROFACIAL DYSOSTOSIS TYPE RODRIQUEZ?

Emma McCann, Lynn Greenhalgh

Department of Clinical Genetics, Royal Liverpool Children's Hospital, Liverpool, L12 2AP

Background. The acrofacial dysostoses are a group of disorders that are genetically heterogeneous and may cause diagnostic difficulty for the clinician. Monochorionic diamniotic twin female fetuses with facial ,limb and brain abnormalities are described. Cytogenetic and biochemical tests were all normal.
A provisional diagnosis of acrofacial dysostosis Rodriquez type was made. Further assistance was sought fron the European Skeletal Dysplasia Network who agreed that the patients most closely resembled this condition.
A literature search was undertaken and 8 other cases identified. There is a slight female predominance (6/10). Facial features consistent in all cases included prominent or broad nasal bridge, malar hypoplasia, severe micrognathia and palatal abnormalities. The present two cases are the only cases described with cleft lip. Limb abnormalities tended to affect the upper limbs more severely than the lower limbs. Internal organ findings varied between cases. Several cases are reported to be inherited in an autosomal recessive pattern; the correct diagnosis is important so that the family may be given an accurate risk of recurrence.

SKELETAL DYSPLASIA WITH MUSCLE SPASMS: A NEW DISORDER?

Costa T, Desilets V, Perreault G, Van Vliet G, Verellen-Dumoulin C, Sica REP

Dept Pediatrics and Diagnostic Imaging, Sainte-Justine Hospital, Montreal, Canada; Division of Neurology, Hospital Ramos Mejia, Buenos Aires, Argentina; Centre for Human Genetics, Brussels, Belgium

A dwarfing condition associated with hypotrichosis evident at birth or early childhood and painful muscle spasms starting in the second decade was first reported in a family of two adult brothers in 1995. We present a follow-up of this family, and of a second family of two affected boys reported in 1996 as "Brussels type" short stature syndrome. The development of muscle spasms in the surviving brother of family 2 suggests that this is one and the same condition. Prognosis is variable. One affected boy in family 2 died from respiratory difficulties in the newborn period. One individual in family 1 died in his 30's of "heart failure"; he had been found to have biventricular hypertrophy at age 30. The cause of the muscle disease is not known. CK is acutely elevated during episodes, but muscle biopsy and EMG are normal. Radiographic abnormalities include: delayed bone age and unusual metaphyses in childhood, short tubular bones, short femoral neck, small iliac wings. Adult height in the 3 surviving males was 119 -134 cm. The first family is Argentinian, of Spanish ancestry. By history the index cases' father and their double first cousin had a similar phenotype. The family history in the second family, of Greek and Belgian ancestry, was negative. Mode of inheritance is most likely autosomal recessive, with father-to-son transmission in family 1 representing pseudo-dominance.

NOVEL AUTOSOMAL DOMINANT SYNDROME WITH PECULIAR SKELETAL AND CLINICAL FEATURES, IN TWO UNRELATED FAMILIES

M. Ottaviani*, M. Levi*, L. Carosi*, S. Stagi** P. Fiorini***, E. Agostani***, L. Giunti*, E. Lapi*, M.L. Giovannucci Uzielli*

* University of Florence, Department of Paediatrics, Children's Hospital A. Meyer, Genetics Unit
** University of Florence, Department of Paediatrics, Children's Hospital A. Meyer, Endocrinology Unit
*** Children's Hospital A. Meyer, Florence, Italy, Intensive Care Unit

A syndrome of congenital joint contractures, expressionless face with blepharophimosis and microstomia, short stature and several skeletal abnormal aspects, was observed in mother and son, and in a child of a second unrelated family. We consider this syndrome different from the distal arthrogryposis, since the clinical spectrum and natural history, observed during a twenty year follow-up programme in the first family, look really peculiar. We also excluded other genetic disorders with some overlapping features, such as Marden-Walker syndrome and Schwartz-Jampel syndrome. The three patients showed a motor development delay with sitting between 11 and 12 months and independent walking between 2 and 6 year-age. Social and language development appeared appropriate, except a mild delay for the child of the first family, because of a large congenital palatoschisis. No mental impairment. Normal constitutional karyotype.
From the skeletal point of view, we underline some of the abnormal features: mild microcephaly with hypertelorism and prognathism, short clavicle, cylindrical chest with mild pectus excavatum, congenital vertebral anomalies, pelvic changes, peculiar aspect of the thin long bones, multiple radio-ulnar abnormalities, dysmorphic metacarpals and metatarsal bones and multiple phalangeal abnormalities. A progressive and severe scoliosis, developed during adolescence, was observed in the adult patient, with general arthrotic degeneration.

A SECOND FAMILY WITH CZECH DYSPLASIA METATARSAL TYPE

A Turner[1], G Parasivam[2], D Sillence[3], K Kozlowski[4].

Department of Medical Genetics, Sydney Children's Hospital[1], ACT Genetics Service[2], Canberra and Department of Clinical Genetics[3] and Radiology[4], The Children's Hospital at Westmead Australia.

Background: Czech Dysplasia Metatarsal type is a dominantly inherited multiple epiphyseal dysplasia characterized by irregular shortening of metatarsals and metacarpal bones in older subjects. We report a second family with four generation in which all affected are from Northern Serbia.
Method: Clinical and skeletal radiographic features were documented in 2 generations of the family.
Results: Four of the seven offspring of the last 3 generations were affected. The proband was a 33 month old boy with normal stature and gait. A skeletal survey showed mild platyspondyly and delayed maturation of femoral epiphyses. Metacarpals and phalanges were of normal length. The mother of the proband was a 36 year old with normal stature but severe hip and knee arthropathy with marked shortening of metatarsals 3, 4, 5 in both feet and metacarpals 4, 5 in both hands.
Discussion: Czech Bone Dysplasia Metacarpal type is likely to be a more common cause of progressive osteoarthritis in some communities and is readily diagnosable by short metatarsals and metacarpals which are present from late childhood/ adolescence.

CLINICAL AND RADIOGRAPHIC FINDINGS IN TEN PATIENTS WITH METATROPIC DYSPLASIA, DEMONSTRATING LONG-TERM NATURAL HISTORY

Ravi Savarirayan[1], Peter Kannu[1], and Salim Aftimos[2]

1.Genetic Health Services Victoria, Australia, 2. Northern Regional Genetics Service, Auckland, New Zealand.

We present clinical and radiographic data in ten cases of metatropic dysplasia (MD), ranging in age from 20 weeks of gestation to 70 years, with 30-year follow-up in three cases. Included in this cohort is a pair of sibs (aged 56 and 52 years) and a father and daughter (aged 70 and 33 years).

Two patients died in infancy (aged 3 months and 4 months) from laryngeal/upper respiratory tract dysfunction while a third infant had a respiratory arrest secondary to severe laryngotracheomalacia. Long term intellectual function is normal in the five individuals surviving to adulthood. Progressive and severe kyphoscoliosis occurred in all three patients followed over 30 years, despite having several spinal surgical procedures. Overall functioning with regard to activities of daily living remains reasonable in all five adult patients (ranging in age from 33 to 70 years) and joint and back pain were not reported as being significant in these patients. Final adult height ranged from 110-135cms.

The classification of metatropic dysplasia into various subtypes, based on radiographic findings, is unclear. We suggest that this condition might be caused by the pleiotopic effects of a single dominant gene, with gonadal mosaicism reconciling sib recurrences.

MICROARRAY AND PROTEOMICS TO STUDY THE PHENOTYPIC VARIABILITY IN BRTLIV MICE.

Forlino A.1,3, Rossi A. 1, Lupi A. 1, Campari E. 1, Bini L. 2, Liberatori S. 2, Cetta G. 1, Marini J.C.3

1.Dept of Biochemistry, U of Pavia, Italy;2. Dept of Molecular Biology, U of Siena, Italy; 3. BEMB, NICHD, NIH, Bethesda, USA. E-mail: aforlino@unipv.it

BrtlIV, a murine model for Osteogenesis Imperfecta (OI), shows a moderate (70%) or a lethal (30%) OI outcome. To understand the molecular basis of this variability we investigated the expression of a pool of extracellular matrix proteins by microarray and we studied the bone protein profile by proteomic approach. Total RNA from calvarial bone of BrtlIV and WT mice was used for custum array EC Matrix (MEMOREC). Protein from calvarial bone of BrtlIV and WT mice were analyzed by 2D gels. Mass spectrometry was used for spot identification, PDQuest software (BioRad) for data analysis and western blotting for validation. Seven transcripts resulted consistently more expressed in the lethal with respect to the surviving BrtlIV mice: GADD153, Bmp4, Bmp6, Bmp7, TP53BP1, PRELP, Col13a1. The transcription factor GADD153, activated by ER stress, resulted increased also at the protein level suggesting that a different response to ER stress could be involved in different OI outcome. We generated the first reference 2D map for newborn calvarial tissue. The comparison between protein pattern of lethal, surviving and WT mice showed in Brtl an increase of alpha and beta fibrinogen and in lethal Brtl an increase of dihydropyrimidinase related protein 2, PGK-1 and alphaB crystallin.

HUMAN CHONDROCYTIC LINES PROVIDE A MODEL FOR ACHONDROPLASIA AND THANATOPHORIC DYSPLASIA.

Catherine Benoist-Lasselin, Linda Gibbs, Arnold Munnich, Laurence Legeai-Mallet.

INSERM U393-Hôpital des Enfants Malades-149 rue de Sèvres-75015 Paris-France; mallet@necker.fr

Achondroplasia (ACH) and thanatophoric dysplasia (TD) are human skeletal disorders of increasing severity accounted for by mutations in the fibroblast growth factor receptor 3 (FGFR3) gene. We generated six immortalized human chondrocyte lines that express a constitutively heterozygous mutant of FGFR3. Mutation analyses showed that the chondrocytic lines carried respectively the G380R mutation (ACH phenotype), the S249C, R248C, G370C, Y373C mutations (TDI phenotype) and the K650E mutation (TDII phenotype).
Chondocytes were isolated from human fetal growth cartilage and immortilazed by transfection of the SV40 large T antigen gene. The cell lines were characterized and analyzed for factors controlling chondrocyte differentiation. Cell lines, were subcloned according to the following parameters : cell morphology, mRNA and protein levels of extracellular matrix molecules to confirm a cartilage-specific and stable phenotype. We selected cell lines associated with an expression of extensive extracellular matrix components including proteoglycans (aggregan, byglican, decorin), collagens type II and type IX, MMP3 and signaling molecules (Ihh, Pthrp, FGFR3). Here we show the constitutive phosphorylation of FGFR3 and the activation of the STAT pathway in these immortalized cells. The cell lines provide a good model for ACH, TDI and TDII phenotypes, in addition we show for the first time the excessive activation of signaling cascades mediated by the FGFR3 mutants in human chondrocytic cell lines. Availability of this model will permit rational strategies for targeting the FGFR3 signaling pathways and to address new strategies in the treatment of achondroplasia.

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T583M COMP KNOCK-IN MOUSE – A MODEL OF MILD PSACH RESULTING FROM A C-TERMINAL COMP MUTATION

Katarzyna Piróg-Garcia, Karl Kadler, David Thornton, Raymond Boot-Handford and Michael Briggs

Faculty of Life Sciences, University of Manchester, UK
mike.briggs@manchester.ac.uk

Pseudoachondroplasia (PSACH) results exclusively from mutations in cartilage oligomeric matrix protein (COMP). COMP is a large pentameric glycoprotein found in cartilage, tendon and ligament. It consists of N-terminal oligomerisation domain, followed by 4 EGF-like repeats, 8 TSP type 3 repeats and a large globular C-terminal domain (CTD). Most of the COMP mutations identified to date cluster in the type 3 repeat region (85%) and the cell-matrix pathology of these mutations has been studied in detail; abnormal COMP protein is retained in the rER of chondrocytes together with other ECM proteins forming large aggregates, which finally result in cell death and a reduction in the number of viable cells in the tissue.
The pathomolecular mechanisms of PSACH resulting from CTD mutations remains largely unknown due to the difficulty in obtaining suitable tissues. This study describes the generation and phenotypic analysis of a knock-in mouse model of PSACH resulting from a T585M mutation in the CTD of COMP. Mutant mice are normal at birth but by nine weeks of age homozygous mice have developed a short-limb chondrodysplasia with a distinctive hip dysplasia. Histological analysis of cartilage from mutant mice demonstrate sparser and less organised cell columns in the growth plate, which is most pronounced in homozygous mice. Furthermore, there are reduced levels of COMP in the extracellular matrix of nine week old growth plate cartilage, but with no apparent accumulation of mutant protein. Further in-depth analysis of tissues from these mice will be undertaken to determine comprehensively the disease mechanisms in this form of PSACH.

A KNOCK-IN MOUSE MODEL OF MULTIPLE EPIPHYSEAL DYSPLASIA CAUSED BY A MATRILIN-3 MUTATION

M Leighton, R Meadows, S Nundlall, R Wagener, K Kadler, D Thornton, R Boot-Handford, M Briggs.

Faculty of Life Sciences, University of Manchester and Institute for Biochemistry, University of Cologne. mike.briggs@manchester.ac.uk

Autosomal dominant multiple epiphyseal dysplasia (MED) can result from missense mutations in matrilin-3 (MATN3) and is characterised by joint pain and stiffness and delayed irregular ossification of epiphyses. All MATN3 mutations resulting in MED are localised to the A-domain of matrilin-3, but the disease mechanism remains unresolved. The expression of matrilin-3 is restricted to epiphyseal cartilage and in particular the proliferative zone of the growth plate.
Although a MATN3 knock-out mouse has been developed this demonstrated no discernible phenotype and there is currently no relevant mouse model of MED. Therefore, we have used a gene targeting strategy based on the cre-loxP system to introduce the murine equivalent of Val194Asp into the mouse matn3 gene. Val194Asp has previously been shown to cause a moderate form of MED in a large Belgium family. A targeting construct containing the modified gene was integrated into the mouse genome using homologous recombination in R1 ES cells. Subsequent injection into blastocysts yielded high quality chimeric mice that transmitted the mutation through the germline in a mendelian ratio.
Mice were analysed by growth rate measurements, radiography and bone length measurements, skeletal preparations, histology, immunohistochemistry and protein/RNA studies. Mut/Mut mice appeared normal at birth but displayed a chondrodysplasic phenotype from 3-6 weeks old, characterised by reduced body weight and shortening of the long bones. Histological analysis demonstrated a disorganised growth plate and abnormal chondrocyte morphology. Wt/Mut exhibited a milder phenotype, consistent with this being an autosomal dominant disease.
These data demonstrate that mice carrying the Val194Asp mutation have a short-limbed dwarfism and will be used to investigate in-depth the disease mechanisms underlying the pathology of this form of MED.

CONTRIBUTION OF AMINO ACID SULFUR TO PROTEOGLYCAN SULFATION IN A MOUSE MODEL OF DIASTROPHIC DYSPLASIA.

F. Pecora1, B. Gualeni1, A. Forlino1, A. Superti-Furga2, G. Cetta1 and A. Rossi1 (e-mail: antrossi@unipv.it).

1Department of Biochemistry, University of Pavia, Pavia, Italy; 2Centre for Pediatrics, University of Freiburg, Freiburg, Germany.

Sulfate transporter chondrodysplasias are caused by mutations in the diastrophic dysplasia sulfate transporter (DTDST) gene that lead to impaired uptake and intracellular depletion of sulfate with ensuing undersulfation of newly synthesized cartilage proteoglycans (PGs). We have used our mouse model of diastrophic dysplasia to estimate the contribution of cysteine-derived sulfur to cartilage PG sulfation. Cartilage fragments from newborn wild-type and mutant animals were double labeled with [3H]glucosamine and [35S]cysteine and the 35S/3H ratio in glycosaminoglycans was determined; the 35S/3H ratio was 3 fold higher in mutant animals compared to the controls. Subsequently, wild-type and mutant animals at 1 day of age were injected with [35S]cysteine and after 24h, the specific activity (dpm/nmol) of the 4-sulfated disaccharide was measured in skin and cartilage. In both tissues the specific activity was increased in mutant compared to wild-type littermates. These data confirm that the pathway by which sulfate is recruited from the intracellular oxidation of thiol compounds for PG sulfation is active in cartilage in vivo. On the basis of these data, mutant and wild-type mice were injected with N-acetylcysteine to test a potential therapy of DTD and cartilage PG sulfation analysis is underway.

AN INVERSION INVOLVING THE MOUSE SHH LOCUS RESULTS IN BRACHYDACTYLY THROUGH DYSREGULATION OF SHH EXPRESSION

M. Niedermaier1,2, G.C. Schwabe1,2, S. Fees3, P. Seemann1, S. Stricker1, E. Schröck4, P.B. Selby5, S. Mundlos1,2

1Max Planck Institute for Molecular Genetics, Berlin, Germany; 2Institute for Medical Genetics, Charité, Berlin; 3Children's Hospital, University of Mainz; 4Institute for Clinical Genetics, Technical University Dresden; 5 RiskMuTox, Oak Ridge, USA

Short Digits (Dsh) is a radiation induced mouse mutant. Homozygous mice are characterized by multiple defects strongly resembling Sonic hedgehog (Shh) inactivation. Heterozygous mice show a limb reduction phenotype with fusion and shortening of the proximal and middle phalanges in all digits, similar to human brachydactyly type A1, a condition caused by mutations in Indian hedgehog (IHH). We mapped Dsh to chromosome 5 in a region containing Shh and were able to demonstrate an inversion comprising 11.7 Mb. The distal breakpoint is 13.298 kb upstream of Shh separating the coding sequence from several putative regulatory elements identified by interspecies comparison. The inversion results in almost complete downregulation of Shh expression during the developmental stages E9.5 to E12.5, explaining the homozygous phenotype. At E13.5 and E14.5, however, Shh is upregulated in the phalangeal anlagen of Dsh/+ mice, at a time point and in a region where wt Shh is never expressed. The dysregulation of Shh expression causes the local upregulation of hedgehog target genes such as Gli1-3, patched, and Pthlh, as well as the downregulation of Ihh and Gdf5. This results in shortening of the digits through an arrest of chondrocyte differentiation and the disruption of joint development.

CRTAP AND 3-PROLYL HYDROXYLATION OF FIBRILLAR COLLAGENS

Roy Morello1, Terry Bertin1, Yuqing Chen1,2, Patrizio Castagnola3, David R. Eyre4, Brendan F. Boyce5, and Brendan Lee1,2

1Dept. Molecular and Human Genetics and 2the Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX; 3National Institute for Cancer Research, Genoa, Italy; 3Dept. Orthopedic Surgery, University of Washington, Seattle, WA; 4Dept. of Pathology, University of Rochester Medical Center, Rochester, NY.

A poorly understood collagen post-translational modification is 3-prolyl-hydroxylation. Fibrillar collagens are thought to undergo only one such modification in the alpha helical domain as compared to the much more abundant 4-prolyl-hydroxylation. Recently we described the isolation and characterization of a novel protein, Crtap, differentially expressed in chicken hypertrophic chondrocytes compared to proliferating chondrocytes in vitro. Mice null for Crtap exhibit growth delay, kyphoscoliosis, and osteoporosis. Interestingly, null mice exhibit a pure osteoblastic defect with decreased osteoid production and bone formation. Ex vivo functional studies show normal osteoblastic proliferation and differentiation. Moreover, osteoclastic function and differentiation were normal. Because CRTAP has been co-purified with the first isolated protein with 3-prolyly hydroxylase activity (P3H1 or Leprecan), we tested Crtap null mice types I and II collagen for 3-hydroxy proline content by MS/MS analysis of tryptic digested CNBr peptides. Interestingly, mutant collagens were devoid of the 3-prolyl-hydroxylation modification. The altered post-translation modification of fibrillar collagens together with defective osteoid formation suggest a critical role of prolyl 3-hydroxylation for proper bone matrix formation and point to a key role for Crtap during skeletal development and bone mass acquisition. Moreover, these data point to a novel pathophysiologic mechanism leading to a new type of collagenopathy perhaps in the osteogenesis impefecta spectrum of disorders.

THE SKELETAL DYSPLASIAS: HOW MANY CLASSIFICATIONS ARE NECESSARY?

David Rimoin, MD,PhD

Medical Genetics Institute, Cedars-Sinai-Medical Center Los Angeles, CA
email: david.rimoin@cshs.org

Over the past decade, the molecular basis of many human skeletal dysplasias has been discovered and attempts have been made to consolidate the clinical and molecular classifications and nomenclature. In some instances, the clinically predicted families of disorders have been found to share a common etiology (e.g. the achondroplasia group), whereas in other bone dysplasia families, clear locus heterogeneity was defined (e.g. the chondrodysplasia punctata group). It has also become apparent that previous clinical classifications of these disorders, based simply on age of onset, dysplasia versus dysostosis, or presence or absence of a single clinical feature were not valid, because a wide clinical spectrum can result from different mutations in the same gene. In addition, the consequences of mutations in the heterozygous and homozygous state may result in similar phenotypes of varying severity (e.g. achondroplasia) or quite different phenotypes (e.g. brachydactyly type C and Grebe dysplasia).

This raises the question of whether we should group conditions which share a common phenotype, regardless of their genetic basis (e.g. MED) or group together conditions because they all result from mutations in the same gene (e.g. sulfate transport defects. As our knowledge regarding the specific molecular and pathogenic mechanisms in the skeletal dysplasias expands, a variety of approaches to their nomenclature and classification will be necessary. Each system should be designed to help define further basic mechanisms, or to enhance clinical diagnosis, genetic counseling, natural history and prognosis and treatment. A multidimensional electronic cross-referenced classification incorporating clinical, radiological, morphological, biochemical, molecular and developmental criteria will be required for the skeletal dysplasias and most other groups of genetic syndromes.

MUTATION ANALYSIS OF LEMD3 IN OSTEOPOIKILOSIS, BUSCHKE-OLLENDORFF SYNDROME AND MELORHEOSTOSIS PATIENTS

Hellemans J, Debeer P, Savarirayan R, Verdonk P, Roth J, Janecke A, Brooks A, Basel-Vanagaite L, Van Hul W, Wright M, Kjaer K, Doherty E, De Paepe A, Coucke P, Mortier G

Correspondence: G Mortier, Dept Med Genet, Ghent Univ Hosp, Ghent, Belgium

We have shown that heterozygous mutations in LEMD3 can cause osteopoikilosis (OP), Buschke-Ollendorff syndrome (BOS) and melorheostosis (MELO). The goal of this study was to identify the genetic defect in a larger series of patients with these disorders. We aimed to investigate allelic heterogeneity and correlate genotype with phenotype in this group of dysplasias. A total of 21 unrelated patients were analysed. Group A consisted of 10 patients with OP. Skin lesions reminiscent for BOS were present in some of these patients. Group B consisted of 2 patients with the co-occurrence of OP and MELO. In both instances, other family members were affected by OP. Group C included 9 sporadic patients with only manifestations of MELO. Genomic DNA was extracted from blood and sequenced for all the LEMD3 exons and flanking intronic parts. A total of 12 different mutations were identified in the LEMD3 gene. All mutations were shown to cause a premature stop codon and therefore most likely result in a loss of function of the protein. In 9/10 patients from group A and 2/2 patients from group B, the LEMD3 mutation was identified. In contrast, in only 1/9 patients from group C a mutation was found after sequencing of the complete LEMD3 gene. In addition, no LEMD3 mutation was found after analysing gDNA extracted from a bone lesion in one of those patients with MELO and no germline mutation (group C). Our data confirm that heterozygous loss-of-function mutations in LEMD3 can result in either isolated OP or OP in combination with BOS/MELO. A low mutation detection rate was observed in patients with only MELO. Additional experiments are necessary to further explore the role of LEMD3 in the pathogenesis of isolated and sporadic melorheostosis.

WEILL-MARCHESANI SYNDROME IS AN HETEROGENEOUS DISORDER DUE EITHER TO FBN1 OR ADAMTS10 MUTATIONS.

N Dagoneau1, C Benoist-Lasselin1, C Huber1, C. Baumann2, Y. Watanabe1, L Faivre1, A. Mégarbané3, H Dollfus4, A Alswaid5, Y. Alembik4, A Munnich1, L. Zylberberg6, L Legeai-Mallet1, V Cormier-Daire1

1) Department of Genetics and INSERM U393, Hôpital Necker, Paris, 2) Service de Génétique médicale, Hôpital Robert Debré, Paris,3) Unité de Génétique Médicale, Université Saint Joseph, Beirut, Lebanon; 4) Service de Génétique Médicale, Hôpital de Hautepierre, Strasbourg, France; 5) Clinical Genetics, Riyadh Armed Forces Hospital, Riyadh, Saudi Arabi. 6) CNRS UMR 8570, Université René Diderot, Paris,

Weill-Marchesani syndrome (WMS, [MIM 277600]) is characterized by the association of short stature, brachydactyly, joint stiffness, and eye anomalies including microspherophakia, ectopia of the lenses, severe myopia and glaucoma and occasionally, heart defects. Despite clinical homogeneity, autosomal recessive (AR) and autosomal dominant (AD) modes of inheritance have been reported. We first identified mutations in the fibrillin-1(FBN1)gene in two AD WMS families, one in frame deletion of 24 nucleotides located in exon 41 and a missense mutation (G214S) in exon 6. Using an homozygosity mapping strategy in two consanguineous families from Lebanon and Saudi Arabia, we mapped the AR WMS gene to chromosome 19p13.3-p13.2 in a 12.4 cM interval. and then identified mutations in ADAMTS 10 in two consanguineous families and in two sporadic WMS cases. A total of five distinct mutations were identified including one stop mutation (R237X), two splices mutations (1190+1G>A, 810+1G>A) and two missense mutations (R488S, R996S).). Expression studies of ADAMTS 10 using RT-PCR, Northern blot and dot blot analyses showed that ADAMTS 10 is expressed in skin, fetal chondrocytes and fetal and adult heart. Moreover, electron microscopy and immunological studies of the skin fibroblasts of WMS patients with FBN1 or ADAMTS10 mutations confirmed the impairment of the extracellular matrix and the presence of large bundles of actin microfilaments. Ongoing electron microscopy and immunological studies will help to further understand the relationship between ADAMTS10 and FBN1.

MUTATIONAL ANALYSIS OF EXT1 AND EXT2 GENES IN PATIENTS WITH MULTIPLE EXOSTOSES

[1]Luca Sangiorgi [1]Elena Pedrini, [2]Alessandro De Luca, [1]Veronica Maini, [1]Silvia Capponcelli, [1]Marina Mordenti, [2]Enza Maria Valente, [2]Rita Mingarelli, [2]Bruno Dallapiccola, [3]Piero Picci

[1]Genetics Unit, Rizzoli Orthopedic Institute, Bologna, Italy; [2] CSS-Mendel Institute, Rome, Italy; [3]Lab. Oncology Research, Rizzoli Orthopedic Institute, Bologna, Italy
Corresponding author e-mail: luca.sangiorgi@ior.it

Background: Autosomal dominant Hereditary Multiple Exostoses (HME) is one of the most commonly inherited muscoloskeletal syndromes with two genes identified (EXT1 on chromosome 8q24.1 and EXT2 on chromosome 11p12) and third locus, EXT3, on chromosome 19p where the gene has not been cloned yet.
Objective: Optimised a DHPLC-based mutation screening of the EXT1 and EXT2 genes in Italian patients affected by hereditary multiple exostoses (HME), using a multistep approach.
Patients and Methods: We first analysed 36 unrelated probands for EXT1 mutations by DHPLC analysis and subsequent direct sequencing of all samples with abnormal elution profile. In patients who tested normal at DHPLC screening, all EXT1 and EXT2 exons and splice-site junctions were directly sequenced. In 7 informative families, we also performed a pre-screening linkage analysis to selectively focus the DHPLC testing on the EXT1 or EXT2 gene.
Results: We detected 31 HME-related mutations, of which 23 (74%) were novel. Seven polymorphisms were also found. Twenty-four mutations (77%) were found in EXT1 and 7 (23%) in EXT2. No disease-causing mutations were detected in 5 of 36 patients, with a mutation frequency of 86%. According with previous studies, most mutations (90%) are loss of function. Neither false positive nor false negative results were obtained.
Discussion: This multistep method can be considered a fast and reliable diagnostic strategy for the detection of EXT1/2 mutations, with excellent sensitivity and specificity.

VERTEBRAL SEGMENTATION DEFECTS: PHENOTYPE DELINEATION OF SPONDYLOCOSTAL DYSOSTOSIS TYPE 1 AND 2 AND SEARCH FOR OTHER CANDIDATE GENES

Luisa Bonafé, Belinda Xavier, Lauréane Mittaz-Crettol, Andrea Superti-Furga.

Division of Molecular Pediatrics, Centre Hospitalier Universitaire Vaudois, Lausanne, CH (luisa.bonafe@hospvd.ch).

The genetic dissection of vertebral segmentation defects (VSD) started with the identification of DLL3 mutations in spondylocostal dysostosis (SCD) type 1. Since then, many patients with different VSD have been screened from us and others for mutations in DLL3 and MESP2, the latter found to be responsible for SCD type 2. Both DLL3 and MESP2 participate in the Notch signaling pathway, a complex net of transcription factors and gene regulators.
We have tested 43 patients (from 35 families) with non-syndromic VSD for mutations in DLL3 and MESP2 genes; 13 (from 7 families) were positive for DLL3 mutations (4 known mutations, 4 new, unpublished mutations), 2 siblings were positive for the same MESP2 mutation found previously by the Turnpenny group (SCD type 2). All remaining patients tested negative and were included in the screening of other candidate genes: HES7, an effector of the Notch pathway responsible for the oscillating gene expression in the presomitic mesoderm, and BAPX1, a homeobox gene essential for vertebral ossification and ventral differentiation of the sclerotome in mice. No pathogenic mutation was found in these two genes.
The SCD1 phenotype appear to be very homogeneous, with involvement of the whole spine, fragmented vertebrae often “pebble-beach” shaped, multiple rib fusions, no main asymmetry, no associated malformations, no long-term neurological complications. The SCD2 phenotype in the two sibs was similar to that in the two previously reported sibs and slightly different from CSD1: multiple vertebral dyssegmentations of the thoracic spine and to a lesser degree of the cervical and lumbar regions, non-progressive scoliosis with the apex at the lower thoracic spine, malformed ribs with posterior fusions. While SCD1 is almost always symmetrical (no scoliosis), SCD2 seems to be associated with scoliosis.
Thus, SCD1 seems to be the most frequent genetic form of vertebrocostal dyssegmentation and has a recognizable, rather homogeneous phenotype; SCD” is much rarer and has scoliosis; while the failure to identify gene mutations in candidate genes in most remining patients suggests that multiple, rare pathological mechanisms are at work, including other unrecognized single gene mutations and non-genetic disruptions.

SPONDYLOCOSTAL DYSOSTOSIS (SCD), DLL3 AND MESP2, AND THE SEARCH FOR FURTHER CAUSES OF ABNORMAL VERTEBRAL SEGMENTATION (AVS)

Peter D Turnpenny, Neil V Whittock, Sian Ellard.

Peninsula Medical School, Exeter, UK - peter.turnpenny@rdehc-tr.swest.nhs.uk.

We describe 5 years experience of molecular analysis of SCD and AVS disorders. The DLL3 gene encodes a ligand of the Notch-Delta signalling pathway and consists of Delta-Serrate-Lag (DSL), 6 EGF repeat, and transmembrane (TM) domains. We have identified 19 mutations (15 published) and 11 polymorphisms in DLL3 in 18 families, with a further 4 published by others. Mutations extend from the N-terminus to the G504D missense in the TM domain. The radiological phenotype is very consistent. Of the 18 families, 14 are Turkish, Middle Eastern, or Pakistani, and consanguineous. Three underwent prenatal genetic diagnosis. Four families are originally Northern European, from which it is potentially possible to calculate the carrier frequency in this population (~1:5000). Five of the 19 mutations are missense. These lead to loss of conserved cysteine and glycine residues in EGF domains and affect ligand function, though a poly-morphism >Cys leading to gain of a cysteine residue appears non-pathogenic. No mutation characterised to date acts in a dominant negative manner or through haploinsufficiency – they all appear to be loss of function mutations and only recessively inherited. To date only one family with SCD due to mutated MESP2, a basic HLH transcription factor, has been published. A further 24 cases in our cohort, with variable phenotypes, tested negative. We have screened our cohort for mutations in LNFG and DLL1 with no positive findings. Multiple mechanisms underly the large range of radiological phenotypes with AVS.

THE PHENOTYPIC SPECTRUM IN PATIENTS WITH ARGININE TO CYSTEINE MUTATIONS IN THE COL2A1 GENE

Hoornaert K, Dewinter C, Vereecke I, Beemer FA, Courtens W, Fryer A, Fryssira H, Lees M, Müllner-Eidenbock, Rimoin DL, Superti-Furga A, Temple K, Willems PJ, Zankl A, Zweier C, De Paepe A, Coucke P, Mortier G

Correspondence: G Mortier, Dept Med Genetics, Ghent Univ Hosp, Ghent, BE

Heterozygous mutations in the COL2A1 gene cause a spectrum of phenotypes known as the type II collagenopathies. The majority of COL2A1 missense mutations substitute one of the glycine residues in the triple helical domain of the protein. Only a few non-glycine missense mutations have been reported and among these, arginine-to-cysteine (Arg-to-Cys) substitutions predominate. The pathogenesis of non-glycine mutations is unclear and genotype-phenotypes correlations have not been established so far. In this study, we report 10 new probands with a type II collagen disorder. All affected individuals were heterozygous for an Arg-to-Cys mutation in the COL2A1 gene. Six different mutations were identified: R75C, R365C, R519C, R704C, R789C, R1076C. The phenotype in this group of patients was variable, often difficult to classify within the pre-existing subgroups of the type II collagenopathies, and ranged from SEDC to Stickler syndrome or even mild spondylarthropathy without ocular involvement. When considering each individual mutation, a similar phenotype was observed between our series of patients and those reported in the literature. Spondylarthropathy with normal stature and no ocular involvement were features of patients with the R75C, R519C or R1076C mutation. A distinguishing feature of the R75C mutation were the short third and fourth metatarsals. Ocular involvement but normal stature suggesting Stickler syndrome was observed in patients with the R365C mutation. Patients with the R704C mutation had mild short stature, brachydactyly, severe myopia and sensorineural hearing loss. A SEDC phenotype was present in patients with the R789C mutation. The specific phenotype of each individual Arg-to-Cys mutation in COL2A1 is intriguing and awaits further studies for clinical confirmation and molecular explanation.

ACTIVATING AND DEACTIVATING MUTATIONS IN THE RECEPTOR INTERACTION SITE OF GDF5 CAUSE SYMPHALANGISM AND BRACHYDACTYLY TYPE A2

P. Seemann1,2, R. Schwappacher5, K.W. Kjaer6, D. Krakow7, K. Lehmann2, K. Dawson7, S. Stricker1, J. Pohl4, J. Nickel3, P. Knaus5, S. Mundlos1,2

1Institut für Medizinische Genetik, Charité, Berlin, Germany; 2Max-Planck-Institut für Molekulare Genetik, Berlin; 3Institut für Physiologische Chemie II, Würzburg; 4Biopharm, Heidelberg; 5Institut für Chemie-Biochemie, Freie Universität Berlin, 6Department of Genetics, University of Copenhagen, Denmark; 7Department of Obstetrics and Gynecology, Cedars-Sinai Research Institute, Los Angeles, California, U.S.A.

Specificity of the Tgfß signaling pathway is in part achieved by differential affinities of the ligands to their receptors and to specific inhibitors. Here we describe two mutations in GDF5, L441P and R438L, that alter receptor binding affinities. They cause brachydactyly type A2 (L441P) and symphalangism (R438L), conditions previously associated with mutations in the GDF5 receptor BMPR1B and the BMP-antagonist NOGGIN, respectively. We expressed the mutant proteins in chicken limb bud micromass culture and treated ATDC5 and C2C12 cells with recombinant GDF5. Our results show that the L441P mutant is almost inactive, but the R438L mutant shows increased biological activity when compared to WT GDF5. Biosensor interaction analysis revealed loss of binding to BMPR1A and BMPR1B ectodomain for the L441P mutant. In contrast, the R438L mutant has normal binding to BMPR1B, but increased binding to BMPR1A, the receptor normally activated by BMP2. The binding to NOGGIN was normal for both mutants. Thus, the BDA2 phenotype (L441P) is caused by inhibition of the ligand-receptor interaction, whereas the SYM1 phenotype (R438L) is caused by a loss of receptor binding specificity resulting in a gain of function by acquiring BMP2-like properties. The presented experiments have identified some of the main determinants of GDF5 receptor binding specificity in vivo and open new prospects to generate antagonists and superagonists of GDF5.

CLASSIFICATION OF THE ENCHONDROMATOSES

J.Spranger

Univ.Kinderklinik - Langenbeckstr. 1, D-551331 Mainz

Prognostication and genetic counseling of patients with multiple enchondromata depends on the recognition of various nonhereditary and hereditary forms.
Multiple enchondromata may occur in single tubular and flat bones, alone (Ollier disease) or in association with hemangiomata (Maffucci disease). They may also be constituents of more generalized disorders such as Dysspondylochondromatosis, Cheirospondylochondromatosis and Enchondromatosis with hydroxy-glutaric aciduria. None of these disorders seems to be genetically determined in a Mendelian manner and it is not clear if they are separate entities or varying manifestations of a single causal process.
Spondyloenchondrodysplasia, Metachondromatosis and Genochondromatosis are well established hereditary forms of enchondromatosis. Spondyoenchondro-dysplasia may be heterogeneous with the autosomal recessive subtypes 1 and 2 and an autosomal dominant type. Autosomal recessive Vandraager-Pena metaphyseal dysplasia also appears to be a generalized enchondromatosis.

SPONDYLOENCHONDRODYSPLASIA WITH SPASTICITY, CEREBRAL CALCIFICATIONS, AND IMMUNE DYSREGULATION: COMPLETING THE CLINICAL PICTURE OF A PLEIOTROPIC DISEASE.

Renella R [1], Schaefer E [2], Eich GF [2,3], Giedion A [2], Costa T [3], Ballhausen D [2], Boltshauser E [2], Unger S [1,4], Superti-Furga A [1,2,4]

1 Division of Molecular Pediatrics, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, 2 Universitätskinderklinik, Kinderspital, Zürich, Switzerland, 3 Hospital for Sick Children, Toronto, Canada, 4 Centre for Pediatrics and Adolescent Medicine, University Hospital, Freiburg, Germany.

Enchondromas are a feature of several constitutional disorders of bone, and the nosologic classification of different entities is still provisional. Among these disorders, spondyloenchondrodysplasia (SPENCD), as outlined by Schorr et al in 1976, is defined by the presence of radiolucent spondylar and metaphyseal lesions that represent persistence of islands of chondroid tissue within bone. Careful review of radiographic findings is needed to distinguish SPENCD from the many other disorders combining enchondromas with spinal lesions. Even when strict criteria are applied, it appears that SPENCD is clinically heterogeneous, as some SPENCD patients are neurologically intact while others present with spasticity, mental retardation, cerebral calcifications in different combinations, and it has been suggested that SPENCD should be divided in two types.
We herein report of eight individuals from four families selected for having homogeneous, typical radiological signs of SPENCD as defined by Schorr et al. Four individuals had CNS manifestations including spasticity, developmental delay, and late-onset cerebral calcifications. We also noted that five individuals had clinical manifestations of autoimmunity (auto-immune thrombocytopenic purpura, auto-immune hemolytic anemia, auto-immune thyroiditis, and SLE) and one had been diagnosed with immune deficiency. Neurological and autoimmune manifestations were seen in different combinations within one single family. These observations suggest that Spondyloenchondrodysplasia (SPENCD) may be a single entity defined by specific radiographic features, but with remarkably pleiotropic manifestations that include CNS disease (spasticity, mental retardation and calcifications) as well as immune dysregulation ranging from autoimmunity to immunodeficiency. The responsible gene(s) remain to be determined.

BISPHOSPHONATE THERAPIES IN SKELETAL DYSPLASIA – NEW INDICATIONS, NEW TRIALS AND WIDENING PRECAUTIONS

D Sillence.

Centre for Children's Bone Health, The Children's Hospital at Westmead, NSW 2145 Australia.

Background: Cyclic Intravenous Pamidronate (CIP) is regarded as the gold standard of therapy in Osteogenesis Imperfecta. It reverses the osteoporosis, reduces fracture frequency, relieves bone pain and produces a marked improvement in quality of life. Early studies were based on an hypothetical anti-resorbtive effect in bone.

Method: The "pioneering" study protocol used CIP 1mg/kg monthly. Many variant treatment regimes have been treated over the past decade with generally similar excellent results.

Results: Over 100 patients have been treated with CIP at this centre. Three clinical "syndromes" demonstrate unequivocal clinical benefit, Osteogenesis Imperfecta, Chronic Recurrent Multifocal Osteomyelitis (CRMO) and Mucolipidosis II/III (ML II/III). Our experience confirms increased bone density and decreased fracture frequency. In addition, CIP in children results in increased growth velocity and restoration of skeletal bone structure. In the Mucoliplidoses there is increased range of joint movements raising the possibility of non-skeletal effects of bisphosphonates. There are many side effects including the "first" dose "flu-like" illness and non-union of chronic stress fracture.

Discussion: Recent studies demonstrate that cyclic intravenous bisphosphonates induce transient hyperparathyroidism which acts on the CBFA1 and other promoters to induce bone formation as well as inhibit bone resorbtion. Bisphosphonate therapies should be investigated in the many skeletal dysplasias complicated by severe osteoporosis/osteopenia. However some potential complications such as "undiagnosed" chronic stress fractures and induction of malignancy in patients with enchondromatoses are of greatest concern.

LIMB DEFORMITY CORRECTION AND BISPHOSPHONATE THERAPY IN JANSEN METAPHYSEAL CHONDRODYSPLASIA-

Zeitlin L, Segev E, Wientroub S.

Dept of Pediatric Orthopaedics, Dana Children's Hospital - TASMC, Israel; pedorth@tasmc.health.gov.il

Jansen metaphyseal chondrodysplasia is a rare, dominantly- inherited disorder that is caused by activating mutations of PTH/PTHrP receptor. It is characterized by growth plate abnormalities, limb shortening and deformities associated with hypercalcemia and hypercalciuria. Our patient, his brother and father were previously diagnosed with a milder form of Jansen metaphyseal chondrodysplasia due to novel PTH/PTHrP receptor missence mutation (published elsewhere). He gradually developed leg shortening and difficulty in walking because of severe tibia valga. In addition there were normal serum calcium levels, hypercalciuria and renal stones. At the age of 11, he underwent double level correction of tibia valga, tibial derotation and lengthening with Ilizarov frame. Despite preoperative intravenous pamidronate, he developed hypercalcemia and his hypercalciuria worsened postoperatively during immobilization period. The serum levels of calcium normalized after oral administration of alendronate. Despite bisphosphonate therapy, complete bone healing was achieved with correction of the deformity. Renal function and stone size remained unchanged after surgery. To our knowledge, it is the first description of limb deformity correction and bisphosphonate therapy in Jansen metaphyseal chondrodysplasia.

QUANTIFICATION AND ANALYSIS OF CRANIOFACIAL FEATURES IN SKELETAL DYSPLASIAS BY MORPHOMETRIC ANALYSIS USING 3-DIMENSION LASER SURFACE SCANS.

C.A. Bacino, B. Dawson, S. Carter, G. Milne, A. Tran, C. Shaw, B. Lee.

Dept. of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas and Howard Hughes Medical Institute.

To facilitate both the speed of diagnosis and to create a quantitative and reproducible method of analyzing variation in craniofacial size and shape in skeletal dysplasias, we are currently developing Cyberware 3-dimensional laser surface scanning to gather morphometric data on affected populations with cleidocranial dysplasia (CCD), achondroplasia (ACH), and comparing with control groups. We demonstrate high reproducibility of the scanning process by use of standard operating procedures. With this method we have developed a a way to quantify the variation and to discriminate between CCD (n=12), ACH (n=14), and a control population (n=47). After performing a 3-D laser scan, we measure the linear distances between a set of carefully chosen facial landmarks based on existing human craniofacial indices. Using methodology based on 25 landmarks, over 300 unique linear distances are generated. By utilizing Euclidean Distance Matrix Analysis (EDMA), we generated a matrix containing linear distance between all pairs of landmarks, and measure the variance of each set of distances in comparison to each other and the norm. A variable selection procedure identified the measurements which most distinguish the groups. T-statistics were calculated for each measurement (300) for each pair of groups. For each pairwise comparison, the measurements were ranked by the absolute value of the pairwise T-statistic. We then selected the best k features based on the T-statistic in order to perform the classification. We used classical Linear Discriminant Analysis (LDA) to devise an assignment rule to predict the class of each patient based on the feature data. Data from this cohort show that morphology software coupled with computational analysis can differentiate between populations with two separate conditions with distinct craniofacial phenotypes such as CCD and achondroplasia. This data form the basis for new tools that can be used in clinical diagnosis and research to quantify normal and dysmorphic traits in humans.

AUTOSOMAL RECESSIVE METAPHYSEAL CHONDROPLASIA TYPE SCHMID

Mustonen A[1], Stelzer C[2], Wildhardt G[3], Spranger J[2], Zabel B[2]

[1] Dept. Clinical Genetics, Oulu Univ. Hospital, Oulu, Finland, aki.mustonen@ppshp.fi ; [2] Children's Hospital, University of Mainz, Mainz, Germany, stelzer@molgen.medizin.uni-mainz.de; spranger@molgen.medizin.uni-mainz.de; zabel@molgen.medizin.uni-mainz.de ; [3] Bioscientia Institute, Ingelheim, Germany, gabriele.wildhardt@bioscientia.de

The metaphyseal chondrodysplasias (MCD) are a heterogeneous group of disorders associated with flaring and irregularity of various metaphyses. A number of well defined MCDs have been delineated based on clinical and radiological criteria. They include MCD, Schmid type (MCDS), an autosomal dominat condition due to COL10A1 mutations and MCD, McKusick type or cartilage hair hypoplasia (CHH), with autosomal recessive inheritance as result of RMRP mutations.
We report on a 3-year-old Finnish boy presenting with short stature (length since birth slightly under or along the 3rd percentile) with relatively short limbs and waddling gait. Radiographic features include metaphyseal changes with greater involvement of the lower extremities with mild coxa vara. The femoral necks are not yet in varus position. Hand X-rays show metaphysael irregularities of distal radius and ulna, mildly shortened tubular bones with metaphyseal cupping of the proximal phalanges. The clinically unaffected parents have no information on possible consanguinity (father's and mother's stature is 192cm and 165cm, respectively).
After negative tests for CHH (RMRP gene) and for HCH (FGFR3 gene), molecular analysis of COL10A1 revealed a homozygote missense mutation in exon 3 (G209S) resulting in an amino acid substitution Gly209Ser. The parents proved to be heterozygous carriers of this mutation which was not found in 50 German controls but in 2 of 62 Finnish probands.
Thus, we have identified a MCDM phenotype demonstrating that type X collagenopathies could present as an autosomal recessive condition when a rare COL10A1 polymorphism is found as homozygote mutation. Further studies have to clarify the functional consequences of the involved missense mutation.

ALBRIGHT OSTEODYSTROPHY AND ACROSCYPHODYSPLASIA COULD BE DUE TO A GNAS MUTATION.

Anne Coeslier1, Anne Marie Kottler 2, Sylvie Manouvrier1, Martine Le Merrer 3.

1 Genetics Department, Hopital Jeanne de Flandres, Lille, France ; 2 Genetics and reproduction department , CHU Caen, France ; 3 U393 and Genetics Department, Hopital Necker, Paris, France (lemerrer@necker.fr)

Acroscyphodysplasia was delineated in 1991 by Verloes et al and the main clinical features are micromelia, flexion deformities of the knee and severe brachydactyly. On radiographies, the lower femoral and upper tibial epiphyses are embedded in the metaphyses, which are severely cup-shaped; there are also brachyphanlangy and brachymetacarpy with cup shapped epiphyses. No endocrinologic abnormalities are mentioned but mental retardation could occur. Autosomal recessive inheritance was suggested. These radiological findings of the hand are similar in Albright osteodystrophy, where abnormal bone density and soft-tissue calcification and multiple endocrinopathies could be present. Pseudohypoparathyroidism type IB (PHPIB) is associated with abnormal imprinting of GNAS whereas PHPIA is due to inactivating maternal mutation.
We report here a woman exhibiting short stature, short hands and feets, normal long bones, pseudohypoparathyroidism, soft tissue-calcification, celiac disease, hypothyroidism and a low level of GSalpha protein. During the first months of life, her daughter present hypothyroidy, and dysmorphism : round face, short stature with very short hand and soft tissue calcification. The knees were flexed. The Xrays of the knees showed embedded epiphyses in the metaphyses suggesting acroscyphodysplasia. PTH level was normal whereas GSalpha level was decreased. A mutation of the exon of the 1 of GNAS was found both in the mother and the girl. This observation rises the question of the expressivity of the disease of the GNAS mutation and the overlap between PHPIB and acroscyphodysplasia.

PRESENTATION OF AN EXTENDED FAMILY WITH AUTOSOMAL DOMINANT NAGER SYNDROME

R.I. Ortiz-De-Luna*, J. Villa-Morales*, J. Aguirre-Hernández §

* Hospital Infantil de México 'Federico Gómez', México, D.F.

§ Centre for Veterinary Science, University of Cambridge, Cambridge, UK; ja248@cam.ac.uk

Nager syndrome is an acrofacial dysostosis involving antimongoloid slant of palpebral fissures, external ear defects, malar hypoplasia, micrognathia, cleft palate, and preaxial upper limb anomalies such as radial hypoplasia or aplasia, radioulnar synostosis, and thumb agenesis. Close to a hundred cases have been reported; most of them sporadic, with only two known extended families. AD and AR forms have been identified, suggesting genetic heterogeneity; the genes underlying them remain unknown. Different chromosome abnormalities have been reported in a few sporadic cases.
We present a large family with AD Nager syndrome, comprising 14 affected members in four generations. Incomplete penetrance and variable expressivity were observed, with males showing the most severe manifestation, while females present milder phenotypic alterations. The index case is a boy having the most extreme manifestation of the syndrome, as described above. Other family members show hand anomalies, limitation of elbow extension, or lip alterations. Several have hypoacusia, and in one case femur and tibia anomalies were present. No chromosome alterations were found by G banding.

THE EUROPEAN SKELETAL DYSPLASIA NETWORK – A SYSTEM FOR INCREASING ACCESS TO GENETIC TESTING OF BONE DYSPLASIAS.

Jacky Taylor (1) and the ESDN Group – www.esdn.org

(1) National Genetics Reference Laboratory, Regional Genetics Services, St. Mary's Hospital, Manchester

Skeletal dysplasias are a diverse group of genetic diseases affecting the development of the osseous skeleton. Because skeletal dysplasias are rare and exhibit extensive clinical variability and genetic heterogeneity, accurate diagnosis is a challenge for the non-expert. To provide equity of access to diagnostic and research experts we have established the European Skeletal Dysplasia Network (ESDN). ESDN has adopted two approaches; the research component of the project focuses on identifying the genes, mutations and disease processes that underlie skeletal dysplasias, whilst the diagnostic component integrates a network of expert clinicians and laboratories. Since January 2002, ESDN has received 1513 patient referrals from 23 EU and 10 non-EU countries. The causative mutations have been identified in 590 patients following 1100 diagnostic tests. Furthermore, the development of a custom built secure web-based case management system allows clinicians to submit cases to ESDN from anywhere in the world. Through the ESDN case manager, a clinical description and x-rays are assessed by the ESDN's panel of expert reviewers and an initial clinical diagnosis is confirmed or suggested. Patient DNA samples are then sent to the appropriate ESDN partner laboratory for molecular diagnosis. This is the first pan-European approach to the diagnosis of skeletal dysplasias, and therefore has major implications for the delivery of diagnostic services in the EC for the 21st Century. The model established by the ESDN is applicable to the diagnosis and management of any group of rare disease.

GENOTYPE-PHENOTYPE CORRELATIONS IN FRONTOMETAPHYSEAL DYSPLASIA

Stephen P Robertson* and members of the Otopalatodigital Spectrum Disorders Clinical Collaborative Group

*Otago University, Dunedin, New Zealand ;
stephen.robertson@stonebow.otago.ac.nz

Frontometaphyseal dysplasia is considered to be an X-linked trait primarily characterised by a skeletal dysplasia (supraorbital hyperostosis, thickening of the calvarium, sclerosis of the skull base, undermodelling of the the long bones particularly in the metaphyseal regions and undertubulation of the metacarpals, metatarsals and phalanges). Extraskeletal features include tracheobronchial, cardiac and urological malformations. A proportion of individuals have missense mutations or small deletions in the X-linked gene, FLNA.
We report here our experience with comprehensive screening of the FLNA gene in a group of 20 unrelated individuals with FMD. We found missense mutations leading to substitutions in the actin binding domain and in repeats 9, 10, 14, 16, 22 and 23 of filamin A in 50% of individuals in this cohort. Some mutations present with a male phenotype that is characterised by a severe skeletal dysplasia, cardiac and genitourinary malformations that lead death in infancy in affected males. While some individuals with no FLNA mutation identifiable present evidence suggestive for an unidentified X-linked aetiology, an additional autosomal locus cannot be ruled out.

CANDIDATE GENE ANALYSIS IN 4 FAMILIES WITH CDAGS SYNDROME (CRANIOSYNOSTOSIS, DELAYED FONTANEL CLOSURE AND CRANIAL DEFECTS, ANAL AND GENITAL ANOMALIES AND SKIN ERUPTION) MAPPING TO CHROMOSOME 22q

Roberto Mendoza-Londono [1,2], Edward Lammer [3], Rosemarie Watson [4], John Harper [5], Atsushi Hatamochi [6], Dobrawa Napierala [7], Pia Hermanns [1], Sinead Collins [4], Benjamin B. Roa [1], Madhuri R. Hedge [1], David W. Stockton [1], Brendan Lee [1,7] (blee@bcm.tmc.edu)

1. Baylor College of Medicine, Houston, TX , 2. The Hospital for Sick Children, Toronto, Canada, 3. CHORI, Oakland, CA, 4. Our Lady's Hospital for Sick Children, Dublin, Ireland, 5. Great Ormond Street Hospital for Children, London, UK 6. Dokkyo Univ. School of Med., Japan, 7. Howard Hughes Medical Institute, Baylor College of Medicine

CDAGS syndrome is a rare genetic condition characterized by craniosynostosis, delayed closure of the fontanel, cranial defects, clavicular hypoplasia, anal and genitourinary malformations and skin eruption. We have identified 7 patients in 4 families from different geographic regions and ethnic backgrounds with this phenotype. This is an autosomal recessive condition that brings together apparently opposing pathophysiologic and developmental processes, including accelerated suture closure and delayed ossification. Selected candidate genes including RUNX2, CBFB, MSX2, ALX4, TWIST1, and RECQL4 were screened for mutations by direct sequencing of their coding regions, and for microdeletions by FISH. No mutations or microdeletions were detected in any of the genes analyzed. A genome wide screen yielded the maximum estimated LOD score of +2.38 for markers D22S283 and D22S274 on chromosome 22q12-q13. Expression microarray analysis was used to identify candidates for significantly differentially expressed genes between fibroblast from affected individuals compared to normal controls. Genes located in the area of linkage that were significantly down regulated were sequenced. To date we have excluded mutations in the coding regions of RBM9, DDX17 and ATF4. We hypothesize that the gene defect in CDAGS exerts novel context-dependent regulation of multiple signaling pathways, including RUNX2 during osteoblast differentiation and craniofacial morphogenesis.

CLINICAL AND MUTATIONAL HETEROGENENEITY IN CARTILAGE-HAIR HYPOPLASIA AND EVOLUTIONARY COMPARISON OF THE RMRP GENE

[1]L. Bonafé, [1]S. Unger, [1]B. Xavier, [2]S.E. Antonarakis, [1]A. Superti-Furga, [2]A. Reymond

1Division of Molecular Pediatrics, CHUV, CH-1011 Lausanne (luisa.bonafe@chuv.ch); 2Department of Genetic Medicine and Development, University of Geneva, CH-1211 Geneva

We report our experience on RMRP mutation analysis in Cartilage-Hair hypoplasia patients. Forty-two different mutations have been reported so far in 91 Finnish, 47 non-Finnish Caucasian, and 2 Japanese families. We report here yet another series of 20 novel RMRP mutations in 36 unrelated Caucasian non-Finnish CHH patients. We show a wide spectrum of mutations as well as a wide variability of phenotypic features, with no genotype-phenotype correlation. A constant finding is short stature, but this finding is very variable and ranges from extremely severe (adult height below 100 cm) to moderate; at least 10% of patients were not short at birth. Radiological signs of metaphyseal dysplasia were present in all patients but not always in the first months of life: 2 patients had very mild radiological signs when CHH was diagnosed because of severe anemia and immune deficiency. About 33% of patients in our series had only skeletal manifestation of the disease; 1 of them developed malignancy in the third decade of life, indicating that this group of patients is indeed at increased risk of cancer even if immunological/hematological abnormalities are absent. Given the clinical and radiographic variability of CHH, molecular diagnosis is important both for appropriate counseling and to allow for relevant preventive measures.
The small RMRP gene shows a remarkable variety of mutations and a high density of single-nucleotide polymorphisms; the reasons for this apparent high mutability of RMRP in spite of its conservation is unclear but may involve a propensity of the gene to form tertiary structures or the lack of an hypothetical missense or nonsense mediated repair mechanisms. Because the RMRP RNA is not translated into protein, it is difficult to evaluate pathogenicity of a sequence variant. Through a comparative genomic approach, we show that putative pathogenic mutations, but not SNPs, are conserved in the entire mammalian class, thus providing a criterium for evaluation of newly recognised sequence variants.

SEVERELY INCAPACITATING MUTATIONS IN PATIENTS WITH EXTREME SHORT STATURE IDENTIFY RNA PROCESSING ENDORIBONUCLEASE RMRP AS AN ESSENTIAL CELL GROWTH REGULATOR

Christian T Thiel1, Denise Horn2, Bernhard Zabel3, Arif B Ekici1, Kelly Salinas4, Erich Gebhart1, Franz Rüschendorf5, Heinrich Sticht6, Jürgen Spranger3,7, Dietmar Müller8, Christiane Zweier1, Mark E Schmitt4, André Reis1, Anita Rauch1*

1Institute of Human Genetics, University of Erlangen-Nürnberg, Erlangen, Germany
2Institute of Medical Genetics, Virchow-Klinikum, Humboldt University, Berlin, Germany
3Children's Hospital, University of Mainz, Mainz, Germany
4Department of Biochemistry & Molecular Biology, SUNY Upstate Medical University, Syracuse, New York, USA
5Gene Mapping Centre, Max-Delbrück-Centre, Berlin, Germany
6Institute of Biochemistry, Department of Bioinformatics, University of Erlangen-Nürnberg, Erlangen, Germany
7Greenwood Genetic Center, Greenwood, South Carolina, USA
8Institute of Medical Genetics, Klinikum Chemnitz, Chemnitz, Germany

The growth of an individual is deeply influenced by regulation of cell growth and cell division, which also contribute to a wide variety of pathological conditions, including cancer, diabetes, and inflammation. In order to identify a major regulator of human growth we performed positional cloning in an autosomal recessive type of profound short stature, Anauxetic ('to let not grow') dysplasia (OMIM 607095). Homozygosity mapping led to the identification of novel mutations in the RMRP gene, which was previously known to cause two milder types of short stature with susceptibility to cancer, cartilage hair hypoplasia (CHH; OMIM 250250) and metaphyseal dysplasia without hypotrichosis (MDWH; OMIM 250460). We show that different human RMRP gene mutations lead to decreased cell growth by impairing ribosomal assembly and altering cyclin dependent cell cycle regulation. Clinical heterogeneity is explained by a correlation between the level and type of functional impairment in vitro and severity of short stature or presence of cancer predisposition.

ACROMESOMELIC DYSPLASIA TYPE MAROTEAUX – CLINICAL SPECTRUM AND NPR2 – MUTATIONS

Alanay Y[1], Balci S[1], Costa T[2], Hamamy H[3], Russo A[4], Hilbert K[4], Wildhardt G[5], Brzezinska R[6], Schumacher R[6], Superti-Furga A [7], Spranger J[4], Zabel B[4] – yalanay@hacettepe.edu.tr, zabel@molgen.medizin.uni-mainz.de

[1] Clinical Genetics Unit, Dept. Pediatrics, Hacettepe University School of Medicine, Ankara, Turkey,; sbalci@hacettepe.edu.tr ; [2] Service de Génétique Medical, Hôpital Saint-Justine, Montréal, Canada; [3] National Center for Diabetes, Endocrinology and Genetics, Amman, Jordan; [4] Children's Hospital, University of Mainz, Mainz, Germany; [5] Bioscientia Institute, Ingelheim, Germany; [6] Dept. Radiology, Children's Hospital, University of Mainz, Mainz, Germany; [7] Centre for Pediatrics, University of Freiburg, Freiburg, Germany

Acromesomelic Dysplasia, Maroteaux type (AMDM, MIM: 602875) is an autosomal recessive condition. The underlying defect has recently been identified (Bartels et al., 2004). We now present a study on five cases with putative AMDM, where we were able to detect the causative NPR2 mutations in four patients:
(1) A 5-month-old boy is compound heterozygous with a splice site mutation (IVS7 +1 G→T) also found in the mother and a missense mutation in exon 15 (R796P) inherited from the father. (2) A 4-year-old boy has a homozygous 1213delT mutation, leading to a premature stop codon in exon 6 at position 427 of the protein sequence. The consanguineous parents are heterozygous carriers of 1213delT. (3) A 6.5-year-old girl is compound heterozygous with a missense mutation R218W in exon 1 coming from the mother and a nonsense mutation R668X most likely inherited from the nonconsanguineous father (not available for analysis). (4) A 7.5-year-old boy is homozygous for a missense mutation in exon 16 (R804C). The mother is heterozygous for the R804C mutation, the consanguineous father was not available for analysis.
A fifth patient, a 16-year-old boy with clinical and radiographic signs of Acromesomelic Dysplasia, but not specifically Maroteaux type, proved negative when tested for NPR2 mutations.
Correlating phenotype and genotype of our AMDM patients helps to link these data and define the clinical spectrum of AMDM. Of specific interest will be to look for overlaps with FGFR-disorders (e.g. Achondroplasia) as related pathways should be affected in both conditions.

THE EFFECTS OF DISEASE-CAUSING MUTATIONS IN LRP5 ON WNT AND NORRIN SIGNAL TRANSDUCTION

Minrong Ai, Matthew L. Warman, and the Osteoporosis-Pseudoglioma Collaborative Group

Mutations in the low-density lipoprotein receptor-related protein 5 (LRP5), a co-receptor for Wnt and Norrin ligands, have been described in humans with two distinct bone disorders. LRP5 mutations predicted to result in a loss-of-function cause the autosomal recessive Osteoporosis-Pseudoglioma syndrome (OPPG) and in a gain-of-function cause autosomal dominant High Bone Mass (HBM) phenotypes. Mutations in LRP5 have also been reported in some patients with Familial Exuditive Vitreoretinopathy (FEVR). We have identified 42 mutations, including 17 missense mutations, in a cohort of 37 patients with OPPG. To distinguish disease-causing missense mutations from benign variants, we expressed OPPG-causing mutants in 293T cells and assessed their ability to transduce Wnt 1, Wnt 10b, and Norrin signal. Of the seven OPPG mutants tested thus far, none were able to transduce signal at levels comparable to wild-type LRP5, and none acted in a dominant-negative manner. We also expressed missense mutants that have been associated with HBM and FEVR phenotypes. None of the seven tested HBM mutants had impaired Wnt signal transduction; instead each HBM mutant was less inhibited by DKK1 than wild-type LRP5. FEVR mutants had varied effects on the Wnt and Norrin signaling, with some mutants having a complete loss of signal transduction and others appearing indistinguishable from wild-type LRP5.

It is now possible to determine whether in vivo phenotypes due to LRP5 mutation correlate with ex vivo assays of signal transduction. Additionally, precisely defining the mechanism by which specific missense mutations affect LRP5 function (e.g., at the level of protein trafficking, ligand binding, co-receptor interaction, or interaction with endogenous inhibitors) should lead to improved therapies for disorders of high and low bone mass.

POSTER ABSTRACTS

(In alphabetical order according to presenter's name)

SPONDYLO-OCULAR SYNDROME: CONFIRMATION OF AN ENTITY INVOLVING THE EYE AND SPINE

Yasemin Alanay (1), Andrea Superti-Furga (2), Fatih Karel (3), and Ergul Tuncbilek (1)

(1) Hacettepe University, Dept of Pediatrics, Genetics Unit (2) University of Freiburg, Centre for Pediatrics, (3) Ankara University, Dept of Ophthalmology

In 2003, Rudolph et al. described five siblings with consanguineous parents who had cataract, crystalline lens malformation, retinal detachment, osteoporosis, and platyspondyly. Linkage to several known genes (COL11A1, COL11A2, COL2A1, and LPR5) was excluded and a new disorder, “spondylo-ocular syndrome”, was proposed.

We observed a 6 years old boy with clinical and radiologic features of spondylo-ocular syndrome. He is the second child of a non-consanguineous couple with a healthy daughter. At birth, bilateral cataract and a harsh murmur were recognized. He was operated for the cataract at one year age, and followed for the subaortic ventricular septal defect. At age 3 years he had generalized osteoporosis and platyspondyly. At age 5 years, he had short stature with short trunk, full cheeks, a long philtrum with thin upper lip, low set ears with thick helices, anti-helix abnormality and preauricular pits. AP chest diameter was increased, and pansystolic murmur was heard. Kyphosis, bilateral pes planus, joint hyperextensibility, and smooth hyperelastic skin were noted. Xrays confirmed generalized osteoporosis, severe platyspondyly with fish vertebrae, and increased intervertebral disc spaces. The diagnosis of spondylo-ocular syndrome was considered. Since then, he is being treated with calcium and Vit D supplement and there is improvement in motor development and in BMD measurements.

Ocular findings in infancy were congenital bilateral dense cataract and nystagmus. Visual acuity was limited to light perception. Intraocular pressure and ultrasound examination were normal. Lensectomy, posterior capsulorhexis and anterior vitrectomy were performed bilaterally. On the most recent examination visual acuities were 0.2 with correction. He had +14.00 D aphakic glasses and visual axes were clear. Corneal curvature had extremely low values. Keratometric mean values was +34 D in the right eye and +33 in the left eye. Pressure was 10 mmHg bilaterally. Fundoscopy showed a myopic crescent, hyper- and hypopigmented retinal areas and thin retinal vessels. US showed myopic shift with axial lengths 27.35 mm (right) and 26.66 mm (left) but no retinal detachment. VEPs showed normal latencies bilaterally.

The ocular and skeletal features are identical to those described by Rudolph et al. and seem to confirm "spondylo-ocular syndrome" as a distinct entity.

UNUSUAL CLINICAL FEATURES IN A PATIENT WITH AUTOSOMAL RECESSIVE FORM OF MULTIPLE EPIPHYSEAL DYSPLASIA EXTENDING THE PHENOTYPE OF THIS ENTITY

Boyan Dimitrov, Luisa Bonafe, Irina Balikova, Geert R. Mortier, Andrea Superti-Furga, Jean-Pierre Fryns

B.D, I.B. and J.P.F. - Centre for Human Genetics, KU Leuven, Belgium
L.B. and A.S.F. - Division of Molecular Pediatrics, Centre Hospitalier Universitaire Vaudois Rue du Bugnon, Lausanne, Switzerland
G.R.M. - Department of Medical Genetics, University Hospital of Gent, Belgium
Dimitrov.Boyan@uz.kuleuven.ac.be

Multiple epiphyseal dysplasia is a clinically relatively mild and genetically heterogeneous skeletal dysplasia caused by mutations in six genes (COMP, COL9A2, COL9A3, COL9A1, MATN3 and DTDST). The observed phenotype correlate on some degree with the genetic background thus giving an opportunity on this level the clinicians to decide which molecular defect(s) to be screened. However currently between 30% and 50% of the patients with such a phenotype remain negative for a mutation in any of these alleles challenging an appropriate genetic counselling and long-term prognosis.
We report a female patient referred to the Clinic at 14 years of age because of progressive skeletal deformations starting since 1 year of age. X-ray examination revealed skeletal abnormalities consistent with a multiple epiphyseal dysplasia. At the age of 24 years she presented a precocious hip osteoarthrosis requiring arthroplasty with replacement of a prothesis. Because of this quit progressive natural history, there was re-evaluation of the diagnosis and a Progresive Pseudorheumatoid Chondrodysplasia was discussed as an option, as well an Autosomal Dominant Spondylarthropathy due to mutation in COL2A1 gene as shortness of 4th metatarsal bone of left foot was observed. However X-ray re-examination revealed a double-layer patella in addition to the abnormities of the foot bones. Molecular analysis identified that the patient is a carrier of two mutations in the DTDST gene c.1984T>A(p.C653S) and c.2171C>T(p.A715V) (compound heterozygousity). Analysis of COL2A1 gene did not detect any mutation thus sowing that the observed extended phenotype with involvement of metacarpal bones is the result of the disturbed function of the DTDST gene only.

HYDROMETROCOLPOS, POSTAXIAL POLYDACTYLY, AND HYPOTHALAMIC HAMARTOMA IN A PATIENT WITH PROBABLE PALLISTER-HALL SYNDROME: DIFFERENTIAL DIAGNOSIS WITH THE MCKUSICK-KAUFMAN SYNDROME

S. Kos, K. Roth, G. Zeilinger and G. Eich

Kinderspital, Kantonsspital Aarau, Switzerland

We present a preterm born girl (36 0/7 wks) with postaxial heptadactyly of both hands. Vaginal atresia with massive hydrometrocolpos, elevation of both diaphragms, and respiratory distress required emergent tracheal intubation and percutaneous insertion of a vaginal catheter for drainage of urine at birth. Both kidneys were small and hydronephrotic. Contrast studies of the vagina and urinary bladder and endoscopy showed a fistula connecting the bladder neck to the vagina. X-ray findings of the hands are consistent with Pallister-Hall syndrome (PHS). Cranial ultrasonography revealed a large hypothalamic mass which on magnetic resonance imaging showed characteristics of a hamartoma.

This patient was considered initially to represent McKusick-Kaufman syndrome, but the radiographic features of the hands and the hypothalamic lesion clearly indicate PHS as the underlying disorder. This therefore is the second description of the association of PHS with hydrometrocolpos due to vaginal atresia.

MUTATIONS AND POLYMORPHISMS IN THE SINGLE A-DOMAIN OF MATRILIN-3 AFFECT THE STRUCTURE AND FUNCTION OF THIS IMPORTANT CARTILAGE STRUCTURAL PROTEIN

Maryline Fresquet, Tom Jowitt, David Knight, David Thornton and Mike Briggs

Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester; mike.briggs@manchester.ac.uk

Mutations in the single A-domain of matrilin-3 gene have been shown to result in multiple epiphyseal dysplasia (MED). With one exception all disease-causing mutations are located within the central beta-sheet of the A-domain, suggesting that they may disrupt the structure and/or function of this important domain. In addition a non-disease causing polymorphism (E252K) was identified in the alpha-7 helix, which may act as a genetic modifier of phenotypic severity.
Expression of wild type and mutant full-length matrilin-3 in mammalian cells has confirmed that the mutations prevent the secretion of the mutant protein, whilst expression of A-domain constructs alone has demonstrated that the MED mutations actually disrupt the folding of the A-domain and prevent the formation of an intrachain disulphide bond. To investigate the role of E252K as a genetic modifier of phenotypic severity, wild type and E252K A-domain proteins were expressed in 293-EBNA cells and purified using affinity chromatography. The identity of both recombinant proteins was confirmed by mass spectrometry, whilst size exclusion chromatography coupled with laser light scattering showed that the A-domain was a single 24kDa species. In order to determine the structural and functional significance of E252K a range of biomolecular analysis techniques were used including light scattering, analytical ultracentrifugation and circular dichroism.

MUTATION OF SNAPc BINDING SITE IN RNASE MRP PROMOTER IN CARTILAGE-HAIR HYPOPLASIA

Carola Vaccaro1, Anna Schito1, Marco Musso2, Beicong Ma3, Aldo Pagano1, Sara Tavella1, Achille Iolascon4, Nouria Hernandez3, William A. Horton5 , Ranieri Cancedda1, and Silvio Garofalo1

1 Department of Oncology, Biology and Genetics at National Cancer Research Center and University of Genova Medical School, L. R. Benzi 10, 16132 Genova, Italy.
2 G. Gaslini Institute, Largo G. Gaslini 5, 16148 Genova, Italy.
3 Howard Hughes Medical Institute and Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724 USA.
4 CEINGE Biotecnologie Avanzate and University of Naples Medical School, Via Comunale Margherita n. 482, 80145 Napoli, Italy.
5 Shriners Hospital for Children and Oregon Health & Sciences University, Portland, OR, USA.

Cartilage-Hair Hypoplasia is a pleiotropic human disorder characterized by short stature, hypoplastic hair, immune defect, megacolon, and predisposition to cancer. RNAse Mithochondrial RNA Primer (RNAse MRP or RMRP) was identified as the causative gene of the disease. Such gene encodes for a small RNA with riboenzymatic activity that is not translated into any protein. RMRP mutations can be distingushed into two classes: mutations in the RNA nucleotide sequence non-affecting gene expression and insertion/duplications in the promoter that directly affect transcriptional activity. Since the RNA from the alleles with the last mutations cannot be amplified by RT-PCR and homozygous CHH patients with promoter mutations have never been identified, it is believed that they create null alleles leading to embryonic lethality.
We have identified an Italian patient affected by CHH, who was double heterozygote for two mutations in the RMRP promoter. One allele carried 8 nucleotides insertion/ duplication at -6, while the other allele was carrying a single A to G substitution at -54 from the transcription start site. In this position it is placed an important cis-element, called Proxymal Sequence Element (PSE), which is critical for the binding of the pentameric complex of activating polypeptides known as SNAPc. This mutation reduces the affinity of SNAPc to the promoter, decreasing Pol III transcriptional activity and the level of RMRP RNA. By precise real time measurement in a defined cell system, we calculated that the alleles identified in the patient reduced RMRP RNA to 1/5 of normal, showing that this reduction of RMRP RNA is still compatible with the clinical spectrum of CHH.

PECULIAR SKELETAL CHANGES ASSOCIATED WITH MATERNAL UNIPARENTAL HETERODISOMY FOR CHROMOSOME 14 IN A PHENOTYPICALLY ABNORMAL t(13;14) ROB. TRANSLOCATION CARRIER

L. Giunti°, L. Carosi*, U. Ricci°, M. Ottaviani*, M. Levi*, S. Stagi**, C. Fonda°°, L. Di Medio*, S. Toccafondi*, E. Lapi°, M.L. Giovannucci Uzielli* uzielli_ml@unifi.it

° Children's Hospital A. Meyer, Genetics Unit
* University of Florence Department of Paediatrics, Genetics
** University of Florence Department of Paediatrics, Endocrinology
°° Children's Hospital A. Meyer, Radiodiagnostics Unit, Florence (Italy)

Uniparental disomy(UPD) corresponds to the presence of two homologous chromosomes or chromosomal segments derived from one parent in a diploid offspring. The adverse phenotypic effect is due to the existence of parent of origin differences in the expression of the same gene. Molecular analysis demonstrated for many human chromosomes the concept introduced by Engel in 1980. More than 20 cases of (UPD)(14)mat have been reported in the literature: the majority was found in balanced carriers of Robertsonian translocations with an abnormal phenotype.
A distinct phenotype is emerging from the reports of the literature, but also for our experience the clinical expression of (UPD)(14)mat is variable. In a 31-year old lady, referred for a genetic evaluation aimed to a programme of procreation, we especially underline some skeletal aspects: severe short stature and hypochondroplasia-like phenotype, macrosomia with plagiocephaly and flat face, scoliosis, small hands and feet, short limbs, congenital clubfoot, normal intelligence. X-rays images exclude the hypochondroplasia patterns and show few congenital and acquired abnormal aspects.

DESBUQUOIS DYSPLASIA: RADIOLOGICAL AND CLINICAL PATTERNS FOR THE DIAGNOSIS OF A RARE AUTOSOMAL RECESSIVE CONDITION

Miriam Levi*, Maddalena Ottaviani*, Lisa Di Medio*, Silvia Toccafondi*, S. Stagi°, L. Carosi*, L. Giunti°°, C. Fonda°°°, E. Lapi°°, M.L. Giovannucci Uzielli*; uzielli_ml@unifi.it

* University of Florence, Department of Paediatrics, Genetics
° University of Florence, Department of Paediatrics, Endocrinology Unit
°° Children's Hospital A. Meyer, Genetics Unit
°°° Children's Hospital A. Meyer, Radiodiagnostics Unit, Florence (Italy)

In a 7 year old girl referred for "short stature of prenatal onset and severe kyphoscoliosis", on the basis of the clinical phenotype we firstly hypothesized a diagnosis of Larsen's syndrome. The skeletal changes, revealed by X-ray performed in different ages, suggested the definitive diagnosis of Desbuquois chondrodysplasia: a rare autosomal recessive disorder characterized by facial dysmorphisms, generalized and severe hyperlaxity with multiple large joint dislocations, and short stature. The proposita is the first child of healthy non-consanguineous italian parents. Delivery at 34 weeks gestation: twins pregnancy characterized by maternal gestosis in the second trimester (the twins female baby died for intracranial hemorragy, soon after birth). Birth weight was 1400 g (3rd centile), head circumference 29 cm (3rd centile), and length cm 41 cm (< 3rd centile).

At birth, cutis laxa, general hypotonia, weak crying, round flat face, micrognathia, bifid ugola, long upper lip with flat philtrum. Small thorax with pectus carinatum. Bilateral clubfoot with flipper-like aspect. From age of 6 months, evident, progressive joint laxity with multiple severe dislocations, and characteristic changes at hand and foot level, with radially deviated fingers at the metacarpophalangeal and interphalangeal joints, abnormalities of phalangeal and carpo-tarsal bones, abnormal ossification, elevated greater trochanter, flat acetabular root, vertebral and ribs abnormalities with kiphoscoliosis. Adult stature was 114 cm. The girl died at age 22 from incomplete, postsurgical, wound cicatrisation.

CLINICAL AND MOLECULAR CHARACTERIZATION OF TWO ADULTS WITH AUTOSOMAL RECESSIVE ROBINOW SYNDROME

Denise Horn (1), Fatih Tufan (2), Stefan Mundlos (1)

(1) Institute of Medical Genetics, Charité, Berlin, Germany
(2) Department of Internal Medicine, Istanbul Medical Faculty, Istanbul, Turkey

Autosomal recessive Robinow syndrome is caused by mutations in ROR2 and is characterized by short stature, mesomelic limb shortening, brachydactyly, vertebral abnormalities, and a characteristic “fetal face” dysmorphology. We report the clinical and molecular studies on two adults with this condition. Besides typical skeletal and facial features, one patient developed hydronephrosis, nephrocalcinosis, and renal failure. The second patient had characteristic skeletal manifestations including severe spinal involvement and showed endocrinological abnormalities including elevated gonadotropic hormones. The facial phenotype in both patients remained distinctive into adulthood. Analysis of the ROR2 gene revealed a homozygous c.1937_1943delACAAGCT mutation in patient 1, and compound heterozygosity for c.355C>T (p.R119X) and c.550C>T (p.R184C) in patient 2.

GROWTH HORMONE TREATMENT IN 35 PREPUBERTAL CHILDREN WITH ACHONDROPLASIA

NT Hertel*, I. Kaitila**, I Sipilä***, M Ritzen**** & L Hagenäs****.

Paediatric Dept. Odense University Hospital, Odense, Denmark, **Clinical Genetics Research, Haartman Institute, Helsinki, Finland, ***Paediatric Endocrinology, Childrens Hospital, Helsinki, Finland, ****Paediatric Endocrinology, Karolinska Hospital, Stockholm Sweden. E-mail: ilkka.kaitila@hus.fi

Achondroplasia is a skeletal dysplasia with extreme, disproportionate, short stature. In a five year GH-treatment study including one year off treatment we investigated growth and body proportion response in 35 children with achondroplasia. Patients were randomised to either 0.1 IU/kg (n=18) or 0.2 IU/kg (n=17) per day. GH-treatment was interrupted for twelve months after two years of treatment in prepubertal patients to study catch-down growth. Mean height-SDS (HSDS) at start were for the low/high dose groups -5.6/ -5.2 respectively and mean age 7.3/6.6 years. Mean growth velocity (baseline 4.5/4.6 cm/yr for the groups), increased significantly by 1.9/3.6 cm/yr during first year and by 0.5/1.5 cm/yr during second year. During the 3rd year a decrease of growth velocity was observed at 1.9/1.3 cm/yr below baseline values. HSDS increased significantly by 0.6/0.8 during the first year of treatment and in total by 1.3/1.6 during the five years of study. Sitting height SDS improved significantly from -2.1/-1.7 to -0.8/0.2 during the study. Body proportion (sitting height/ total height) or armspan did not show any significant change. There was no marked advancement in mean bone age compared to chronological age. Bone age was close to or matched chronological age after 4 to 5 years of hGH treatment (ratio ΔBA/ΔCA mean (SD): 1.1(0.3). There were no apparent differences between dose groups.
Conclusion: GH-treatment of children with achondroplasia improves height during four years of therapy without adverse effect on trunk-leg disproportion. The short-term effect is comparable to that reported in Turner and Noonan syndrome and in idiopathic short stature.

FAMILIAL CAMPOMELIC, NON-FRACTURING OSTEOGENESIS IMPERFECTA

I Kaitila, E. Marttinen

Clinical Genetics Research, Haartman Institute, University of Helsinki, and Hospital for Children and Adolescence, Helsinki University Central Hospital, Helsinki, Finland

The hallmark OF osteogenesis imperfecta (OI) is bone fragility. However, the interfamilial and intrafamilial clinical variablity of phenotype is remarkable. We have encountered with a five-generation family in which the proband, the first son, and her mother presented with severe campomelic deformities of tibiae and femurs at birth. By the age of three years the deformities had completely straightened without treatment and the only sign of OI was moderately short stature. The extended family history revealed six affected members. The grand-uncle had suffered of more than 100 fractures by the age of 42 years, mainly on the lower legs whereas the fracture number in other members of the family varied from 5 to 15. The common clinical sign was short stature. The condition is due to IVS46 +1G>A mutation in COL1A2. Studies on splice variation are in progress.

GROWTH CHARTS FOR WEIGHT, HEIGHT AND OTHER ANTHROPOMETRIC MEASUREMENTS IN CHILDREN WITH SKELETAL DYSPLASIAS.

J.E. Hoover-Fong [1,2], J. McGready [1,3], K.J. Schulze [1,3], H. Barnes [2], C.I. Scott [4]. (presented by Iain Macintosh)

1) Johns Hopkins University, Baltimore, MD 2) McKusick-Nathans Institute of Genetic Medicine, Greenberg Center for Skeletal Dysplasias, Baltimore, MD 3) Bloomberg School of Public Health, Baltimore, MD 4) AI DuPont Hospital for Children, Wilmington, DE.

Accurate assessment of growth parameters in skeletal dysplasias patients is problematic with current growth curves. Most were constructed from a small number of patients with a paucity of longitudinal data. Furthermore, data were compiled from multiple clinical settings using potentially non-standardized observational methods, and the curves were derived from very basic parametric analysis. Of clinical significance, weight-for-age norms are currently unavailable, despite significant negative orthopaedic, neurologic and general health sequelae caused by unrecognized and untreated obesity in this patient population. We have collected extensive, longitudinal anthropometric data from medical records of patients with a variety of skeletal dysplasias. The majority of the data were from patients with achondroplasia (n=334), with >2000 datapoints for height, weight and head circumference. Other skeletal dysplasias considered include hypochondroplasia, spondyloepiphyseal dysplasia congenita, diastrophic dysplasia, and Morquio syndrome. Patients were born between 1931 and 2004, and all anthropometric measurements were obtained by a single observer (Scott). Gestational age and birth weight, length and head circumference were also analyzed for each skeletal dysplasia type. Percentiles (5, 25, 50, 75, and 95th) were estimated across the age continuum for each growth parameter using a moving 6 month window. Percentiles were then smoothed using a quadratic, penalized smoother. This improves upon previous approaches for generating growth curves by taking advantage of the longitudinal nature of the data, thereby improving the precision of the percentile estimates. New growth charts constructed from these data conform to the current CDC curve structure for average stature individuals, with one chart for each anthropometric parameter for ages 0-36 months and another for 2-20 years.

SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA WITH SEVERE FAILURE TO THRIVE AND PSYCHOMOTOR RETARDATION IN A CHILD WITH A GLY904GLU SUBSTITUTION IN COL2A1

Mendoza-Londono R.1, 2, Kleppe S. 1, Potocki L. 1, Bacino C.A. 1 and Leroy J.G. 1 (mendozal@bcm.tmc.edu)

1. Department of Molecular and Human Genetics, Baylor College of Medicine, Texas Children's Hospital, Houston, USA 2. Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada.

Mutations in type II collagen result in a spectrum of conditions with distinctive skeletal phenotype and normal intellect and brain development. We present the case of a Hispanic female evaluated at 2 months of age because of history of intrauterine growth retardation, poor feeding and failure to thrive. COL2A1 sequence analysis revealed a G>A transition in exon 47 resulting in a a Gly904Glu substitution in the fibrillar domain of type II collagen. Initial X-ray evaluation showed retarded ossification of the skeleton with flattening and anterior ossification defects of the vertebral bodies, and epiphyseal and metaphyseal irregularities of the long bones. Throughout infancy and early childhood, the patient failed to meet early developmental milestones and required gastrostomy tube feeding. Evaluation at age 4.5 years revealed a length of 68 cm, weight of 6965 g and head circumference of 44 cm (50th centile for a 7 month-old). She was profoundly hypotonic with no head control and no language development; had conductive hearing impairment, bilateral optic nerve hypoplasia, abnormal electroretinogram and visual evoked potentials. Brain MRI showed marked atrophy with bilateral enlargement of the frontal and temporal horns of the III ventricle, generalized delayed myelination and thin corpus callosum. Chromosome analysis, telomere FISH, plasma aminoacids, urine organic acids, very long chain fatty acids, arylsulfatase A and plasma sterol panel were normal. To our knowledge this is the first report of this constellation of findings associated to this mutation; the glycine residue at position 904 is very conserved in all fibrillary collagens, and mutations of glycine residues in the proximity have resulted in lethal forms of type II achondrogenesis. Type II collagen is expressed primarily in mesenchymal tissues during chondrocyte development, but it is also expressed in tissues such as the notochord, neural retina, heart, fetal brain, and the epithelium of the otic vesicle. We propose that this specific COL2A1 mutation may have severe deleterious effects to the developing CNS starting at an early developmental stage, and result in features that are reminiscent of microcephalic osteodysplastic primordial dwarfism. Alternatively the encephalopathy may have an independent cause. Further discussion will help provide direction in determining a definitive diagnosis in this interesting young patient.

METAPHYSEAL DYSPLASIA WITH CONE SHAPED EPIPHYSES OF THE LOWER LIMBS (BELLINI TYPE): TWO ADDITIONAL PATIENTS WITH UNIQUE EXTRA-SKELETAL MALFORMATIONS.

Roberto Mendoza-Londono1,2, Michael J Gambello3, Alan E Schlesinger4, V Reid Sutton1 (vsutton@bcm.tmc.edu)

1.Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; 2. Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada; 3.Department of Pediatrics, Division of Medical Genetics, University of Texas Health Sciences Center, Houston; 4. Department of Radiology, Baylor College of Medicine

Bellini type metaphyseal dysplasia is a rare skeletal dysplasia identified by unusual, cone-shaped metaphyses of the distal femora. Some patients have acrodysostosis with metaphyseal cupping of bones in the hand and alopecia and this constellation has been termed “metaphyseal acroscyphodysplasia” (MIM#250215). In other case reports, hand abnormalities have not been seen. Common manifestations of both metaphyseal acroscyphodysplasia and isolated metaphyseal chondrodysplasia with cone-shaped epiphyses include short stature, cone-shaped metaphyses of the distal femora, knee contractures and occasionally metaphyseal abnormalities of the arms, scoliosis and vertebral abnormalities. In the subset of patients with metaphyseal abnormalities of the hands, psychomotor delay and alopecia are common. We describe two unrelated patients with Bellini metaphyseal dysplasia without hand involvement or alopecia, both of whom have various extra-skeletal abnormalities. Patient one is now a 10-year-old African-American boy who has mild mental retardation, short stature, joint contractures of the knees with an 8 cm leg-length discrepancy and had precocious puberty that began at 9 years-of-age. He does not have any facial dysmorphism. Patient two is a 3-year-old girl of Northern European descent who has short stature, knee contractures, nystagmus, hypotelorism, a single upper central incisor with normal intellectual development and a normal brain MRI. We present the details of the clinical histories, radiographs and photographs of phenotypic abnormalities. Based on the previous fifteen case reports and these two cases, there is significant variability in extra-femoral involvement in all of the cases with many other rare and unique phenotypic features in each individual patient. We therefore suggest that “metaphyseal chondrodysplasia with cone-shaped epiphyses” is not always a specific diagnosis in and of itself, but may be either isolated or part of a constellation of variable abnormalities.

IDENTIFICATION OF AN UNBALANCED X-AUTOSOME TRANSLOCATION BY ARRAY-CGH IN A BOY WITH A SYNDROMIC FORM OF CHONDRODYSPLASIA PUNCTATA BRACHYTELEPHALANGIC TYPE

Menten B, Buysse K, Vandesompele J, De Smet E, De Paepe A, Speleman F, Mortier G.

Dept Med Genetics, Ghent University Hospital, Ghent, Belgium

Screening of a large series of patients with unexplained mental retardation with a 1Mb BAC array resulted in the detection of several cryptic chromosomal imbalances. In this paper we present the findings of array-CGH screening in a 14-year-old boy with mental retardation, obesity, short stature and brachydactyly. The proband was born at term after an uncomplicated pregnancy. Birth measurements were normal and the perinatal course uneventful. At the age of 1 month, he presented with hypotonia, facial dysmorphism with small, deeply set nose, and short limbs with brachydactyly. A normal male karyotype was found. Excessive weight gain was observed around the age of 3 years. At the age of 5 years he was referred because of short stature, obesity and moderate mental retardation. Physical examination revealed a weight of 22 kg (P90; BMI=22.2), length of 99.5 cm (-2.5 sd) and head circumference of 52.3 cm (P50-P98). The face was round with flat profile, high forehead and short nose. Brachydactyly was noted with short distal phalanges of third and fourth fingers. Hand radiographs showed bilaterally short and dysplastic distal phalanges. Evaluation of earlier radiographs did not reveal punctuate calcifications but changes reminiscent for the brachytelephalangic type of chondrodysplasia punctata. The possibility of a microdeletion on the short arm of the X-chromosome, encompassing the ARSE gene, was considered. However, molecular analysis at that time failed to detect any abnormalities of the ARSE gene. On follow-up the boy developed severe obesity with hyperinsulinism (BMI=41.4). Screening with array-CGH resulted in the detection of a distal 9p trisomy and distal Xp nullisomy caused by an unbalanced X;9 translocation: 46,Y,der(X)t(X;9)(p22.32;p23). The identification of this de novo chromosomal rearrangement not only made accurate genetic counseling possible but also explained most of the phenotypic abnormalities observed in this patient.

MULTIPLE EXON-SKIPPING OF THE ALPL GENE IN A PATIENT WITH SEVERE HYPOPHOSPHATASIA

Brun-Heath I (1), Chabrol E (1), Fox M (2), Serre J-L (1), Taillandier A (3), Mornet E (1,3)

(1) EA 2493, Université de Versailles, Versailles, France; (2) UCLA Genetics, Los Angeles, CA, USA; (3)Laboratoire SESEP, Université de Versailles, Versailles, France. etienne.mornet@cytogene.uvsq.fr

Hypophosphatasia is a rare inherited bone disease due to mutations in the ALPL gene. Some cases of moderate hypophosphatasia are dominantly transmitted. We report the molecular study of a patient prenatally diagnosed with lethal hypophosphatasia and carrying the heterozygous dominant mutation D361V (c. 1133A>T) and no other detectable mutation in the coding sequence. Quantitative RT-PCR of ALPL mRNA extracted from fetal fibroblasts showed that mRNA level was 14 times increased when compared with control fibroblasts. By using exon 1L and 1B tissue-specific oligonucleotides, we showed that mRNA was bone-specific and not liver-specific.The alkaline phosphatase activity of fetal fibroblasts measured in vitro was found to be almost undetectable compared with control fibroblasts. Cloning and sequencing the cDNAs showed that most of the cDNAs did not carry D361V and exhibited multiple exon-skipping involving exons 2-4, 7 and 9. Only exons with a AG 5' exonic splice site were affected. Our results suggest that in addition to the D361V mutation in the ALPL gene, the patient carried a mutation affecting ALPL splicing regulation that results in accumulation of aberrant transcripts.

MULTIPLE EPIPHYSEAL DYSPLASIA WITH HERNIAS, HYPERMOBILITY AND DYSMORPHISMS

Nikkel SM
Department of Genetics, CHEO, Ottawa, ON, Canada, snikkel@cheo.on.ca

Multiple epiphyseal dysplasias (MED) are heterogeneous. To date, a number of mutated genes have been found to be responsible (COL9A1, COL9A2, COL9A3, COMP, MATN3, SLC26A2). They encode extracellular structural proteins or are involved in the transport of substrate. However, they account for only a proportion of cases. The recessive type of MED is often associated with other findings including scoliosis, clubfoot and cleft palate. The dominant types typically do not have these features. MEDs can be difficult to diagnose after the growth plates are fused, and thus patients may be missed. We describe a MED in the setting of a dysmorphic syndrome.

Our patient was initially referred to the genetics clinic at one year of age because of dysmorphic features, hypotonia, clubfoot, microcephaly and umbilical hernia. The family is French-Canadian with an unremarkable medical history and no consanguinity. He was lost to follow-up and re-referred at 7 years of age by orthopedics after epiphyseal changes were noted during investigations of an ulnar fracture. In the intervening years, he had the umbilical hernia repaired and later had epigastric and bilateral inguinal hernias repaired. He has significant joint hypermobility. Vision and hearing along with cognitive development have been normal. Clinical features include flat facial profile with mid face hypoplasia and micrognathia. Palate is intact. He has prominent eyes with ptosis. There is a single palmar crease and persistent fetal fingertip pads. Height is at the 75th percentile and head circumference is -2SD. A skeletal survey revealed delayed ossification of some carpal bones and small flattened epiphyses, especially in the distal radial and fibular epiphyses. Mild endplate irregularities were present in many vertebral bodies, but no platyspondyly. The association of MED with this constellation of features has not been previously reported to our knowledge.

SPONDYLOEPIMETAPHYSEAL DYSPLASIA ASSOCIATED WITH JOINT LAXITY AND MULTIPLE DISLOCATIONS, MENTAL RETARDATION, RETINOPATHY AND DEAFNESS

J. Pinto-Basto1, J. Ramos-Alves2, G. Soares1, C. Dias1, M. Martins1, A. Fortuna1, M. Reis-Lima1;

1Instituto de Genética Médica, Porto, Portugal, 2Hospital S.João, Porto, Portugal.
jorge.pintobasto@igm.min-saude.pt

The term spondyloepimetaphyseal dysplasia (SEMD) embraces a large group of disorders, distinguished on the basis of clinical and radiological features.
We report the first and only son of a consanguineous couple (first cousins once removed), referred to us at 33 months of age for confirmation of bone dysplasia. He showed severe short stature of prenatal onset, severe kypho-scoliosis and a skeleton x-ray compatible with a spondyloepimetaphyseal dysplasia. He also presented with congenital hip dislocation, joint laxity and multiple dislocations. Large eyes with blue sclera, and short neck were noted, but no real facial dysmorphism. Mild mental retardation and bilateral sensorineural deafness were first noted at age 5. He also had astigmatism, mild optic atrophy and retinitis pigmentosa diagnosed at age 6.
All the investigations performed thus far were negative (karyotype, metabolic screen, VLCFA, lysosomal disorders screening, brain MRI, abdominal US and echocardiogram).
The father has a similar face appearance, joint laxity with multiple dislocations, but no short stature or other anomalies.
It is very difficult to establish a clear mode of inheritance in this family, since SEMD with multiple dislocations has an autosomal dominant pattern and SEMD with joint laxity an autosomal recessive one. On the other hand, the association MR, retinopathy and deafness lead to mandatory exclusion of a mitochondrial disorder in despite of consanguinity.
We believe this patient may represent a unique form of spondyloepimetaphyseal dysplasia associated with other anomalies. To our knowledge, the only similar previously reported patient was also of Portuguese origin (Liberfarb RM et al., 1986).

SKELETAL DYSPLASIAS IN A BRAZILIAN PERINATAL GENETIC SERVICE

Denise Pontes Cavalcanti

Programa de Genética Perinatal, Depto. Genética Médica, FCM, UNICAMP, Campinas, São Paulo, Brazil

Skeletal dysplasias (SD) are an important group of genetic disease that contributes to the morbimortality in the perinatal period. The precise diagnosis of these dysplasias is fundamental to the genetic counseling. The aim of this study is presenting the casuistic of bone dysplasias diagnosed in a Genetic Perinatal Program (PGP). This is a genetic unit within a reference medical center attending a population over a million people located in the Southeast Brazil. In the last 15 years this program has monitored all malformed babies born at the hospital and also has assisted some external families referred for genetic counseling. During the studied period (1990 to 2004) 69 families with at least one affected patient by SD were identified by the PGP. From 71 probands 43 (60%) have had a lethal skeletal dysplasia with the following diagnosis: thanatophoric dysplasia (14), ostegenesis imperfecta (9), short-rib dysplasias (6), achondrogenesis II (4), opsismodysplasia (2), chodrodysplasia punctata (2), Campomelic dysplasia (1), fibrochondrogenesis (1), hypochondrogenesis (1) and three undiagnosed dysplasia. In the group of non lethal SD the main diagnosis were osteogenesis imperfecta (8), achondroplasia (5), cleidocranial dysplasia (2) and dyschondrosteosis (2). Isolated diagnosis in the last group were campomelic dysplasia, pointer syndrome, otopalatodigital syndrome, chondrodysplasia punctate, dyssegmentar dysplasia, Larsen dysplasia, congenital SED and two undiagnosed SD. Among all probands the sex ratio was 1.2, parental consanguinity was observed in seven families, and prenatal diagnosis was performed in 46 cases. Among these, lethality was suggested in 24 cases, but in two of them, the postnatal diagnosis was actually a non lethal SD. Genetic counseling was offered to all the families. Conclusions: the number of diagnosed cases in this series of SD shows the importance and the need for a well structured perinatal genetic service capable of account for a comprehensive diagnostic of SD.

THE INTERNATIONAL SKELETAL DYSPLASIA REGISTRY.

David L. Rimoin, Daniel H. Cohn, William R. Wilcox, Deborah Krakow and Ralph S. Lachman.

Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA
email: david.rimoin@cshs.org

The skeletal dysplasias are a heterogeneous group of disorders that result in disproportionate short stature and/or skeletal deformities. There are over two hundred fifty distinct skeletal dysplasias, which must be differentiated one from another for specific genetic counseling, prognosis and treatment. There has been an explosive increase in the delineation of the biochemical and molecular defects in the skeletal dysplasias, however the gene locus and/or molecular defect is still not known for over half of these disorders.

The International Skeletal Dysplasia Registry (www.cedars-sinai.edu/skeletaldysplasia) was established over 30 years ago and currently has over 13,000 cases in a secure, web-accessible computerized database with an anonymous code for each individual. It is the largest resource in the world for research on the skeletal dysplasias. Materials accumulated include clinical information, radiographs, fixed and frozen chondro-osseous tissue samples, histology slides, electron micrographs, cultured fibroblasts and chondrocytes, lymphoblastoid cell lines and DNA. Radiographic and chondro-osseous morphological findings are coded in the database in a searchable format for rapid identification of cases with similar findings. Cases entered into the Registry include patients seen in our Short Stature Clinics, as well as cases submitted from around the world. To date, we have received specimens from over 2,500 physicians from over 44 different countries.

The International Skeletal Dysplasia Registry provides human clinical and biological materials to numerous investigators internationally. It also provides a computerized web-based database for retrieval of cases, clinical information and the ability to search for cases that might share a common molecular or pathogenetic mechanism.

DESBUQUOIS SYNDROME: DILEMMA WHAT TO SAY DURING ANTENATAL PERIOD?

B. Saha, C. Agwe

Sandwell Hospital, West Bromwich, Birmingham, U.K.
bhramarsaha@doctors.org.uk

RD, 2yrs old of Yemen origin, antenataly noted to have severe IUGR, short limbs, small chest, and micrognathia. Termination was offered, but parent refused. These features were confirmed postnataly. Skeletal survey revealed advanced carpal bone age, additional ossicles between proximal phalanges, and multiple coronal cleft vertebrae. Radiological features in association of clinical facial and hand features confirm the diagnosis of Desbuquois syndrome.
His condition was complicated by micrognathia and small chest, predisposing to recurrent respiratory arrest requiring resuscitation. On one occasion required ventilation for 18 days. He is also oxygen dependent due to low respiratory reserve, which is unique and not frequently described in this condition.
At present he is very short (height & weight well below 0.4th C) and oxygen dependent. He also has global developmental delay and needs NG feed.
The disease is a clinically heterogeneous with variable severity. Moreover no genetic defect has been identified yet. Therefore to confirm the diagnosis antenatally and offering meaningful counselling to parents to help them to enable to take informed decision is difficult.

CLINICAL HYPOCHONDROPLASIA IN A FAMILY CAUSED BY A HETEROZYGOUS DOUBLE MUTATION IN FGFR3 ENCODING GLY380LYS

Heloísa G. Santos 1, Rosário Almeida 1, Helena C. Fernandes 2, Andrew O.M. Wilkie 3 - heloisa.santos@mail.telepac.pt

1GenoMed, Lisbon; 2Centro Hospitalar, Funchal; 3Weatherall Institute of Molecular Medicine, Oxford

Achondroplasia (Ach) and Hypochondroplasia (Hch) are two common chondrodysplasias caused by heterozygous mutations in different regions of the fibroblast growth factor receptor 3 gene (FGFR3). Biochemical analysis suggests that these mutations cause a gain of function leading to defects of differentiation of the cartilage growth plates of the long bones. From a clinical and radiological point of view Ach and Hch present different characteristics including a well-known gestalt face in Ach and almost normal facial features in Hch.
In Ach virtually all patients have localised point mutations (either 1138G>A or 1138G>C) at codon 380, located within the transmembrane domain, causing the normal glycine residue to be replaced by an arginine (Gly380Arg). Hch mutations are more widespread in FGFR3, with a hotspot in the tyrosine kinase domain at Asn540Lys. To our knowledge, mutations in the transmembrane domain have not previously been described in patients with Hch.
In a family with two female patients (mother and daughter) with radiological and clinical features of Hch, including an almost normal face, we report a heterozygous double mutation (1138_1139GG>AA) encoding Gly380Lys. This is the first substitution different from the usual arginine described at the classical Ach mutation codon.
Webster and Donoghue demonstrated using cellular assays that the Gly380Arg mutation causes constitutive activation of receptor signalling, and proposed that this was mediated through hydrogen bonding of the large basic arginine side chain to a neighbouring receptor. Lysine, the amino acid encoded by the novel double substitution, is also basic but is less bulky than arginine, and was shown to be activating, although more weakly than arginine, in the same assay. This is consistent with our patients' milder Hch phenotype.
Our family contributes to the further delineation of the genotype/phenotype correlation, and mechanisms of gain of function, associated with the FGFR3 mutations. A similar phenomenon whereby rare double nucleotide mutations encode chemically similar amino acids to those arising from the usual single nucleotide mutations was recently described for FGFR2.

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MEDIAL TEMPORAL LOBE DYSGENESIS IN HYPOCHONDROPLASIA

Peter Kannu1, Ian M Hayes1, Simone Mandelstam2,3, Leo Donnan2,3, Ravi Savarirayan1,3,4

1 Genetic Health Services Victoria
2 Royal Children's Hospital, Melbourne, Australia
3 University of Melbourne, Australia
4 Murdoch Children's Research Institute

We describe two patients who have hypochondroplasia with medial temporal lobe dysgenesis. This association has only been reported once before. Both patients had an FGFR3 mutation: 1620C- A, resulting in Asn540Lys. FGFR3 is expressed in the brain during development and plays a role in hippocampal formation. We suggest FGFR3 mutations might cause cerebral malformations in hypochondroplasia as well as in thanatophoric dysplasia. Further neuroimaging studies of patients with hypochondroplasia and epilepsy or developmental delay may clarify the proportion of patients with hypochondroplasia who have this pattern of central nervous system abnormalities.

LETHAL HYPOPHOSPHATASIA DIAGNOSED PRENATALLY: CLINICAL AND MOLECULAR STUDIES.

Daniela Varela Luquetti a, Alfredo Nazzaro b, Etienne Mornet c, Matteo Della Monica a, Gioacchino Scarano a, Andrea Superti-Furga d.
a Medical Genetics Department, b Prenatal Diagnosis Unit, Gaetano Rummo Hospital, Benevento, Italy, c Centre d'Etudes de Biologie Prénatale- SESEP, Université de Versailles-Saint Quentin en Yvelines, Versailles, France, d Centre for Pediatrics, University of Freiburg, Germany.

Hypophosphatasia is an autosomal recessive disorder characterized by defective bone mineralization and deficiency of tissue non-specific alkaline phosphatase activity. The perinatal form is frequently lethal. Mutations of the gene Alkaline Phosphatase Liver form (ALPL) are responsible for this disorder. Few mutations are recurrent in unrelated patients, most of them are unique for each family. We report a case of perinatal lethal hypophosphatasia with the homozygous mutation A360V in an Italian family. This supports the hypothesis that A360V mutation corresponds to a severe allele responsible for perinatal lethal hypophosphatasia thus permitting correlation between the genotype and the phenotype. The same genotype was observed in another family from Italy, suggesting a founder effect.

NOVEL MALIGNANCIES IN A BOY WITH MAFFUCCI SYNDROME TREATED WITH CYCLIC INTRAVENOUS PAMIDRONATE

J Ault, J Briody, S Kellie, P Haywood, D Sillence.

Departments of Rehabilitation, Oncology, Nuclear Medicine, Plastic Surgery, Clinical Genetics, The Children's Hospital at Westmead, Westmead NSW 2145, Australia

Background: Treatment with Cyclic IV Pamidronate (CIP) is recognized as an effective therapy for osteoporosis in the Osteogenesis Imperfecta Syndromes. The Enchondromatoses are complicated by an increased frequency of fractures and osteoporosis in addition to characteristic enchondromata.
Case Report: A six year old boy with Maffucci Syndrome was treated with CIP 30mg/m^2/monthly to correct severe osteoporosis. Dual Energy X-ray Absorbtiometry revealed a right femoral shaft BMD z = -4.06 and left femoral shaft z = -2.46. Twenty four months after commencing therapy he was diagnosed with an encroaching tumour most likely a chondrosarcoma of the anterior cranial base, pressing on the optic decussation. Pamidronate therapy was ceased but he went on to develop acute lymphoblastic leukaemia 8 months after Pamidronate was ceased. The patient has had repeated surgeries to debulk cutaneous hemangiomas but these have recurred repeatedly.
Discussions: Although non-skeletal malignancy is not unknown in Maffucci syndrome, Acute Myeloblastic Leukaemia is extremely rare. Recent insights into the mode of action of bisphosphonates show that the induction of transient lowering of ionized serum calcium provokes a prolonged PTH response. The response is similar to daily treatment with recombinant human parathormone, which has been shown to induce osteosarcoma in prepubertal experimental animals. PTH is a powerful promoter of many genes including mesenchymal growth regulators.

FETAL GROWTH PARAMETERS CAN OVERESTIMATE SEVERITY OF HYPOPHOSPHATASIA

Smithson SF[1], Soothill P[2], Grier D[3], Gargan M[4], Mornet E[5]

Departments of Clinical Genetics[1], Fetal Medicine[2], Radiology[3] and Orthopaedics[4] Bristol Children's Hospital, UK, Laboratoire de Biologie Moléculaire, Université de Versailles, France[5]. sarah.smithson@ubht.swest.nhs.uk

Background: Hypophosphatasia is characterised by decreased bone density but the clinical severity is highly variable. Autosomal dominant and recessive inheritance has been observed resulting from mutations in the TNSALP gene (chromosome 1p36.1-p34).
Objectives: To investigate the natural history and clinical outcome of hypophosphatasia from 20 weeks of gestation until six years of age in a consanguineous family.
Methods: Serial ultrasounds scans were undertaken in 4 pregnancies at risk of hypophosphatasia (1 on-going). After birth 3 children were followed up in a multi-disciplinary skeletal dysplasia clinic.
Results: In all affected infants, prenatal scans from 22 weeks of gestation showed severe shortening of the long bones throughout the skeleton. At birth 3 of the infants were well and thrived (1 required minimal respiratory support) apart from short bowed lower limbs with skin dimples/bony spurs. The radiological findings in these patients included short long bones in the limbs, broad irregular metaphyses with radioloucent lesions and fibula spurs. The skulls and spines appeared normally mineralised. The clinical, radiological and biochemical findings pointed to a diagnosis of hypophosphatasia, confirmed by the identification of homozygous 815G>A mutations. Follow up at ages 1,3 and 6 years showed spontaneous improvement in growth (heights 0.4th centile) and limb bowing and no surgical or other intervention was required.
Discussion: This report highlights the difficulty in predicting the prognosis of hypophosphatasia from prenatal ultrasound scans, which in this family, was much better than anticipated. The 815G>A mutation (corresponding to R255H) in the tissue non-specific alkaline phosphatase gene (TNSALP), has not been previously described in hypophosphatasia, but similar mutations have been associated with severe/lethal forms.

DLL3-MUTATIONS IN SPONDYLOCOSTAL DYSOSTOSIS TYPE1 (SCD1) - REPORT OF 2 PATIENTS

E. Steichen-Gersdorf1, G. Reiter1, B. Fiebig2;

1Medical University of Innsbruck, Innsbruck, Austria, 2Institute for Medical Genetics, Berlin, Germany.

The spondylocostal dysostosis (SCD) are a heterogenous group of disorders with severe axial skeletal malformations, characterised radiologically by multiple vertebral segmentation defects and rib anomalies, mainly reduction in number and dorsal fusion.
An autosomal recessive form, designated SCD type1 (OMIM #277300) is linked to 19q13, which harbours the DLL3-gene (delta like 3). DLL3 encodes a ligand for the Notch signalling pathway.
Clinically the patients present with an extremely short neck, low set nuchal hairline, a short chest, abdominal protrusion and an increased abdominal pressure. Therefore, inguinal hernia occurs frequently in male patients. Interestingly, despite of severe vertebral malformations, neurological complications are uncommon. Scoliosis is fixed and not progressive. The two male patients were born to consanguinous turkish parents.
Patient 1: born at term, c-section, BW 3380g, L 48cm, HC 36cm, no respiratory problems at birth, mild symptoms, slightly dysproportionate stature. Homozygous missense mutation in the DLL3-gene C209R within the delta-serrate-lag2 region (DSL)
Patient 2: born at term, BW 2960g, L 43 cm, HC 34cm, developed a respiratory distress syndrome and was ventilated for 24h hours. Reduced compliance of the chest was noticed. An right sided inguinal hernia was operated in the neonatal period. Homozygous insertion of cDNA 603_604 ins GCGGT in exon 5 of DLL3 leading to a stop codon and protein truncation .
We stress, that an essential prerequesite for genetic testing of DLL3 ist that there is irregular formation of all vertebrae (not segmental) usually in association with abnormally aligned ribs, showing points of fusion.

BINDER SYNDROME ASSOCIATED WITH EARLY ONSET PRIMARY OSTEOPOROSIS

S. Toiviainen-Salo, M. Mäyränpää, E. Marttinen, K.Hurmerinta, J.Hukki, O. Mäkitie

Hospital for Children and Adolescents, Departments of Pediatrics and Radiology, and Cleft Palate and Craniofacial Centre, University of Helsinki, Helsinki, Finland

Binder syndrome (BS) (MIM 155050) is a maxillonasal dysplasia characterized by midfacial hypoplasia with a flat nose, lack of anterior nasal spine, midmaxillary hypoplasia and malocclusion. Other infrequently associated anomalies include cervical spine and congenital heart anomalies and terminal phalangeal hypoplasia of the hand. Osteoporosis has not previously been reported in association with BS. The etiology and mode of inheritance are unknown. We describe a 15 year old boy who was referred to the Metabolic Bone Clinic, University of Hel-sinki, because of recurrent fractures. He was III/3 child of healthy non-consanguineous parents. There was no family history of fractures or features of BS. The diagnosis of BS was made at age 13 years based on the typical craniofacial features. He had had 8 upper limb fractures, most of them after low-impact trauma. Clinical findings included midfacial hypoplasia, white sclerae, normal stature (-1.5 SDS), normal pubertal development (Tanner 4) and mild joint laxity. Biochemical findings showed normal calcium homeostasis. Radiographic findings included osteopenia with marked bowing of the lower limbs and mild bowing of both antebrachii. Spinal radiographs showed several wedged vertebrae in the thoracic spine and end plate compressions in several lumbar vertebrae as well as LV-SI spondylolysis and spondylolisthesis. Skull x-ray demonstrated midfacial hypoplasia, retropositioned maxilla, missing nasal spine, and large frontal and ethmoidal sinuses. The bone mineral density (BMD), assessed with dual-energy x-ray absorptiometry, showed a Z-score of -3.4 for the lumbar spine and -1.5 for the femoral neck, consistent with marked osteoporosis. A transiliac bone biopsy showed marked decrease in trabecular bone volume with high bone turn-over. This is the first reported patient with BS and radiologically and histologically proven primary os-teoporosis resulting in recurrent fractures. We propose that BS and osteoporosis in this patient are pathogenetically associated.

METAPHYSEAL CHONDRODYSPLASIA WITH CONE-SHAPED EPIPHYSES OF THE LONG BONES: REPORT OF A SIXTH PATIENT

Kym M. Boycott1, D. Ross McLeod1, and Sheila Unger2

Dept Med Genetics, Alberta Children's Hospital, Calgary, Alberta, Canada; and Institute of Human Genetics, University of Freiburg, Germany.

A specific form of metaphyseal chondrodysplasia with cone-shaped epiphyses involving the lower limbs was reported in three patients by Dieux-Coeslier et al. in 2004 (AJMG124A:60). Two other cases reported by Kozlowski were felt to show significant similarity (Radiol Med 89:330). We report a 7 year old boy with a metaphyseal chondrodysplasia characterized by radiological features similar to these 5 patients. Past medical history was signficant for normal birth length, E. coli sepsis at 4 days of age and normal development. Family history was unremarkable. Concern was raised regarding decreased range of motion at his large joints at 2 years of age. At 7 years of age his is clinical features included fairly symmetric rhizomelic shortening of the lower extremities, asymmetric rhizomelic shortening of the left arm, and decreased range of motion at both knees, hips and the left shoulder. Radiographs of the skull, spine and hands showed no abnormality. Cone-shaped epiphyses embedded in cup-shaped metaphyses characterized the upper and lower left humerus, upper and lower left and right femurs, and upper tibias bilaterally. This patient's clinical and radiographical presentation suggests that he represents the sixth case of a new form of metaphyseal dysplasia with cup-shaped metaphyses and cone-shaped epiphyses involving predominantly the lower limbs.

DECOMPRESSIVE CRANIOTOMY AND BARREL-STAVE OSTEOTOMIES FOR INCREASED INTRACRANIAL PRESSURE IN A PATIENT WITH CAMURATI-ENGELMANN DISEASE AND SKULL HYPEROSTOSIS.

Raymond Wang (1), Stephanie Wallace (2), Moise Danielpour (3), Maureen Bocian (4), William Wilcox (1).

(1) Med Genet Inst, Steven Spielberg Pediat Res Ctr, Cedars-Sinai Med Ctr, Los Angeles, CA. (2) Dept of Med Genet, Univ. of Washington Children's Hosp. and Regional Med Ctr, Seattle, WA. (3) Maxine Dunitz Neurosurgical Institute, Dept of Pediat Neurosurgery, Cedars-Sinai Med Ctr, Los Angeles, CA. (4) Div. of Human Genetics, Dept of Pediatrics, Univ. Children's Hosp., Univ. of California-Irvine, Irvine, CA. - raymond.wang@cshs.org

BACKGROUND: Progressive diaphyseal dysplasia (PDD) is an autosomal dominant skeletal dysplasia characterized by progressive craniodiaphyseal sclerosis and hyperostosis. Severe cranial hyperostosis can result in cranial nerve entrapment and increased intracranial pressure (ICP). A novel cranial decompression with 20-month followup is reported in a 35-year-old female with mutation-proven disease (R218H in TGF-beta1), visual scotomata, papilledema, vertigo, gait imbalance, right facial nerve palsy, and daily severe headaches. MRI did not reveal stenosis of optic nerve foramina but instead compression of the cerebrum and ventricles was present.
OBJECTIVES: To demonstrate the possibility that patients with PDD and symptomatic cranial hyperostosis can have sustained relief with the 'barrel-stave' craniotomy/osteotomy procedure.
METHODS: Bilateral frontal/parietal/temporal/occipital craniotomies were performed, thickness of the resultant bone flaps was reduced from 2 to 1 cm, and osteotomies were created. Patient was re-evaluated 2 weeks, 3 months, 5 months, and 20 month post-surgery.
RESULTS: The patient's visual scotomata, decreased visual acuity, vertigo, and gait imbalance resolved 8 weeks following surgery. Right facial nerve palsy, while still present, is improved. While hearing has not been formally tested, she reports improved hearing and increased sensitivity to sound. Headaches occur with decreased frequency, duration, and severity. She describes difficulty with short-term memory that was not present prior to surgery.
DISCUSSION: A patient with PDD and symptomatic cranial hyperostosis was successfully treated with a novel neurosurgical procedure. The extent of cranial involvement in this patient is unusual for PDD but has been seen in other disorders. While previous reports of surgical decompression described only temporary relief due to bone regrowth within 12 months, this procedure resulted in sustained resolution of symptoms.

AUTOSOMAL DOMINANT METAPHYSEAL ANADYSPLASIA

Lausch E, Zabel B, Spranger J

Children's Hospital, University of Mainz, Mainz, Germany, lausch@molgen.medizin.uni-mainz.de; zabel@molgen.medizin.uni-mainz.de; spranger@molgen.medizin.uni-mainz.de

We saw a 16-year-old boy and his 12,5-year-old sister, both presenting with mildly short stature (at and slightly below the 3rd percentile, respectively) mild scoliosis, and bowing of the femura and tibiae with only discrete rhizomelic micromelia. Radiographic features included metaphyseal widening and irregularity of long bones.
Family history revealed that the father was first diagnosed to have rickets and later Metaphyseal Chondrodysplasia, type Schmid at the age of two years. His skeletal changes regressed. As adult he had mild scoliosis with a final height of 179cm. The paternal grandfather was short during childhood with genua vara and waddling gait. His final height was 175cm.
The course of the skeletal condition reported and observed in this family is compatible with Metaphyseal Anadysplasia (MAD), a rare form of chondrodysplasia characterized by early and severe metaphyseal alterations which regress and result in normal stature.
The pathogenesis of MAD is unknown and transmission is unclear. The condition was observed in male cousins, suggesting X-linked inheritance and in sibs born to unaffected parents suggesting autosomal recessive inheritance.
Our observation now suggests autosomal dominant inheritance of one MAD form, confirming an earlier report with questionable father to son transmission. In addition, with our familial case we are involved in efforts to identify the gene locus and possible candidate genes.

OSTEOGLOPHONIC DYSPLASIA WITH SEVERE OSTEOLYTIC FIBROUS MANDIBULAR DEFECTS

Coerdt W[1], Wildhardt G[2], Steinberger D[2], Stelzer C[3], Spranger J[3], Zabel B[3]

[1] Dept. Ped. Pathology, University of Mainz, Mainz, Germany, coerdt@kinderpatho.klinik.uni-mainz.de
[2] Bioscientia Institute, Ingelheim, Germany, gabriele.wildhardt@bioscientia.de; daniela.steinberger@bioscientia.de
[3] Children's Hospital, University of Mainz, Mainz, Germany, stelzer@molgen.medizin.uni-mainz.de; spranger@molgen.medizin.uni-mainz.de; zabel@molgen.medizin.uni-mainz.de

We have been involved in medical care for a female baby presenting with rhizomelic short-limb dwarfism, craniofacial abnormalities with frontal bossing, depressed nasal bridge, anteverted nostrils, nasal obstruction, mandibular prognathism and hypertelorism. Despite some psychomotor delay intelligence seemed to be almost normal. Major radiographic features included craniosynostosis, lucent defects in mandibular rami, some flattening of vertebral bodies with anterior beaking and posterior scalloping, multiple symmetrical lucent metaphyseal defects, brachydactyly with hypoplasitc distal phalanges.
The combination of clinical and radiologic findings were indicative for Osteoglophonic Dysplasia, a rare autosomal dominant skeletal dysplasia characterized by distinct bone lesions, disproportionate dwarfism, and severe craniofacial defects (MIM 166250).
Corrective neurosurgical procedures included treatment of craniosynostosis and frontal advancement to ameliorate midface hypopplasia. Later on tracheostoma was necessary to treat complications due to nasal and tracheal obstructions. In addition, with recurrent operations it was unsuccessfully attempted to stabilize the osteolytic mandibular defects. Finally, our patient died unexpectedly at home at 4 years of age of respiratory infections.
As Osteoglophonic Dysplasia is a disorder that shares skeletal characteristics with both the craniosynostoses and the dwarfing syndromes, it was tempting to speculate the involvement of the FGFR genes or pathways in the disorder. Recently White at al. (2005) identified activating mutations in FGFR1 in four patients. Molecular analysis revealed one of the described mutations (missense mutation C379R in exon 10 of the FGFR1 gene) in our patient.

PRESELECTION OF CASES THROUGH EXPERT CLINICAL-RADIOLOGICAL REVIEW SIGNIFICANTLY INCREASES MUTATION DETECTION RATE IN AUTOSOMAL DOMINANT MULTIPLE EPIPHYSEAL DYSPLASIA

A. Zankl1, G. Jackson2, A. Superti-Furga1, M. Briggs2 and the ESDN Clinical-Radiological Review Panel3

1Division of Molecular Pediatrics, CHUV, Lausanne, Switzerland
2Wellcome Trust Centre for Cell Matrix Research, Manchester, UK
3 www.esdn.org

Skeletal dysplasias are difficult to diagnose for the nonexpert. In a previous study of patients with multiple epiphyseal dysplasia (MED), we identified COMP mutations in only 36% of referred cases. These patients were diagnosed by their referring physician, mostly clinical geneticists, and we suspected that the low mutation detection rate was at least partially due to misdiagnosis. We have now instituted a clinical-radiographic review system in which all cases are evaluated by a panel of skeletal dysplasia experts. Only patients in which the diagnosis of MED was confirmed, or considered likely by the expert panel, were screened for COMP mutations. Under this regime, mutation detection rate increased to 58%. In addition, a number of cases were given an alternative diagnosis that could be confirmed through mutation analysis. We conclude that expert clinical-radiological review can significantly enhance mutation detection rates and should be part of any diagnostic mutation screening protocol for patients with skeletal dysplasias.

Participants

Jesus Aguirre-Hernandez
Centre for Veterinary Science
University of Cambridge
Madingley Road
Cambridge CB3 0ES
UK
Phone: + 441223337648
Fax: + 441223337610
Email: ja248@cam.ac.uk

Yasemin Alanay
Hacettepe University School of Medicine
Ihsan Dogramaci Children's Hospital
Dept. of Pediatrics
Clinical Genetics Section
06100, Sihhiye, Ankara
Turkey
Phone: + 90 312 3115522
Fax: + 90 312 3115522
Email: yalanay@hacettepe.edu.tr

Carlos A. Bacino
Clinical Care Center
Texas Children's Hospital
6701 Fannin St. Suite 1560
Houston, Texas 77030
USA
Phone: + 832 822 4291
Fax: + 832 825 4294
Email: cbacino@bcm.tmc.edu

Irina Balikova
Centre for Human Genetics
UZ Gasthuisberg, KU Leuven
Herestraat 49
3000 Leuven
Belgium
Phone: + 32 16 345903
Fax: + 32 16 346060
Email: Irina.Balikova@uz.kuleuven.ac.be

Frits A. Beemer
Dept. Medical Genetics. Mail nr. KC 04.084.2
University Medical Center Utrecht
P.O. Box 85090, 3508 AB
3508 AB Utrecht
Netherlands
Phone: + 31 30 2503811
Fax: + 31 30 2503801
Email: f.a.beemer@dmg.azu.nl

Luisa Bonafe
Div. Molecular Pediatrics CHUV
Clinique Infantile 02-35
Av. Pierre Decker 2
CH-1011 Lausanne
Switzerland
Phone: + 41 21 314 3480
Fax: + 41 21 314 3546
Email: luisa.bonafe@chuv.ch

Simeon Boyadjiev Boyd
McKusick-Nathans Institute of Genetic Medicine
Johns Hopkins University
733 N. Broadway, BRB 469
Baltimore, MD 21205
USA
Phone: + 410 502 6067
Fax: + 410 502 1853
Email: sboyd@mail.jhmi.edu

Michael D. Briggs
Faculty of Life Sciences
The Michael Smith Building
University of Manchester
Oxford Road
Manchester M13 9PT
Great Britain
Phone: +44 161 275 5642 (Office)
Fax: +44 161 275 5082
Email: mike.briggs@manchester.ac.uk

Denise P. Cavalcanti
Programa de Genética Perinatal
Depto. De Genética Médica
FCM, UNICAMP
Campinas, Sao Paulo
Brazil
Phone: + 551937889395
Fax: + 551937889395
Email: denisepc@unicamp. br

Valérie Cormier-Daire
Département de Génétique et INSERM U393
Hopital Necker
149 rue de Sevres
75015 Paris
France
Phone: + 33144495163
Fax: + 33144495150
Email: cormier@necker.fr

Teresa Costa
Service de Génétique Médicale
Hôpital Sainte Justine
3175 Côte Sainte-Catherine
Montréal, Québec H3T 1C5
Canada
Phone : + 514 345 4727
Fax : + 514 345 4766
Email: teresa.costa.hsj@ssss.gouv.qc.ca

Nathalie Dagoneau
Department of Medical Genetics and INSERM U393
Hopital Necker
149 rue de Sevres
75015 Paris
France
Phone:+ 33144495163
Fax: + 33144495150
Email: dagoneau@necker.fr

Boyan Dimitrov
Centre for Human Genetics
UZ Gasthuisberg, KU Leuven
Herestraat 49
3000 Leuven
Belgium
Phone: + 3216345903
Fax: + 3216346060
Email: Dimitrov.Boyan@uz.kuleuven.ac.be

Dawn Earl
2836 NE 178th Street
Seattle, WA 98155
USA
Phone: + 2069874279
Fax: + 2069872495
Email: dawn.earl@seattlechildrens.org

Georg F. Eich
Kinderradiologie
Kantonsspital Aarau
Tellstraße
5001 Aarau
Switzerland
Phone: + 41 62 8385205
Fax: + 41 62 8385206
Email: g.f.eich@access.unizh.ch

Francesca Forzano
S. C.Genetica Umana
E. O. Ospedali Galliera
Via Volta 8
16128 Genova
Italy
Phone: + 39 010 5634374
Fax: + 39 010 5634381
Email: forzanof@galliera.it

Claire Francomano
NIA/NIH
Laboratory Genetics
333 Cassell Dr, Ste 3000
Baltimore MD 21224
Phone: + 410 558 8201
Fax: + 410 558 8087
Email: francomanocl@grc.nia.nih.gov

Maryline Fresquet
The University of Manchester
Smith Building
Oxford Road
Manchester M13 9PT
Great Britain
Phone: + 441612751559
Fax: + 441612755082
Email: maryline.fresquet@manchester.ac.uk

Silvio Garofalo
Centro Biotecnologie Avanzate (room C3-19)
Largo Rosanna Benzi 10
16132 Genova
Italy
Phone: + 39 0105737241
Fax: + 39 0105737257
email: silvio.garofalo@unige.it

Robert Gensure
Ochsner for Children
1315 Jefferson Highway
New Orleans, LA 70121
USA
Phone: + 504 842 2028
Fax: + 504 842 5648
Email: rgensure@ochsner.org

Andres Giedion
Im Doldertal 7
CH-8032 Zürich
Switzerland
Phone : +41 44 2517767
Email : andres@giedion.ch, giedion@freesurf.ch

Maria Luisa Giovannucci-Uzielli
Centro di Genetica e Medicina Molecolare
Dipartimento di Pediatria
Università di Firenze
Via Luca Giordano 13
50132 Firenze
Italy
Phone: + 39 0555662 931
Fax: + 39 0555662 931
Email: uzielli_ml@unifi.it

Gabriele Haeusler
Medical University of Vienna
Pediatric Department
Waehringer Guertel 18-20
1090 Vienna
Austria
Phone: + 43 1 404003232
Fax: + 43 1 404003238
Email: Gabriele.Haeusler@meduniwien.ac.at

Christine Hall
Department of Radiology
Great Ormond St. Children's Hospital
London WCIN 3 JH
Great Britain
Phone: +44 207 405 9200 ext 5281
Fax: + 44 207 829 8665
Email: hallc@gosh.nhs.uk

Jan Hellemans
Gent University Hospital - MRB
De Pintelaan 185
9000 Gent
Belgium
Phone: + 3292405535
Fax: + 3292406549
Email: Jan.Hellemans@UGent.be

Michael Hill
Department of Radiology
George Washington University Hospital
900 23rd Street NW
Washington, DC 20037
USA
Phone: + 202 715 5168
Fax: + 301 983 2312
Email: mhill@mfa.gwu.edu

Suvimol Hill
N.I.H.
9000 Rockville Pike, Building 10, Room 1c660
Bethesda, MD 20854
Phone: + 301 9835723
Fax: +301 496 9933
Email: shill@cc.nih.gov

Kristien Hoornaert
Department of Medical Genetics
Thent University Hospital
De Pintelaan 185
9000 Gent
Belgium
Phone: + 3292405791
Fax: + 3292404970
Email: kristien.hoornaert@ugent.be

Denise Horn
Institut für Med. Genetik,
Charité Berlin
Germany
Phone: + 49 30 450569132
Fax: + 49 30 450569914
Email: denise.horn@charite.de

William Horton
5503 SV Downsview Ct
Portland, OR 97221
USA
Phone: + 503 221 1537
Fax: + 503 221 3451
Email: wah@shcc.org

Celine Huber
INSERM U393, Hopital Necker
149 rue de Sevres
75015 Paris
France
Phone: + 33144495163
Fax: + 33144495150
Email: huberceline@hotmail.com

Shiro Ikegawa
4-6-1 Shirokanedai,
Institute of Medical Science,
University of Tokyo,
Minato-ku,
Tokyo 108-8639,
Japan
Phone: + 81-3-54495393
Fax: + 81-3-54495393
Email: sikegawa@ims.u-tokyo.ac.jp

Ilkka Kaitila
Clinical Genetics Research
PO Box 21 (Haartmaninkatu 3)
University of Helsinki
00014 Helsinki
Finland
Phone: + 358 9 19126818
Fax: +358 9 47176089
Email: ilkka.kaitila@hus.fi

Ok-Hwa Kim
Department of Radiology
Ajou Univ. Hospital
Woncheon-dong
Yeongtong-gu, Suwon-si
Gyeonggi-do 443-721
South Korea
Phone: + 82 31 219 5828
Fax: + 82 31 219 5862
Email: kimoh@ajou.ac.kr

Alexander Krebs
Orthopädisches Spital Wien Speising
Speisingerstr. 109
1130 Wien
Austria
Tel. + 431 801821272
Fax: + 43 1 80182575
Email: Alexander.krebs@oss.at

Martine Le Merrer
Departement de Genetique
Hopital Necker
149 rue de Sevres
75015 Paris
France
Phone: + 33144495157
Fax: + 33144495150
Email: lemerrer@necker.fr

Brendan Lee
Howard Hughes Medical Institute
Department of Molecular and Human Genetics
Baylor College of Medicine
One Baylor Plaza Rm 635E, Mail Stop 225
Houston, TX 77030
USA
Phone: + 713 798 8835/5443
Fax: + 713 798 5168
Email: blee@bcm.tmc.edu

Laurence Legeai-Mallet
Tour Lavoisier 2ème étage
Hopital des Enfants Malades
149 rue de Sevres
75015 Paris
France
Phone: + 33 14449400 ext 97833
Fax: + 33 147348514
Email: mallet@necker.fr

Matthew Leighton
Wellcome Trust Centre for Cell Matrix Research
Faculty of Life Sciences
Michael Smith Building
University of Manchester M13 9PT
Great Britain
Phone: + 441612751559
Fax: + 441612751505
Email: matthew.p.leighton@manchester.ac.uk

Jules Leroy
Ghent University Hospital

De Pintelaan 185
9000 Ghent
Belgium
Phone: + 32 9 2403592
Fax: + 32 9 2404970
Email: juliaan.leroy@ugent.be

Outi Mäkitie
Hospital for Children and Adolescents
Metabolic Bone Clinic
Helsiniki University Hospital
PO Box 281
Fin-00029 Hus
Finland
Phone:+ 358 9 47173361
Fax:+ 358 9 47175299
Email: outi.makitie@helsiniki.fi

Carlo Marcelis
Department of Human Genetics
Radboud University Nijmegen Medical Centre
PO-Box 9101
6500 HB Nijmegen
Netherlands
Phone: + 31 243613946
Fax: + 31 243565026
Email: c.marcelis@antrg.umcn.nl

Eino Marttinen
Erupellontie 9 D
00680 Helsinki 68
Finland
Phone: + 35897283124
Email: eino.marttinen@kolumbus.fi

Valerie Mayne
54 Gratton Street, Carlton Victoria
Australia 3053
Phone: + 61413437386
Email: c/o ravi.savarirayan@ghsv.org.au

Emma McCann
Department of Clinical Genetics
Royal Liverpool Children's Hospital
Eaton Road
Liverpool, L12 1AP
Great Britain
Phone: + 441512525238
Fax: + 441512525951
Email: emma.mccann@rlc.nhs.uk

Iain McIntosh
McKusick-Nathans Institute of Genetic Medicine
Greenberg Center for Skeletal Dysplasias
Johns Hopkins University
733 N. Broadway / BRB 407
Baltimore, MD 2105
USA
Phone: + 410 955 7948
Fax: + 410 502 5677
Email: mcintosh@jhmi.edu

Roberto Mendoza-Londono
Division of Clilnical and Metabolic Genetics
The Hospital for Sick Children
525 University Avenue, Suite 940
Toronto, ON M5G1X8
Canada
Phone: +416 813 7325
Fax: +416 813 5345
Email: Roberto.mendoza-londono@sickkids.ca

Else Merckoll
Radiology Department, Rikshospitalet
Sognsvannsvn. 20
0027 Oslo
Norway
Phone: + 47 23073937
Fax: + 47 23072610
Email: else.merckoll@rikshospitalet.no

Kay Metcalfe
Department Clinical Genetics
St. Mary's Hospital
Hathersage Road
Manchester M130JH
Great Britain
Phone: + 44 1612766264
Fax: + 44 1612766145
Email: kay.metcalfe@CMMC.nhs.uk

Lauréane Mittaz-Crettol
Div. Molecular Pediatrics CHUV
Clinique Infantile 02-32
Av. Pierre Decker 2
CH-1011 Lausanne
Switzerland
Phone: + 41-21-314-3839
Fax: + 41-21-314-3546
Email: laureane.mittaz-crettol@hospvd.ch

Etienne Mornet
Université de Versailles St. Quentin en Yvelines
Laboratoire SESEP
Bat Fermat
45 avenue des Etats-Unis
78035 Versailles Cedex
France
Phone: + 33-139254676
Fax: + 33-139254678
Email: etienne.mornet@cytogene.uvsq.fr

Geert Mortier
Department of Medical Genetics
Ghent University Hospital
De Pintelaan 185
B-9000 Gent
Belgium
Phone: +32 9 2403603
Fax: +32 9 2404970
Email: geert.mortier@UGent.be

Stefan Mundlos
Institut für Medizinische Genetik
Charité - Universitäts-Medizin Berlin
Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
Phone: + 49 30 450569121

Fax: + 49 30 569915
Email: stefan.mundlos@charite.de

Sarah Nikkel
Department of Genetics
Children's Hospital of Eastern Ontario
401 Smyth Road Ottawa
Ontario K1H 8L1
Canada
Phone: +1 613 737 7600 ext 2611
Fax: +1 613 738 4822
Email: snikkel@cheo.on.ca

Peter G. J. Nikkels
Department of Pathology
University Medial Center Utrecht
PO Box 85500
3508 GA Utrecht
Netherlands
Phone: + 31 302506565
Fax: + 31 302544990
Email: p.g.j.nikkels@azu.nl

Gen Nishimura
Department of Radiology
Tokyo Metropolitan Kiyose Children's Hospital
1-3-1 Umezono, Kiyose-Shi
Tokyo 204-8567
Japan
Phone: + 81424910011
Fax: + 81424910044
Email: gen-n@pc4.so-net.ne.jp

Seema Nundlall
Faculty of Life Sciences
University of Manchester
B 3081 Smith Building
Oxford Road
M13 9PT Manchester
Great Britain
Phone: + 44-161-2751559
Fax: + 44-161-2755082
Email:
seema.nundlall-2@postgrad.manchester.ac.uk

Rosa Isela Ortiz-De-Luna
Dept. de Genética
Hospital Infantil de México
Dr. Márquez 162, Col. Doctores
México, D.F.CP 06720
Mexico
Phone: + 52-555 228 9917

Jorge Pinto-Basto
Institute for Medical Genetics
Praça Pedro Nunes, 88
4099-028 Porto
Portugal
Phone: +351 22 60 70 322
Fax: +351 22 60 70 399
Email: jorge.pintobasto@igm.min-saude.pt

Katarzyna Pirog-Garcia
Wellcome Trust Centre for Cell Matrix Research
Faculty of Life Sciences
Michael Smith Building
University of Manchester M13 9PT
Great Britain
Phone: + 44-161-2751559
Fax: + 44-161-2751505
Email: k.a.pirog@student.manchester.ac.uk

Andrew Poznanski
2400 N Lakeview F 2402
Chicago IL 60614
USA
Phone: + 1 773 935 8909
Email: apoznanski@ameritech.net

Raffaele Renella
Département médico-chirurgical de Pédiatrie
Centre Hospitalier Universitaire Vaudois
1011 Lausanne
Switzerland
Phone: +41 21 314 1111
E-mail : raffaele.renella@chuv.ch

David L Rimoin
Medical Genetics Institute
8700 Beverly Blvd, Suite 665 W
Los Angeles, CA 90048
USA
Phone: +1 310 423 4461
Fax: + 1 310 423 0462
Email: david.rimoin@cshs.org

Stephen Robertson
Department of Paediatrics and Child Health
Dunedin School of Medicine
University of Otago
PO Box 913
Dunedin
New Zealand
Phone: + 64 3 4797469
Fax: + 64 3 4797469
Email: stephen.robertson@stonebow.otago.ac.nz

Antonio Rossi
Department of Biochemistry
University of Pavia
Via Taramelli, 3/B
27100 Pavia
Italy
Phone: +39 0382 987229
Fax: +39 0382 423108
Email: antrossi@unipv.it

Massimiliano Rossi
Departmento di Pediatria
Universita Federico II
Via S. Pansini 5
80131 Napoli
Italy
Phone: +39 081 7464814
Fax: +39 081 7463116
Email: masrossi@unina.it

Bhramar Saha
145, Halton Road
Sutton, Coldfield
BT3 GNY
Great Britain
Phone: +44 121 6813524
Fax: +44 121 6073596
Email: bhramarsaha@doctors.org.uk

Luca Sangiorgi
Genetics Unit
Rizzoli Orthopedic Institute
Via di Barbiano 1/1
40136 Bologna
Italia
Phone: + 39 0516366519
Fax: + 39 0516366681
Email: luca.sangiorgi@ior.it

Heloisa G. dos Santos
GenoMed, Diagnósticos de Medicina Molecular
Edificio Egas Moniz
Av Prof Egas Moniz, Piso 3
1649-028 Lisboa- Portugal
Phone: +35 1 2172047
Fax: +35 1 2179995500
Email: heloisa.santos@mail.telepac.pt

Ravi Savarirayan
Genetic Health Services Victoria
10th Floor, Royal Children's Hospital
Parkville
Victoria 3052
Australia
Phone: + 61383416304
Fax: + 61383416390
Email: ravi.savarirayan@ghsv.org.au

Gioacchino Scarano
Medical Genetics Department
Azienda Ospedaliera "Gaetano Rummo"
Via dell'Angelo 1,
Padiglione S. Pio da Pietrelcina, IV piano
82100 Benevento
Italy
Phone: +39 082 457216
Fax: +39 082 457495
Email: gioacchino.scarano@ao-rummo.it

Elke Schaefer
Bansenstr. 15
21075 Hamburg
Germany
Phone: +49 40 7923221
Fax: +49 40 79142635
Email: emschaefer@t-online.de

David Sillence
The Children's Hospital at Westmead
Locked Bag 4001
Westmead NSW 2145
Australia
Phone: +61 2 9845 3215
Fax: +61 2 9845 3204
Email : davids@chw.edu.au

Marleen Simon
Department of Clinical Genetics
Erasmus MC Rotterdam
Westzeedijk 112
3016 AH Rotterdam
The Netherlands
Phone: + 31 10 4366577
Fax: + 31 10 4367133
Email: m.simon@erasmusmc.nl

Sarah Smithson
Department of Clinical Genetics
St. Michaels Hospital
Southwell Street
Bristol
BS2 8EG
Great Britain
Phone: + 44 117 9285653
Fax: + 44 117 9285108
Email: sarah.smithson@ubht.swest.nhs.uk

Jürgen Spranger
Uni.-Kinderklinik Mainz
Langenbeckstr. 1
55133 Mainz
Germany
Phone: +49 7221 987999
Fax: +49 7221 987998
Email: Spranger@wserv.kinder.klinik.uni-mainz.de

Elisabeth Steichen-Gersdorf
Universitätsklinik für Kinder- u. Jugendheilkunde
Anichstr. 35
6020 Innsbruck
Austria
Phone: +43 51250423600
Fax: +43 51250423484
Email: Elisabeth.Steichen@uibk.ac.at

Irene Stolte-Dijkstra
Department of Clinical Genetics
University Medical Center Groningen
Hanzeplein 1 - PO Box 30.001
9700 RB Groningen
The Netherlands
Phone: + 31 503637417
Fax: + 31 503632950
Email: i.stolte@medgen.umcg.nl

Andrea Superti-Furga
Centre for Pediatrics and Adolescent Medicine
Freiburg University Hospital
Mathildenstr. 1
79106 Freiburg
Germany
Phone: +49-761-270-4305
Fax: +49-761-270-4454
Email: asuperti@uniklinik-freiburg.de

Reid Sutton
One Baylor Plaza, BCM-225
Houston, TX, 77030-3498

USA
Phone: +1 832 822 4296
Fax: +1 832 825 4294
Email: vsutton@bcm.tmc.edu

Jacky Taylor
National Genetics Reference Laboratory (Manchester)
Regional Genetics Services
St. Mary's Hospital, Hathersage Road
Manchester
M13 OJH
Great Britain
Phone: +44 1612763202
Fax: +44 1612764058
Email: jacky.taylor@cmmc.nhs.uk

Paulien Anna Terhal
Eiklaan 8
3737 RL Groenelan
Netherlands
Phone: + 34 6213598
Email: p.a.terhal@dmg.azu.nl

Christian T. Thiel
Institut für Humangenetik Erlangen
Schwabachanlage 10
91054 Erlangen
Germany
Phone: +49 9131 8526007
Fax: +49 9131 209297
Email: Christian.Thiel@humgenet.uni-erlangen.de

Sanna Toiviainen-Salo
Hospital for Children and Adolescents
Department of Pediatric Radiology
Helsinki University Hospital
POB 281
00029 Hus
Finland
Phone: + 358 405366564
Email: sanna.toiviainen-salo@hus.fi

Peter Turnpenny
Clinical Genetics Department
Royal Devon & Exeter Hospital
Gladstone Road
Exeter EX1 2ED
Great Britain
Phone: +44 1392 405726
Fax: +44 1392 405739
Email: peter.turnpenny@rdehc-tr.swest.nhs.uk

Sheila Unger
Institute for Human Genetics and
Center for Pediatrics and Adolescent Medicine
Breisacher Str. 33
79106 Freiburg
Germany
Phone: +49 761 270 7057
Fax: +49 761 270 7018
Email: sheila.unger@uniklinik-freiburg.de

Raymond Wang
444 South San Vicente Blvd
1001 Los Angeles, CA
USA 90048
Phone: +1 310 423 9941
Fax: +1 310 423 9760
Email: Raymond.wang@cshs.org

Matt Warman
Case Western Reserve University
Dept. Genetics
2109 Adelbert Road, BRB 719
Cleveland, Ohio 44106-4955
USA
Phone: +1 216 368 4919
Fax: +1 216 368 3432
mlw14@po.cwru.edu

Jostein Westvik
Dept. Of Radiology
Section of Pediatric Radiology
Rikshospitalet
0027 Oslo
Norway
Phone: +47 23072487
Fax: +47 23073754
Email: jostein.westvik@rikshospitalet.no

Michael Wright
Institute of Human Genetics
International Centre for Life
Central Parkway
Newcastle-upon-Tyne NE1 3BZ
Great Britain
Phone: +44 191 241 8758
Fax: +44 191 241 8799
Email: m.j.wright@ncl.ac.uk

Belinda Xavier
Faculdade de Medicina de Lisboa
Edificio Egas Moniz
GenoMed - Unidade de Diagnostico Molecular
Sala P3A
1649-028 Lisboa
Portugal
Phone: + 35 1217999506
Fax: + 35 1217999560
Email: bxavier@fm.ul.pt

Bernhard Zabel
Children's Hospital
University of Mainz
Langenbeckstr. 1
55101 Mainz
Germany
Phone: + 49 6131 17 6826
Fax: + 49-6131 17 5528
Email: zabel@wserv.kinder.klinik.uni-mainz.de

Andreas Zankl
Division of Molecular Pediatrics
CHUV
1011 Lausanne
Switzerland
Phone: + 41 213143778
Email: andreas.zankl@gmail.com

Frank Zaucke
Center for Biochemistry
Medical Faculty
University of Cologne
Joseph-Stelzmann Str. 52
50931 Cologne
Germany
Phone: + 49 221 4786943
Fax: + 49 221 4786977
Email: frank.zaucke@uni-koeln.de

Leonid Zeitlin
Dept. Of Pediatric Orthopaedics
Dana Children's Hospital
Tel Aviv Sourasky Medical Center
6 Weizmann Street
Tel Aviv 64239
Israel
Phone: + 97236974269
Fax: + 97236974542
Email: pedorth@tasmc.health.gov.il

ISDS Council

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