THURDAY JULY 19

14h00 ..... OPENING

15h00-15h30 …WELCOME AND INTRODUCTION

Toulouse-Lautrec presented by Pierre Maroteaux.

15h30-16h30 …NEW GENES
Moderators: Dan Cohn, Valérie Cormier-Daire.

15h30…… **GDF5 and OA-of Human and of Mouse.**
S. Ikegawa.Laboratory for Bone and Joint diseases, SNP Research Center. Riken, Japan.

15h45……... **Mutations in PLEKHM1 involved in vesicular transport in osteoclasts cause osteopetrosis.**
B. Perdu. Department of Medical Genetics, University and Hospital of Antwerp, Antwerp, Belgium.

16h00…… **Mutations in aggregan (AGC1) cause Dexter cattle chondrodysplasia.**
R. Savarirayan, Murdoch Childrens Research Institute and University of Melbourne, Melbourne, Australia.

16h15…… **AGC1 gene missense mutation associated with familial osteochondritis dissecans and early osteoarthritis.**
E.L. Stattin, Department of Medical Biosciences, Medical and Clinical Genetics, Umea university, Umea, Sweden.

16h30-17h00….BREAK

17h00-18h00 ... NEW GENES / LATE BREAKING NEWS
Moderators: Deborah Krakow, Stefan Mundlos.

17h00…… **Autosomal recessive hypophosphatemia caused by a homozygous mutation in DMP1.**
O. Mäkitie, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland.

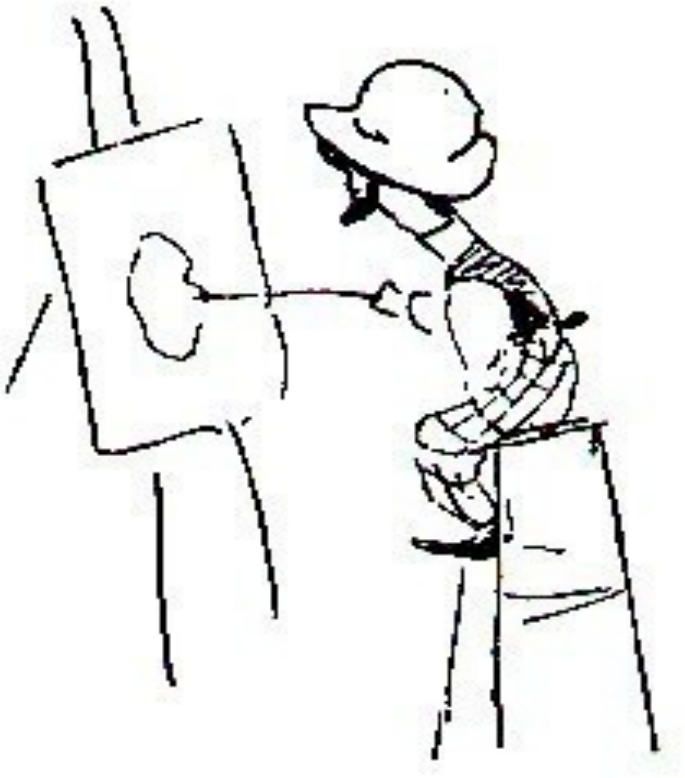
17h15..... **Phenotypic extension of SBDS mutations.**
S. Ikegawa. Laboratory for Bone and Joint diseases, SNP Research Center. Riken, Japan.

17h30 ……... **Molecular pathology of Metaphyseal anadysplasia.**
E. Lausch, Universitäts-Kinderklinik Mainz, Mainz, Germany.

17h45…… **Molecular basis of Ghosal syndrome.**
D. Genevieve, Department of Genetics and INSERM U781, Hôpital Necker-Enfants Malades, Paris, France.

19h30..... DINNER, MAIRIE D'ALBI

HENRI DE TOULOUSE-LAUTREC PRESENTED BY PIERRE MAROTEAUX



GDF5 AND OA – OF HUMAN AND OF MOUSE

Shiro IKEGAWA

Laboratory for Bone and Joint Diseases, SNP Research Center, RIKEN, Japan.

Growth and differentiation factor 5 (GDF5) has been implicated in chondrogenesis, joint formation and osteoarthritis (OA; MIM 165720), the most common form of human arthritis. By combined approach of human and mouse genetics, we are clarifying the role of GDF5 in the etiology and pathogenesis of OA.

Human study

Through a series of case-control association studies, we found that GDF5 is associated with OA. A single nucleotide polymorphism (SNP) in its 5'-UTR (+104T/C) showed a significant association ($P=1.8 \times 10^{-13}$; odds ratio= 1.8) in two independent hip OA populations. This association was replicated for knee OA in Japanese and Chinese. Located in the GDF5 core promoter, this SNP exerted allelic differences on transcriptional activity in chondrogenic cells, with the susceptibility allele showing reduced transcriptional activity. Our findings implicate GDF5 as a susceptibility gene for OA in Asians and suggest that decreased GDF5 expression is involved in OA pathogenesis. The association is replicated in other ethnic groups.

Mouse study

While various human *GDF5* mutations and their phenotypic consequences have been described, only loss-of-function mutations that cause brachypodism have been reported in mice. Here, we report a new Gdf5 allele derived from a large-scale ENU mutagenesis screen. This allele carries an amino acid substitution (W408R) in a highly conserved region of the signaling domain of GDF5 protein. The mutation is semidominant, showing brachypodism and digit ankylosis in heterozygotes, and much more severe brachypodism, ankylosis of the knee, and early-onset OA of the elbow in homozygotes. The mutant GDF5 protein is secreted and dimerizes normally, but inhibits the function of the wild-type protein in a dominant-negative fashion. This study further highlights a critical role of GDF5 in joint formation and the development of OA, and this mouse should serve as a good model for OA.

MUTATIONS IN *PLEKHM1,* INVOLVED IN VESICULAR TRANSPORT IN OSTEOCLAST, CAUSE OSTEOPETROSIS

B Perdu[1*], L Van Wesenbeeck[1*], PR Odgren[2*], FP Coxon[3*], A Frattini[4], P Moens[5], CA, JP Timmermans[6], A Teti[7], MH Helfrich[3], MJ Rogers[3], A Villa[4], W Van Hul[1]

** These authors contributed equally to this work 1 Department of Medical Genetics, University and University hospital of Antwerp, Antwerp, Belgium. 2 Department of Cell Biology, University of Massachusetts Medical School, Worcester MA01655, USA. 3 Department of Medicine and Therapeutics, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK. 4 Instituto Tecnologie Biomediche, Consiglio Nazionale delle Ricerche, Segrate, Italy. 5 Pediatric Orthopaedics, Catholic University of Leuven, Leuven, Belgium. 6 Laboratory of Cell Biology and Histology, University of Antwerp, Antwerp, Belgium. 7 Department of Experimental Medicine, University of L'Aquila, L'Aquila, Italy.*

The osteopetroses are a heterogeneous group of bone disorders characterized by a reduction in bone resorption and a generalized net accumulation of skeletal mass. We have now identified the *plekhm1* gene as the gene responsible for the osteopetrotic phenotype of the *incisors absent* rat and we identified a patient with a homozygous G→A transition at position +1 of the donor splice site of intron 3 (IVS3+1G>A). She was diagnosed with an autosomal recessive intermediate form of the disease. When the girl was 7 years old, an 'Erlenmeyer flask' deformity of the distal femora was detected upon radiographic examination. At the age of 14 years, she suffered from pain in the left leg during walking and a chondrolysis of the left hip was observed. Her younger brother is also homozygous for the mutation but has not yet developed clinical symptoms. However, radiological examination at the age of 8 months and 2 years did show the presence of dense metaphyseal bands. Electron and confocal microscopy analysis demonstrated that osteoclasts (derived from M-CSF-dependent peripheral blood monocytes) from the patient differentiated normally. However, unlike osteoclasts from a healthy brother (lacking the mutation), osteoclasts from the patient showed hardly any evidence of resorptive activity when cultured on dentine discs, and had a more flattened morphology. This is the first evidence for a role of the plekhm1 protein in bone metabolism. The presence of RUN and PH domains suggests that the plekhm1 protein may be involved in small GTPase signaling. Overexpression studies in HEK293 cells demonstrated that the plekhm1 protein is partially associated with intracellular vesicles and colocalizes with Rab7 and Rab9, but not Rab5 or Rab6, suggesting that these vesicles are late endosomes/lysosomes. In cells over-expressing Rab7, plekhm1 becomes completely localized to Rab7–positive vesicles, an effect that is not seen with overexpression of Rab9. Furthermore, inhibiting the prenylation of Rab proteins disrupted the endosomal localization of plekhm1, supporting its role in small GTPase signaling. In conclusion, the identification of *PLEKHM1* as a new osteopetrosis gene indicates its crucial role in bone resorption and its involvement in the Rab7 signaling pathways and late endosomal trafficking in osteoclasts.

MUTATIONS AGGRECAN (*AGC1*) CAUSE DEXTER CATTLE CHONDRODYSPLASIA

Ravi Savarirayan[2]*, Julie Cavanagh[1], Imke Tammen[1], Peter Windsor[1], John Bateman[2], Frank Nicholas[1], Herman Raadsma[1]

1 Reprogen, University of Sydney, Camden, Australia 2 Murdoch Childrens Research Institute, and University of Melbourne, Victoria

Lethal "bulldog" chondrodysplasia in Dexter cattle is one of the earliest Mendelian traits described in animals. Affected (homozygous) fetuses display extreme disproportionate dwarfism, a short vertebral column, marked micromelia, short ribs with abnormal lungs, relatively large head with a retruded muzzle, cleft palate, protruding tongue, and a large abdominal hernia. They typically die around the seventh month of gestation, precipitating a natural abortion. Carriers (heterozygotes) show a milder phenotype, most noticeably having rhizomelic limb shortening in addition to radiographic spinal abnormalities comprising posterior scalloping and irregularity of the vertebral bodies.

Homozygosity mapping in a small Australian Dexter cattle pedigree identified the gene *AGC1* as a positional candidate. *AGC1* encodes aggrecan, the core protein of the most abundant and important structural cartilage proteoglycan. Homozygous *AGC1* mutations have been shown to cause the lethal chondrodysplasia, cartilage matrix deficiency (cmd) in mice and nanomelia in chicks. Heterozygous *AGC1* mutations cause dwarfism and shortened skeletal elements in mouse and chick, and a spondylo-epiphyseal dysplasia (Kimberley type) associated with severe premature joint and spinal arthritis in humans. These data suggested *AGC1* as an excellent functional candidate for this condition.

AGC1 mutation screening revealed a common 4bp insertion in exon 11 (2266_2267insGGCA) (BD1) and a second, rarer transition in exon 1 (-198C>T) (BD2) that co-segregated fully with the disorder. To further investigate the pathogenesis of this chondrodysplasia, we performed allele-specific primer extension analysis of mRNA isolated from chondrocytes of cattle heterozygous for the common insertion (BD1) mutation. This demonstrated that mutant mRNA was subjected to nonsense-mediated decay, showing only 7% of normal expression, suggesting haploinsufficiency for aggrecan as the pathogenetic basis for the carrier phenotype. Genotyping in Dexter cattle families worldwide has shown that these two mutations account for all cases and segregate fully with the heterozygous or homozygous phenotype.

We anticipate that these Dexter cattle will prove extremely useful as a model for investigating and understanding corresponding human chondrodysplasias and arthritis phenotypes.

AGC1 GENE MISSENSE MUTATION ASSOCIATED WITH FAMILIAL OSTEOCHONDRITIS DISSECANS AND EARLY OSTEOARTHRITIS

Eva-Lena Stattin[1], Fredrik Wiklund [2], Yelverton Tegner, [3] and Niklas Dahl[4]

1 Department of Medical Biosciences, Medical and Clinical genetics, Umeå University, Umeå, Sweden , 2 Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. 3 Department of Health Sciences, Luleå Technical University, Luleå, Sweden, 4 Department of Genetics and Pathology, The Rudbeck Laboratory, Uppsala University, Uppsala, Sweden .

Familial osteochondritis dissecans (OCD) is a rare disorder with disturbed chondro-skeletal development, disproportionate growth and deformation of the skeleton. Familial OCD is described in association with multiple OCD, short stature and early osteoarthritis. OCD is defined as a separation of cartilage and subchondral bone from surrounding tissue. We have identified an extended Swedish pedigree segregating autosomal dominant OCD in five generations. Here we report the results of a genome wide linkage scan in this family. A significant two point linkage was found for a 32 cM region on chromosome 15q26 with peak lod score for marker D15S127 (Zmax of 6.36 at theta 0.00). The minimal shared haplotype among affected was determined to 10.5 Mb which contains 111 known genes. The candidate region spans the gene encoding aggrecan (AGC1), an important component of the extra cellular matrix of cartilage. We performed direct sequence analysis of the AGC1 gene and we identified a missense mutation G to A in patients with OCD. The mutation affects a highly conserved residue in the G3 domain of the gene.

Conclusion
This is the first identification of a gene mutation causing familial OCD and osteoarthritis. A single mutation in the AGC1 gene was recently reported in Spondylo epiphyseal dysplasia Kimberley which suggests that these two disorders may be allelic.

AUTOSOMAL RECESSIVE HYPOPHOSPHATEMIA CAUSED BY A HOMOZYGOUS MUTATION IN *DMP1*

Outi Mäkitie[1], Ilkka Kaitila[1], Murat Bastepe[2], Serap Turan[2], and Harald Jüppner[2]

1 Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland, 2 Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Hypophosphatemia (HP) due to renal phosphate-wasting is most frequently inherited as an X-linked dominant disorder (XLH) that is caused by heterozygous *PHEX* mutations, or as an autosomal dominant condition (ADHR) that is caused by heterozygous *FGF23* mutations. Recently, homozygous mutations in *DMP1* (dentin matrix protein 1), which encodes a non-collagenous bone matrix protein expressed in osteoblasts and osteocytes, were identified as the cause of an autosomal recessive form of HP (ARHP). We now describe a family, in which the two members affected by ARHP carry a novel homozygous *DMP1* mutation and we provide a detailed description of their skeletal phenotype.

Patient 1, presently 78 yrs old male, was born to healthy Finnish parents with no known consanginuity. He is the oldest of seven siblings and he suffered from bone pain and varus deformity since age 3 yrs. Lower limb osteotomies were performed at age 18 yrs, but HP was not diagnosed until adulthood. With increasing age, he developed severe joint pain and contractures, calcifications of paraspinal ligaments leading to complete immobilization of the spine, and significant cranial hyperostosis. When assessed for the present study, he was 138 cm in height and wheelchair bound. Skeletal radiographs showed besides the enthesopathies, short and deformed long bones, abnormal bone structure and a pathological fracture of the left femoral neck.

Patient 2, the presently 66 yrs old sister of Patient 1 had bone pain and varus deformities since early childhood. She had lower limb osteotomies at age 6 yrs and subsequently numerous orthopaedic surgeries to correct lower limb deformities and bilateral femoral neck fractures. Her present height is 130 cm. Similar to her brother, she has severe spinal stiffness due to calcifications of all spinal ligaments, as well as lower limb deformities and contractures. Skeletal radiographs showed abnormal bone structure, short and deformed long bones, significant cranial hyperostosis, enthesopathies and calcifications of the spinal ligaments in the cervical, thoracic and lumbar spine. Spinal MRI showed, in addition to the calcifications, large dural ectasia in the mid-thoracic and lumbar spine.

Blood and urine biochemistries were in both patients consistent with hypophosphatemia due to renal phosphate-wasting; markers of bone turnover were significantly increased. Molecular genetic analysis of the *DMP1* gene revealed a novel, homozygous missense mutation in exon 6 (c.205A>T; S69C). The clinical and laboratory observations in this family thus confirmed that DMP1 has an important role in normal skeletal development and that *DMP1* mutations result in a severe skeletal phenotype with short stature, deformed bones, abnormal bone structure, pathological fractures, and severe enthesopathies.

PHENOTYPIC EXTENSION OF *SBDS* MUTATIONS

Shiro Ikegawa, Gen Nishimura

Japanese Skeletal Dysplasia Consortium, Japan.

Phenotype of Shwachman-Bodian-Diamond syndrome (Shwachman syndrome) is variable and diverse, and its phenotypic spectrum has not been delineated so definitely. We report here on two patients with skeletal manifestations at the severest end of the phenotypic spectrum of the SBDS gene mutations. An 11-year-old Japanese girl presented with neonatal respiratory failure necessitating lifelong ventilation support, severe short stature and severe developmental delay. She developed neutropenia in infancy, and decreased serum amylase was noted in childhood. A British boy was a stillbirth with pulmonary hypoplasia and hepatic fibrosis found on autopsy. Both cases had neonatal skeletal manifestations that included platyspondyly, lacy iliac crests and severe metaphysial dysplasia, and thus did not fall in the range of the known Shwachman syndrome skeletal phenotype, but resembled spondylometaphysial dysplasia (SMD) Sedaghatian type (OMIM 250220), a rare skeletal dysplasia characterized by platyspondyly, rhizomelic shortness of long bones, metaphyseal dysplasia and narrow rib cage. The girl harbored a recurrent mutation (183TA->CT) and a novel missense mutation (79T->C), whereas the boy carried two recurrent mutations (183TA->CT and 258+2T->C). We also examined the SBDS mutations in additional cases with neonatal SMD including one typical case with SMD Sedaghantian type, but failed to discover SBDS mutations. Our experience expands the phenotypic spectrum of SBDS mutations, which, at its severest end, results in severe neonatal SMD. Further studies are necessary to define the spectrum.

MOLECULAR PATHOLOGY OF METAPHYSEAL ANADYSPLASIA

Ekkehart Lausch [1], Katja Hilbert [1], Jürgen Spranger [1] and Bernhard Zabel [1, 2]

1 Universitäts-Kinderklinik Mainz, Obere Zahlbacher Str. 63, D-55131 Mainz, 2 Zentrum für Kinderheilkunde und Jugendmedizin, Universitätsklinikum Freiburg, Mathildenstr. 1, D-79106 Freiburg im Breisgau.

Metaphyseal Anadysplasia (OMIM 309645, MAD) is a rare bone dysplasia of unknown aetiology and with a benign clinical course. Characterised by early and severe metaphyseal alterations, the natural course of the disease eventually results in complete regression of the lesions, with normal stature in adulthood. Few cases have been reported since the original description more than 30 years ago, providing only inconclusive evidence for the mode of inheritance.

Here, we report on unrelated familial cases of MAD, presenting with metaphyseal changes of early onset, spontaneously regressive with advancing age. In addition to the known transient clinical features, short stature and varus deformity of the legs, all patients are affected by scoliosis of variable severity. However, not only the exceptional clinical course but also the radiographical appearance and distribution of the metaphyseal irregularities are highly consistent with MAD. Four generation pedigrees strongly suggest autosomal dominant inheritance of MAD, an assumption compatible with all cases published to date. Molecular analyses of several candidates revealed different missense mutations in a gene implicated in matrix biology. Mutations cosegregated with the disease phenotype in all kindreds analysed. Functional analyses *in vitro* reveal the consequences of disease-associated mutations and thus define the molecular pathology of the disease.

THROMBOXANE SYNTHASE MUTATIONS IN HEMATODIAPHYSEAL DYSPLASIA WITH ANEMIA OR GHOSAL SYNDROME (GHDD)

David Geneviève[1], Valérie Proulle[2], Bertrand Isidor[1], Valérie Serre[1], Fatima Djouadi[1], Capucine Picard[3], Capucine Vignon-Savoye[4], Brigitte Bader-Meunier[5], Stéphane Blanche[3], Marie-Christine De Vernejoul[6], Laurence Legeai-Mallet[1], Marie Dreyfus[2], Anne Marie Fisher[7], Martine Le Merrer[1], Pascale Gaussem[7], Arnold Munnich[1], Valérie Cormier-Daire[1]

1-Department of Genetics and INSERM U781, [3]Immuno-hematology department, Hôpital Necker Enfants Malades ; [2]Hematologic laboratory, Kremlin-Bicetre Hospital, [4]Pediatric Unit, CHIC Le Raincy-Montfermeil ; [5]Pediatric Hematology Unit, Robert Debré Hospital, [6]Rhumatology Department, Lariboisiere Hospital, [7]Hematologic laboratory, Georges Pompidou Hospital, Paris, France .

Ghosal hematodiaphyseal dysplasia (GHDD, OMIM 231095) is a rare autosomal recessive disorder characterized by diaphyseal dysplasia with increase bone density (IBD) and abnormal long bone modeling associated with aregenerative corticosensitive anemia.

Using an homozygosity mapping strategy, we first localized the gene responsible for GHDD on chromosome 7q33-q34. After exclusion of 25 candidate genes by direct sequencing, we considered thromboxane synthase gene (*TBXAS1*) as a possible candidate gene. This gene is composed of 17 exons and encodes a protein of 533 amino acids, thromboxane synthase (TXAS), which is one of the terminal prostaglandin H_2 enzymes from the arachidonic acid (AA) metabolism. TXAS products thromboxane A_2 (TXA_2) which is an inducer of platelet aggregation and involved in various normal and pathologic processes including haemostasis/thrombosis, cardiovascular and pulmonary diseases.

By direct sequencing of TBXAS1 in four consanguineous families, we identified four distinct missense mutations present at the homozygote state and absent in 210 control chromosomes.
We then demonstrated a specific anomaly of platelet aggregation induced by AA in GHDD patients but the absence of any hematological disorder, suggestive of redundant mechanisms to induce platelet aggregation. Using real time quantitative PCR, we found that TXAS and TXA_2 modulate *OPG* and *RANKL* expression in primary cultured osteoblasts.

We conclude that *TBXAS1* mutations are responsible for GHDD, a disorder mainly characterised by increase bone density and anemia. Additional studies are currently performed to further understand the key role of TXAS in bone.

FRIDAY JULY 20

9h-10h00……CLINICAL DELINEATION
Moderators: David Rimoin, Mickael Wright.

9h00……**The skeletal phenotype of Schimke immuno-osseous dysplasia.**
SF. Smithson, Department of Clinical Genetics, St Michael's hospital, Bristol, UK.

9h10……**The clinical and radiological phenotype of Shprinzen-Goldberg syndrome: five new cases**.
C. Hall, Department of Radiology and Clinical Genetics, Great Ormond Street Hospital, London, UK

9h20……**Defining disorders with Erlenmeyer Flask Bone Deformity.**
MA. Faden, Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, USA.

9h30……**Towards a better delineation of Odontochondrodysplasia.**
A. Superti-Furga, Ctr for Peds and Inst Hum Genet, University of Freiburg, Germany.

9h40……**Detection of microdeletions in limb malformation syndromes: a microdeletion in thrombocytopenia-absent radius (TAR) syndrome with a unique type of inheritance resembling autosomal recessive inheritance.**
S. Mundlos, Max-Planck-Institut für molekulare Genetik, Berlin, Germany.

9h50……. **Clinical and radiographic features of autosomal dominant brachyolmia.**
DH. Cohn, Cedars-Sinai Medical Center and David Geffen School of Medecine, UCLA, Los Angeles, USA.

10h00 **Spondylo-Megaepiphyseal-Metaphyseal Dysplasia: three new cases of a rare but distinct entity.**
M. Simon, Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands.

10h10-10h45 .... BREAK

10h45-12h00.....VERTEBRAL SEGMENTATION
Moderators: Arnold Munnich, Andrea Superti-Furga.

10h45……. **Segmental patterning of the spine: from clocks to scoliosis.**
O. Pourquié, Stowers Institute for Medical Research/Howard Hughes Medical Institute, Kansas City, USA.

11h45……. **A new classification system for congenital scoliosis and abnormal vertebral segmentation.**
P. Turnpenny, Clinicals Genetics, Royal Devon & Exeter Hospital, Exeter, UK.

12h00-12h45 ….POSTER SESSION

12h45-14h15….LUNCH (*PARC DE ROCHEGUDE*)

14h15-16h00…..MURINE MODELS
Moderators: Shiro Ikegawa, William Horton

14h15**……. Growth plate characterization in TSP35/Col9 Knock-out mice.**
J.T. Hecht, University of Texas Health Science Center-Houston, Houston, USA.

14h30……. **Y367C mutation in mouse FGFR3 causes severe dwarfism by affecting both chondrogenesis and osteogenesis.**
S.Pannier, Department of Genetics, INSERM U781, Hôpital Necker-Enfants-Malades, Paris, France.

14h45……. **Bone phenotype in a mouse model of Diastrophic Dysplasia.**
B. Gualeni. Department of Biochemistry, University of Pavia, Italy.

15h00……. **Reduced cell proliferation and increased apoptosis are significant pathological mechanisms in murine models of mild pseudoachondroplasia and multiple epiphyseal dysplasia resulting from mutations in MATN3 and COMP.**
M. Briggs, Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, UK

15h15……. **Multiple roles of neurofibromin 1 in Skeletal development and growth.**
S. Mundlos, Max-Planck-Institut für molekulare Genetik, Berlin, Germany

15h30……. **Defects in Filamin B produce a variety of skeletal defects.**
D. Krakow, Medical Genetics Institute, Cedars-Sinai Medical Center, UCLA, Los Angeles, USA

15h45……. **An inversion involving Sonic hedgehog (Shh) cis-regulatory enhancers is associated with malformations of the telencephalon and cranial sutures in the "Short digits" (Dsh) mouse.**
G. Schwabe, Institute of Medical Genetics, Berlin, Germany

16h00-16h30…. BREAK

16h30-17h15…. UNKNOWN SESSION
Moderators: Christine Hall, Ralph Lachman

17h15-18h00 … ISDS DIAGNOSTIC COMPETITION
prepared by the Paris team

18h00 ..... ISDS BUSINESS MEETING

19h30 ..... Dinner Château de Mauriac

THE SKELETAL PHENOTYPE OF SCHIMKE IMMUNO-OSSEOUS DYSPLASIA

Smithson SF[1], Cairns R[2], Tizard EJ[3], Hall CM[4], Smith GC[5], Spranger J[6], Boerkoel CF[2]

1 Department of Clinical Genetics, St Michael's Hospital, Bristol, UK 2 Department of Medical Genetics, Children's and Women's Health Centre of BC, Vancouver, Canada 3 Department of Paediatric Nephrology, Bristol Children's Hospital, Bristol, UK 4 Department of Radiology, Great Ormond Street Children's Hospital, London, UK 5 Children's Kidney Centre, University Hospital of Wales, Heath Park, Cardiff, UK 6 Kinderklinik, University of Mainz, Germany

Schimke immuno-osseous dysplasia (SIOD, OMIM 242900) is characterized by renal disease (focal segmental glomerulosclerosis), T-cell deficiency, characteristic dysmorphic features and spondyloepimetaphyseal dysplasia (SEMD). Other features observed in some patients include atherosclerosis with cerebral ischemia, migraine-like headaches, deficiency of other blood cell lineages, corneal opacities, dental anomalies, hyperpigmented macules, opportunistic infections, autoimmune enteropathy, pulmonary hypertension, and hypothyroidism, but they differ in penetrance and expressivity within and among families.
The SEMD in Schimke usually presents with short stature at birth or in infancy and is characterized by a relatively short trunk. The described key radiological findings include short spine with ovoid dorsally-flattened vertebral bodies, small pelvis due to hypoplasia of the basilar part of the ilia, laterally-displaced femoral heads with small epiphyses and mild flattening of the epiphyses of the long bones.

SIOD follows autosomal recessive inheritance and is caused by biallelic putative loss-of-function mutations in the *SMARCAL1* (swi/snf related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1) gene. The function of the *SMARCAL1* protein is not fully understood but it may have a role in gene regulation through a variety of DNA modification processes. Not all patients who have the phenotype of SIOD have mutations in *SMARCAL1*, suggesting another SIOD locus may exist.

We present radiological findings in a small series of patients with SIOD showing the variability and evolution of the skeletal phenotype over time and compare the SEMD in patients with and without *SMARCAL1* mutations.

THE CLINICAL AND RADIOLOGICAL PHENOTYPE OF SHPRINZEN-GOLDBERG SYNDROME: FIVE NEW CASES

Christine Hall[1], Sahar Mansour[2], Louise Brueton[3], Louise Wilson[1], Lesley Ades[4], Stephen Robertson[5], Victoria Murday[6]

1 Department of Radiology and Clinical Genetics, Great Ormond Street Hospital, London. 2 Department of Medical Genetics, St George's, University of London. 3 Clinical Genetics Unit, Birmingham Women's Hospital. 4 Marfan Research Group, The Children's Hospital at Westmead, New South Wales, Australia. 5 Department of Paediatrics and Child Health, Dunedin School of Medicine, New Zealand.6 Ferguson Smith Centre for Clinical Genetics, NHS Greater Glasgow and Clyde.

Shprinzen and Goldberg first described this condition in 1982. Descriptions of the clinical features, skeletal abnormalities and radiological findings are reported in the medical literature. Little has been made of the considerable phenotypic overlap between Shprinzen-Goldberg syndrome , Melnick-Needles osteodysplasty and fronto-metaphyseal dysplasia.

3 male and 2 female previously unreported cases of Shprinzen-Goldberg syndrome. All 5 presented with marked hypotonia. They became increasingly dysmorphic with age, with distinctive facies: marked hypertelorism, shallow orbital ridges, downslanting palpebral fissures, high arched palate, micrognathia and a large anterior fontanelle. The skeletal abnormalities include arachnodactyly, Camptodactyly, severe pectus deformity, kyphoscoliosis, and deformities of the feet. All 5 had mild to moderate development delay. Umbilical and inguinal hernias were a common feature.

The radiological features are characteristic but do overlap with the changes in Melnick-Needles osteodysplasty and with fronto-metaphyseal dysplasia. However Shprinzen-Goldberg syndrome has striking arachnodactyly and varying degrees of craniosynostosis, not seen in the other conditions.

Three of the patients have had extensive molecular analysis and excluded mutations in FilaminA, Fibrillin1 and the hotspots in TGFBR1 and 2.

DEFINING DISORDERS WITH ERLENMAYER FLASK BONE DEFORMITY

Maha A. Faden, M.D. [1, 2], Deborah Krakow, M.D.[2,3,5], Fatihy Ezgu, M.D. [2], David L. Rimoin, M.D., Ph.D. [2,3,4,6] and Ralph S. Lachman, M.D. [2,3,6,7]

[1]Clinical Genetics, Department of Pediatrics, Riyadh Medical Complex Hospital, Riyadh, Kingdum of Saudi Arabia, [2] Medical Genetics Institute, Cedars-Sinai Medical Center
[3] Departments of Human Genetics, [4]Internal Medicine, [5]Obstetrics and Gynecology, [6]Pediatrics, and [7]Radiology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Erlenmeyer flask bone deformity (EFD) is a long-standing term used to describe a specific abnormality of the distal femora. The deformity consists of broadening and widening of the metaphysis, with abnormal cortical thinning and medullary cavity widening of the metaphysis and adjacent diaphysis that results in an Erlenmeyer flask-like appearance. On review of the litrature, 15 distinct disorders have been associated with EFD. To determine which skeletal dysplasias or syndromes are associated with EFD, whether it is a uniform finding in these disorders, and if forms of EFD can be differentiated, the International Skeletal Dysplasia Registry (ISDR) radiographic database (1970-2007) was queried for the term Erlenmeyer flask. Sixty cases were available for analysis. From our observation, we classified EFD into three main groups. The first group is the classic EFD (EFD-C), which has widening of the metaphysis and meta-diaphyseal junction, with an inward diaphyseal inclination that give the typical appearance of an EFD. The best example of this type was seen in dysosteosclerosis. The second group is the non-classic type (EFD-NC), where there is widening of the same above areas with an absent inclination, but still metaphsyeal widening with an EFD appearance. This subtype was been observed in varying metaphyseal bone dysplasias. The third group consists of EFD associated with a band of sclerosis in the metaphysis that becomes "club-like" from lack of modeling (e.g. lead poisoning) and was classified as EFD-like (EFD-L) Among the 60 cases, there were seven distinct disorders, and 19 cases (31.6%) had classic EFD, 27 cases (40%) had nonclassic EFD, and EFD-like was seen in 14 cases (23.3%). Those disorders which had classic EFD were: dysosteosclerosis 4/4 (100%), metaphyseal dysplasia-Pyle type 4/5 (80%), juvenile osteopetrosis 2/6 (33.3%), Osteopetrosis- carbonic anhydrase deficiency type 1/3 (33.3%), craniometaphysel dysplasia 4/13 (30.7%), with Melnick-Needles Osteodysplasty 3/15 (20%), and Gaucher disease 1/8 (12.5%).

Conclusion:
EFD has a variable appearance in different disorders. The classic EFD is more commonly seen in dysosteosclerosis and Metaphyseal dysplasia-Pyle type. Importantly, it is not uniformally seen in disorders where it has been considered a characteristic finding. Further, the differentiation of EFD into classical, nonclassical and EFD-like categories can help differentiate disorders with the finding of EFD.

TOWARDS A BETTER DELINEATION OF ODONTOCHONDRODYSPLASIA

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The association of dentinogenesis imperfecta with chondrodysplasia (odontochon-drodysplasia; ODCD) has been reported in five individuals so far (Goldblatt et al 1992, Bonaventure et al 1992, Maroteaux et al 1996). We diagnosed ODCD in six unreported children (two of whom were sibs) and retrospectively in two brothers reported previously as metatropic dysplasia variant (Crowle et al 1976). This brings the total number of subjects with ODCD to thirteen. We review the clinical and radiographic findings in this patient group in order to ascertain the most helpful diagnostic features.

ODCD manifests at birth with short stature, narrow thorax, and severe spondylometaphyseal dysplasia; unlike hitherto assumed, it is not always benign as three of the eleven individuals died in the first two years of life with respiratory insufficiency. In childhood, mesomelic limb shortening, joint laxity, progressive short stature, scoliosis, and dentinogenesis imperfecta with small, brownish, and fragile primary teeth become apparent. Mental development is normal and eye or ear complications have not been seen so far.

Radiographic features are severe spondylar dysplasia with coronal clefts in infancy; square iliac wings with wide, lacy borders, horizontal acetabular roofs and coxa valga; progressive metaphyseal splaying with enchondromatous changes and large epiphyses; mesomelic shortening; short metacarpals and phalanges with round cone-shaped epiphyses; and generalized osteopenia with expanded diaphyses and thin cortex. The radiographic differential diagnosis in the newborn is with SMD Sedaghatian type and PLSD Torrance type (platyspondyly with spiked metaphyses) and with collagen 2 disorders in general (platspondyly with coronal clefts); later, the disorder resembles metatropic dysplasia (narrow thorax and spondylar changes), Dyggve-Melchior-Clausen syndrome (SEMD with lacy iliac crests), severe Shwachman-Diamond syndrome (narrow thorax and metaphyseal changes) and spondyloenchondrodysplasia (SPENCD). The natural history observed so far shows that the changes in the vertebral bodies tend to lessen with age while those at the metaphyses increase dramatically throughout childhood.

The peculiar but consistent combination of findings in a total of thirteen individuals confirms that ODCD is a distinct entity, with some similarities to COL2A1 disorders but otherwise different. The molecular basis remains unresolved; in one case, the COL2A1 and FGFR3 were sequenced, and in a second case, the SBDS gene; all results were negative. We speculate that the findings of abnormal collagen 2 made some years ago (Bonaventure et al 1992) may be related to some posttranslational modification mechanism rather than to primary COL2A1 mutations, but this remains to be proven. Three pairs of affected sibs born to unaffected parents suggest recessive inheritance, although dominant inheritance with mosaicism remains a possibility.

DETECTION OF MICRODELETIONS IN LIMB MALFORMATION SYNDROMES: A MICRODELETION IN THROMBOCYTOPENIA-ABSENT RADIUS (TAR) SYNDROME WITH A UNIQUE TYPE OF INHERITANCE RESEMBLINGAUTOSOMAL RECESSIVE INHERITNACE

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Thrombocytopenia-absent radius (TAR) syndrome is characterized by hypomegakaryocytic thrombocytopenia and bilateral radial aplasia in the presence of both thumbs. Other frequent associations are congenital heart disease and a high incidence of cow's milk intolerance. Evidence for autosomal recessive inheritance comes from families with several affected individuals born to unaffected parents but several other observations argue for a more complex pattern of inheritance. In this study we describe an interstitial microdeletion of 500kb on chromosome 1q21.1 in all of the investigated 30 TAR syndrome patients detected by microarray-based comparative genomic hybridization (array CGH). Analysis of the parents revealed that this deletion occured *de novo* in 25% of affected individuals. Intriguingly, inheritance of the deletion along the maternal as well as the paternal line was observed. The absence of this deletion in a cohort of control individuals argues for a specific role of the microdeletion in the pathogenesis of TAR syndrome. We hypothesize that TAR syndrome is associated with a deletion on chromosome 1q21.1 but the phenotype develops only in the presence of an additional as yet unknown modifier (mTAR). Array CGH was used in a series of other conditions with limb deformaties. We identified microdeletions in several conditions, among them a case of Nievergelt-like syndrome and a severe form of mesomelic dysplasia. Microdeletions are more frequent than previously thought and may account for rare cases with yet undiagnosed malformations.

CLINICAL AND RADIOGRAPHIC FEATURES OF AUTOSOMAL DOMINANT BRACHYOLMIA

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The brachyolmias comprise a clinically heterogeneous group of short-trunk short stature phenotypes characterized by platyspondyly and irregular margins of the vertebral bodies. This group of spondylodysplasias is genetically heterogeneous, with at least one autosomal dominant form and several recessively inherited forms. Brachyolmia type 1 includes the recessively inherited Hobaek and Toledo types, and is distinguished by flat, elongated vertebrae. The Toledo type is differentiated from the Hobaek type by the presence of corneal opacities. Histologic studies in one type 1 case demonstrated absent growth plate chondrocyte columns and clusters of chondrocytes separated by acellular areas of cartilage matrix. Reserve chondrocytes had dense staining of collagen fibrils surrounding the lacunae, reminiscent of the DTDST group of sulfate transport disorders. Type 2 brachyolmia, the Maroteaux type, is also recessively inherited and has characteristic flat, rounded vertebrae.The dominant form of brachyolmia (type 3) is particularly poorly characterized, with only three families reported in the literature. From a radiographic viewpoint, type 3 is most similar to type 1 brachyolmia, but the platyspondyly may be more severe in some type 3 cases. The molecular basis is not known for any of the brachyolmias.

We have ascertained a large, four generation family with autosomal dominant brachyolmia. Clinical features include mild short-trunk short stature, mild but variable scoliosis and degenerative arthrosis of the spine. Radiographs show platyspondyly, particularly in the cervical and thoracic spine, without significant end plate irregularities. The cervical vertebrae were quite flat during childhood, but largely reconstituted their height in most affected adults. The most characteristic diagnostic feature was overfacing of the pedicles, which was observed in an AP view of the spine. Progressive degenerative arthrosis of the spine began by about the fourth decade of life and included narrowed disc spaces, disc calcification and spur formation. The hips were well formed with very mild metaphyseal abnormalities in the proximal femora which could only be observed in the prepubertal period. There was mild brachydactyly with short metacarpals and a slight delay in carpal ossification, but no epiphyseal irregularity. The epiphyses of the knees and wrists were also normal.

Among three other families with dominantly inherited brachyolmia, one had similar radiographic findings, while two others had distinct features. Thus it is likely that there is some genetic heterogeneity within autosomal dominant brachyolmia.

SPONDYLO-MEGAEPIPHYSEAL-METAPHYSEAL DYSPLASIA: THREE NEW CASES OF A RARE BUT DISTINCT ENTITY

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We report clinical and radiographic features in three newly recognized, unrelated individuals with SMMD: case 1 is a 20-year-old young man, case 2 is a seven-year-old girl, and case 3 is an 18-year-old girl. Parental consanguinity was present in cases 1 and 3 (both of Turkish origin) and likely in case 2 (Indian). All individuals have marked body dysproportion caused by the combination of short trunk and neck with long limbs, fingers and toes. Intelligence, eyes and hearing seem to be unaffected. The radiographic changes are striking and include poorly modeled long bones with tall growth zones and large and round epiphyses; a delay in maturation of vertebral bodies that throughout childhood retain four distinct ossification nuclei giving sagittal and coronal clefts; absence of pubic bones; and a peculiar ossification pattern of hand bones with angel-shaped phalanges and presence of pseudoepiphyses in metacarpals and phalanges. The most dramatic radiographic finding is underossification of the cervical vertebrae with swan-neck deformity of the fibrous axial elements. Surprisingly, there were no prominent neurologic findings in spite of marked spinal chord deformation in the two girls; the boy underwent laminectomy and VPS at age 13 yrs because of progressive hydrocephalus and pyramidal symptoms.

During childhood, the findings in the hands, long bones and vertebrae are diagnostic; after puberty, the epiphyseal changes are no longer recognizable but underossification of the cervical and sacral spine and underossification and diastasis of the pubic bones are suggestive. A second pregnancy in the family of case 1 was interrupted because of abnormal proportions: the radiographic changes in the fetus were normal long bones but completely absent ossification of vertebral bodies.

Changes in the hands and pubis are reminiscent of cleidocranial dysplasia (as noted by Silverman and Reiley in the original description 1985) but clavicles are normal in SMMD. The vertebral findings are reminiscent of diaphanospondylodysostosis (DSD) but phalangeal changes and pubic underossification are not reported in DSD. The similar clinical and radiographic pattern in these individuals confirm that SMMD is a distinct entity to be considered in the next revision of the Nosology. Frequency of parental consanguinity and multiple affected sibs suggest autosomal recessive inheritance.

SEGMENTAL PATTERNING OF THE SPINE: FROM CLOCKS TO SCOLIOSIS

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The human body can be subdivided along the antero-posterior (AP) axis into repeated structures called segments. This periodic pattern is established during embryogenesis by the somitogenesis process. Somites are generated in a rhythmic fashion from the paraxial mesoderm and subsequently differentiate to give rise to the vertebrae and skeletal muscles of the body. Somite formation involves an oscillator, the segmentation clock whose periodic signal is converted into the periodic array of somite boundaries. This clock drives the dynamic expression of cyclic genes in the presomitic mesoderm and requires Notch, FGF and Wnt signaling. Whereas the segmentation clock is thought to set the pace of vertebrate segmentation, the translation of this pulsation into the reiterated arrangement of segment boundaries along the AP axis involves FGF and Wnt signaling. The FGF pathway controls the positioning of the wavefront, which corresponds to the level of the presomitic mesoderm where cells respond to the clock. This mechanism provides an efficient means to couple the spatio-temporal activation of segmentation to the posterior elongation of the embryo. In humans, mutations in genes associated with the function of this oscillator result in abnormal segmentation of the vertebral column such as those seen in congenital scoliosis.

We will discuss ongoing microarray-based strategies to identify novel cyclic genes associated with the segmentation clock and how this research can be applied to medicine to help unravel the molecular basis of human vertebral defects.

A NEW CLASSIFICATION SYSTEM FOR CONGENITAL SCOLIOSIS AND ABNORMAL VERTEBRAL SEGMENTATION

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Congenital scoliosis and abnormal vertebral segmentation is a common birth defect, occurring in isolation, in association with a wide range of well-delineated syndromes, and as part of a wide variety of imprecisely defined and poorly understood phenotypes. Hitherto, there has been no comprehensive classification and both eponymous and non-eponymous terms are used interchangeably between widely variable phenotypes.

A multidisciplinary group met in 2006 under the auspices of the International Consortium for Vertebral Anomalies and Congenital Scoliosis (ICVAS). Prior to the meeting an informal survey of radiologists confirmed that there is widespread confusion in using existing terminology such as spondylocostal/spondylothoracic dysostosis/dysplasia, Jarcho-Levin syndrome, and congenital scoliosis. In proposing a classification system for abnormal spinal segmentation disorders the three-fold aims were to produce a system that: 1) helps to remove current confusion; 2) is clinically useful to radiologists, spinal surgeons and clinical geneticists; and 3) is readily transferable to bioinformatic approaches being developed by segmentation biologists.

The classification proposed concerns dysostoses, not dysplasias, is primarily descriptive from a radiological perspective, and systematic. Vertebral segmentation defects (VSD) should be identified by number affected, including contiguity, and spinal region(s) involved, ie multiple (MVSD), single (SVSD), cervical ⇨⇨⇨ sacrococcygeal. Spinal curvatures (eg scoliosis) and vertebral morphology (eg hemivertebrae – complete, incarcerated or wedge; fusion; cleft; block; bar) should be described. It is acceptable to use specific radiological signs, eg pebble beach, tramlines, and sickle-shaped, as these appearances are linked to specific phenotypes. The size, shape and symmetry of the thoracic cage should be described; similarly, rib number, symmetry and fusion (with site) should be described. Specific terms such as *spondylocostal dysostosis* (SCD), should be reserved for specific phenotypes – in this case contiguous involvement of ≥ 10 segments but without the presence of a bar, a generally symmetrical thoracic cage and rib number, plus the presence of intercostal rib fusion(s). This phenotype correlates with the genotypes of the *DLL3*, *MESP2* and *LNFG* genes, which define SCD1, SCD2 and SCD3 respectively. Similarly, the term *spondylothoracic dysostosis* should be restricted to a specific combination of phenotypic features. The terms *Jarcho-Levin* and *Klippel-Feil* should be discontinued because of their indiscriminate usage. The classification does, however, allow for retention of well-established and eponymous syndromic associations, eg *Alagille* and *Robinow*.

The new system has been evaluated by testing interobserver correlation (6 persons) on 10 previously unseen spinal radiographs. The overall kappa value was 0.77, which is very high for a classification with so many parts. We conclude that the system is reliable.
It is hoped that the classification will bring some order and consistency to a difficult area, at the same time retaining terms with which clinicians are comfortable. As segmentation biologists working on animal models identify candidate developmental genes, the use of a transferable classification system based on accurate phenotopic description will facilitate stratification and testing in patient cohorts.

GROWTH PLATE CHARACTERIZATION IN TSP35/Col9 KNOCK-OUT MICE

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Cartilage oligomeric matrix protein (COMP/TSP5), the fifth member of the thrombospondin gene family is abundant in the growth plate of long bones. Mutations in this gene cause two skeletal dysplasias with a cellular phenotype characterized by intracellular retention of TSP5 and with other ECM proteins, types II and IX collagen, matrilin-3 in the rER of growth plate chondrocytes. Although studies have focused on defining this disease process, the function of TSP5 plays in growth plate is unclear. TSP5 knock-out mice have no obvious skeletal abnormalities suggesting that TSP5 is not essential in the growth plate and/or other proteins may compensate for the loss of TSP5. Two other thrombospondins, TSP1 and TSP3, are expressed in the growth plate and may have overlapping roles with TSP5. To define the role of TSP1, TSP3, TSP5 and type IX collagen in the growth plate, detailed analysis of the growth plate of each of these knock-outs and combinatorial knock-out strains was performed. TSP3, TSP5, and type IX collagen contribute to growth plate organization while TSP1 plays a minor, if any, role in the growth plate. Type IX collagen appears to regulate growth plate width and matrilin-3 incorporation into the extracellular matrix. The dramatic changes in growth plate organization in the TSP35Col9 knock-out mice translate into a 20% reduction in limb length. These studies demonstrate that despite significant alterations in growth plate organization, skeletal growth is only mildly disturbed indicating that skeletal growth is a robust system that is not easily perturbed.

Y367C MUTATION IN MOUSE FGFR3 CAUSES SEVERE DWARFIRM BY AFFECTING BOTH CHONDROGENESIS AND OSTEOGENESIS

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Missense mutations in fibroblast growth factor receptor 3 (FGFR3) result in several human skeletal dysplasias, including hypochondroplasia, achondroplasia and thanatophoric dysplasia. A tyrosine-to-cysteine substitution at position 373 (Y373C) in human FGFR3 results in thanatophoric dysplasia type I and causes ligand-independent dimerization and phosphorylation of FGFR3. The equivalent substitution at position 367 (Y367C) in mouse FGFR3 causes dwarfism with features mimicking human achondroplasia. The resulting mutant mice were small in size and exhibited macrocephaly, shortened limbs and shortened ribs.

In mutant growth plates, the proliferation and maturation zones were disorganized and failed to form long chondrocyte columns, which are usually found in wild type growth plates. The hypertrophic zone (collagen type X) was reduced compared with that of the control and cells were small and round in appearence. We found increased levels of osteopontin and osteocalcin expression in the mutant growth plates. Osteocalcin was not only expressed at higher levels in the mutant mice but was also ectopically expressed in pre-hypertrophic and proliferative zones. An increased osteoclast activity (TRAP) was also detected in mutant trabecular bone. In two weeks old mutant mice, replacement of cartilage by bone and the vascular invasion within the secondary ossification center had not yet taken place. This is in contrast to control animals, where ossification in these regions was clearly visible at this stage of development. Mutant mice showed a delay in the formation of the secondary ossification centre which was no longer apparent when compared to wild type mice after five weeks. These results suggest an essential role for FGFR3 in both chondrogenesis and osteogenesis during endochondral ossification. These dwarf mice represent a useful model for developing drugs for potential treatment of human chondrodysplasias.

BONE PHENOTYPE IN A MOUSE MODEL OF DIASTROPHIC DYSPLASIA

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Diastrophic dysplasia (DTD) is a recessive chondrodysplasia caused by mutations in the *diastrophic dysplasia sulfate transporter (DTDST* or *SLC26A2)* gene. We have generated a mouse model for this disease (dtd mouse), characterized by a chondrodysplastic phenotype that recapitulates essential aspects of DTD in man. Even if the skeletal phenotype is mainly restricted to cartilage we observed alterations also in bone: reduced sulfate uptake in cultured osteoblasts, mild undersulfation of bone proteoglycans and osteoporosis. Thus, in order to better characterize the bone phenotype, which has never been studied in DTD patients, we analysed long bones from 1 and 2 months old dtd and wild-type mice. DXA and X-ray analyses showed that long bones of dtd mice are shortened and more bowed than normal, with a significant decrease in mineral content and mineral density. Static histomorphometry on undecalcified bone sections showed that the dtdst mutation has a significant effect on trabecular bone architecture with reduced trabecular bone volume and increased trabecular spacing in the secondary spongiosa at all the age point considered; trabecular thickness and cortical thickness were significantly decreased only in one month old mutant mice. Dynamic histomorphometry, performed on undecalcified bone sections after double fluorochrome labeling, showed that mineralizing surfaces as well as mineral apposition rate and bone formation rate were not affected. Furthermore, the osteoclast number per trabecular bone surface in our mouse model was normal.

These data demonstrate that there is no primary osteoblastic defect in the dtd mouse and suggest that the observed bone phenotype might be a consequence of increased osteoclastic activity.

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REDUCED CELL PROLIFERATION AND INCREASED DYSREGULATED APOPTOSIS IN A MURINE MODEL OF MILD PSEUDOACHONDROPLASIA RESULTING FROM A MUTATION IN THE C-TERMINAL DOMAIN OF COMP

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Pseudoachondroplasia (PSACH) is one of the more common skeletal dysplasias and results exclusively from mutations in cartilage oligomeric matrix protein (COMP). Most of the mutations identified to date (85%) cluster in the TSP3 repeat region of COMP and the mutant protein is retained in the rER of chondrocytes and may result in increased cell death. In contrast, the pathomolecular mechanism of PSACH resulting from C-terminal COMP mutations (15%) remains largely unknown due to a difficulty in obtaining suitable pathological material.

This study describes the generation and analysis of a murine model of PSACH resulting from a T583M mutation in the C-terminal domain of COMP. Mutant animals are normal at birth, but grow significantly slower than their wild type littermates and by 9 weeks of age they have short-limb dwarfism. Furthermore, by 16 months of age mutant animals exhibit severe degeneration of articular cartilage, which is consistent with early onset osteoarthritis seen in PSACH patients.

In the growth plates of mutant mice the chondrocyte columns are sparser and poorly organised. Mutant COMP is secreted into the extracellular matrix, but its localisation is disrupted along with the distribution of several COMP binding proteins. Although mutant COMP is not retained within the rER we detected an unfolded protein/cell stress response suggesting an intracellular disease mechanism was also contributing to the disease phenotype. Indeed chondrocyte proliferation is significantly reduced and apoptosis is both increased and spatially dysregulated.

Overall, these data suggests that COMP harbouring a mutation in CTD exerts a dominant-negative effect on both intra- and extracellular processes. This ultimately affects the morphology and differentiation of growth plate chondrocytes, eventually leading to chondrodysplasia and reduced long bone growth.

MULTIPLE ROLES FOR NEUROFIBROMIN 1 IN SKELETAL DEVELOPMENT AND GROWTH

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Neurofibromatosis type 1 (NF1) is a prevalent genetic disorder primarily characterized by the formation of neural tumors and pigmented skin lesions. Associated skeletal abnormalities, such as tibial bowing, pseudarthrosis of the tibia, sphenoid wing dysplasia, small stature, scoliosis, are common indicating that neurofibromin, the Nf1 gene product, may play an important role in skeletal development and homeostasis. To investigate this hypothesis, we crossed Nf1flox mice with Prx1Cre mice to conditionally inactivate Nf1 in undifferentiated mesenchymal cells of the developing limbs. Similar to NF1 affected individuals, $Nf1^{Prx1}$ mice show bowing of the tibia and diminished growth. Tibial bowing is caused by decreased stability of the cortical bone due to a high degree of porosity, decreased stiffness, and reduction in the mineral content, as well as hyperosteoidosis. Accordingly, osteoblasts show an increase in proliferation and a decreased ability to differentiate and mineralize in vitro. The reduction in growth is due to lower proliferation rates and a differentiation defect of chondrocytes as shown by abnormal growth palte morphology, reduced expression of Ihh, and increased expression of Sox9 and osteopontin. Abnormal vascularization of skeletal tissues is likely to contribute to this pathology as it exerts negative effect on cortical bone stability and cartilage growth. Furthermore, Nf1 has an important role in the development of joints, as shown by joint fusion of the hips and multiple other abnormalities in other joints. Thus, neurofibromin has multiple essential roles in skeletal development and growth and NF1 can be considered a bone dysplasia.

DEFECTS IN FILAMIN B PRODUCE A VARIETY OF PRODUCE A VARIETY OF SKELETAL DEFECTS

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Filamin B (FLNB) is a cytoskeleton protein involved in a variety of cellular processes including actin binding, cell division, cell migration, transport of cellular solutes, and provides a scaffold for signaling molecules. *FLNB*, and it paralogues, *FLNA* and *FLNC* are composed of two calponin homology domains (CHD1 and CHD2) and 24 highly homologous β-sheet repeats that are separated by two hinge regions. Filamin B homodimers localize juxtomembrane and it is hypothesized that the homodimers aid the extracellular matrix to communicate with intracellular processes. Mutations in *FLNB* underlie a variety of skeletal dysplasias; autosomal recessive spondylocarpotarsal syndrome (SCT) and the autosomal dominant disorders, Larsen syndrome (LS), atelosteogenesis I and III (AOI/AOIII) and Boomerang dysplasia (BD). SCT results from nonsense mutations scattered through the 24 repeat structures. The dominant disorders are due to heterozygosity for conserved residues residing primarily in two domains, CHD2 and the repeat domains 14-17 that surround the first hinge of the molecule.

To further understand why mutations in *FLNB*, a ubiquitously expressed protein, results in skeletal dysplasias, a *Flnb* -/- mouse was generated using a fusion genetrap containing β-galactosidase. Studies of embryonic days 11-16 demonstrated that the ubiquitously expressed filamin B is highly expressed throughout the developing skeleton. Homozygous mice were statistically smaller than their wild type and heterozygous littermates. Analysis of the newborn (P1) skeletal preparations revealed aberrant mineralization in the neural arches leading to fusions between the individual vertebrae in the cervical and thoracic region. Analysis of P60 *Flnb* -/- mice showed progressive vertebrae fusions involving the ventral and dorsal vertebral bodies (neural arches and the centrum) in the cervical, thoracic and lumbar regions. Fusions also developed in the sternum. Micro-CT analysis of *Flnb* -/- mice demonstrated both vertebral and carpal fusions, closely phenocoping the human disorder. Future analyses of this animal model will provide insight into the mechanism of disease in SCT and will help determine the functional role of Filamin B in the developing skeleton.

AN INVERSION INVOLVING *SONIC HEDGEHOG* (SHH) CIS-REGULATORY ENHANCERS IS ASSOCIATED WITH MALFORMATIONS OF THE TELENCEPHALON AND CRANIAL SUTURES IN THE "SHORT DIGITS" (DSH) MOUSE

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The *short digits (Dsh)* mouse mutant harbors an 11.7 Mb inversion of the *Shh* locus that dislocates cis-regulatory long-range enhancers from the *Shh* promoter. The inversion results in a complete holoprosencephaly in the homozygous *Dsh* mutant strongly resembling the *Shh* knock out mouse. Heterozygous *Dsh/+* mice are characterized by a limb reduction phenotype, malformations of the cortex and neural crest derived craniofacial skeletal elements. Cortical malformations comprise alterations of the telencephalon architecture, including bifurcation of the midline, perturbed cortical lamination and dysgenesis of the corpus callosum. Craniofacial malformations include shortening of nasal and maxillary bones and perturbed fusion of the posterior frontal, sagittal and coronal sutures. In addition, osseous or tooth-like maxillary stalactites are present on each side within the maxillary diastema, an area between incisors and molars that is normally devoid of teeth in mice. As *Shh* haploinsufficiency does not lead to a phenotype in mice, our findings suggest, that the position effect in the *Dsh/+* mutant may lead to deregulation of the developmental *Shh* expression sequence or pattern. Another possibility to explain the *Dsh/+* phenotype is that genes located at the centromeric margin or within the inverted interval may be juxtaposed under the control of *Shh* enhancers and thereby deregulated. We present a comprehensive expression analysis of *Shh* and the axon guidance molecule *semaphorin 3C (Sema3C)* residing at the opposite site of the inversion in the *wt* and *Dsh/+* mutant. Our analysis indicates that the *Dsh/+* mutant represents an intriguing model to study *Shh* regulation and craniofacial midline development.

SATURDAY JULY 21

8h30-10h30…… MOLECULAR CHARACTERIZATION
Moderators: Sheila Unger, Jacqueline Hecht.

8h30…… **Genotype and phenotype of Stickler syndrome caused by mutation in the COL2A1 gene**.
K.Hoornaert, Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

8h45…… **Genotype and phenotype correlation of POR mutations: phenotypic heterogeneity of Antley-Bixler syndrome.**
G. Nishimura, Department of Radiology, Tokyo Metropolitan Kiyose Children's Hospital, Japan.

9h00…… **SOX9, Campomelic and Acampomelic Dysplasia: A molecular and clinical update.**
G. Scherer, Institute of Human Genetics and Anthropology, University of Freiburg, Freiburg, Germany.

9h15…… **An update on the spectrum of LEMD3 mutations in patients with osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis.**
J. Hellemans, Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

9h30……. **Genotype-Phenotype study in 240 MO patients.**
L. Sangiorgi, Genetic Unit, Rizzzoli Orthopaedic Institute. Italy.

9h45……. **The molecular genetics of Scheuermann disease.**
M. Irving, Murdoch Children's Research Institute, Melbourne, Australia.

10h00……. **Molecular analysis of CUL7 in 3M syndrome.**
C. Huber, Department of Genetics, INSERM U781, Hôpital Necker-Enfants-Malades, Paris, France.

10h15……. **Czech dysplasia metatarsal type: another type II collagen disorder.**
G. Mortier, Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

10h30-11h00 .... BREAK (*TOUR DE FRANCE)*

11h30-12h30..... POSTER SESSION 2

12h30-14h00.....LUNCH *(PARC DE ROCHEGUDE)*
NIH Grant application for rare diseases: William Wilcox, David Rimoin.

14h00-16h15…. CELLULAR-MOLECULAR CHARACTERIZATION
Moderators: Laurence Legeai-Mallet, Mickael Briggs.

14h00…….. **Countering excessive FGFR3 signals in achondroplasia.**
W Horton, Shriners Hospital/ OHSU, Portland, USA

14h30…… **Complexity of FGF signaling in chondrocytes.**
WR. Wilcox, Medical Genetics Institute, Cedars- Sinai Medical Center, Los Angeles, USA.

14h45…… **Wisp1 is expressed during cartilage development.**
P. Kannu, Skeletal Biology and Disease, Murdoch Childrens Research Institute, Melbourne, Australia.

15h00…… **New skeletal dysplasia candidate genes identified in a genome-scale analysis of cartilage-selective gene expression.**
D H Cohn, Medical Genetics Institute, Cedars- Sinai Medical Center, UCLA. Los Angeles, USA.

15h15…… **Consequences of chondrodysplasia-associated point mutations in collagen II at the structural and cellular level.**
F Zaucke, Center for Biochemistry, Medical faculty, University of Cologne, Cologne, Germany.

15h30…… **Structural and functional characterisation of matrilin-3 and its implication for human chondrodysplasias.**
M. Fresquet, Wellcome Trust centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, Manchester, UK.

15h45…… **High-definition imaging infrared micro-spectroscopy of cartilage in mice with normal and impaired diastrophic dysplasia sulfate transporter.**
E. L Mertz, Section on Physical Biochemistry, NICHD, National Institutes of Health, Bethesda, USA.

16h 00…… **Noggin mutations deregulate BMP signaling during limb devopment and lead to joint fusions and brachydactyly.**
P. Seemann, Max-Planck-Institut für molekulare Genetik, Berlin, Germany.

16h15-16h45….. BREAK

16h45-17h45…..MANAGEMENT
Moderators: Geert Mortier, David Sillence.

16h45…… **Orthopedic management of chondrodysplasias.**
G Finidori, Service d'orthopédie infantile, hôpital Necker-Enfants Malades, Paris, France.

17h00…… **Dynamic cervicomedullary cord compression and alterations in cerebrospinal fluid dynamics in children with achondroplasia.**
D. Rimoin, Cedars-Sinai Medical Center. Los Angeles, USA

17h15…… **The Restricted Growth Experience; Quality of Life and Barriers to Participation.**
M. J. Wright, Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, UK.

17h30…… **Obstetrics and obstretical anesthesia issues in women with dwarfism.**
J.E. Hoover-Fong, McKusick-Nathans Institute of Genetic Medecine, Johns Hopkins University, Baltimore, USA.

19h00 ..... SAINTE CECILE CATHEDRAL: VISIT AND CONCERT

20h00 ..... TOULOUSE-LAUTREC MUSEUM: VISIT AND DINNER

GENOTYPE AND PHENOTYPE OF STICKLER SYNDROME CAUSED BY MUTATIONS IN THE COL2A1 GENE

Hoornaert Kristien, Dewinter Chantal, Vereecke Inge, Coucke Paul, Mortier Geert

Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

Background: Stickler syndrome is an autosomal dominant connective tissue disorder with multisystem involvement but considerable intra- and interfamilial variability. The most characteristic clinical features include severe myopia, spontaneous retinal detachments, Pierre-Robin sequence, midface hypoplasia, hearing loss and early-onset degenerative joint disease. Stickler syndrome is a genetically heterogeneous disorder. Mutations in different genes, each coding for a procollagen chain (COL2A1;COL11A1;COL11A2) have been identified. The COL2A1 gene is the most commonly involved gene in patients with Stickler syndrome. The aim of this study was to investigate and correlate the allelic heterogeneity and phenotypic characteristics of Stickler syndrome caused by heterozygous mutations in the COL2A1 gene.

Materials & Methods: The past 10 years, DNA samples of 233 probands with the suspicion of Stickler syndrome were referred to our center for molecular analysis of the COL2A1 gene. All patients were evaluated by a clinical geneticist at the referring center. In 180 probands two or more of the following features were present: severe myopia, spontaneous retinal detachment, cleft palate, sensorineural hearing loss, arthropathy, affected first degree relative. For each sample, the 54 exons and intronic boundaries of COL2A1 were amplified by PCR and analysed by either a mutation scanning technique (SSCP, CSGE, dHPLC) or bidirectional fluorescent DNA sequencing, depending on the time of investigation during this study. The effect of splice site alterations was investigated by analysing RNA extracted from skin fibroblasts or lymphoblastoid cell lines.

Results: In 95 probands a heterozygous mutation in the COL2A1 gene was identified. This panel of 95 mutations included 1 deletion of the entire gene, 26 nonsense mutations, 34 frameshift mutations, 24 splice site alterations, 5 missense mutations resulting in an arginine-to-cysteine substitution and 5 missense mutations (G216D;G219R;G222V;G492D;G1131A) altering a glycine residue in the triple helical domain of the protein. Twelve mutations were recurrent. We were able to study the effect of 12 splice site mutations. In each case, cDNA analysis showed that the splicing error created a premature stop codon and therefore resulted in a loss of function of the protein. More detailed phenotypic data on each proband are currently collected in order to investigate more accurately genotype-phenotype correlations in this series of patients.

Conclusions: The molecular results of this study confirm that Stickler syndrome type 1 is predominantly caused by a quantitative defect in the type II collagen biosynthesis. The observation that missense mutations may also result in Stickler syndrome is intriguing and warrants further analyses to study the effect of these mutations on type II collagen biosynthesis and extracellular assembly. Genotype-phenotype correlations will be discussed at the meeting.

GENOTYE AND PHENOTYPE CORRELATION OF *POR* MUTATIONS: PHENOTYPIC HETEROGENEITY OF ANTLEY-BIXLER SYNDROME

Gen Nishimura, Maki Fukami, Keiko Homma, Tomonobu Hasegawa, Tsutomu Ogata

Department of Radiology, Tokyo Metropolitan Kiyose Children's Hospital (GN); Department of Endocrinology and Metabolism, National Research Institute for Child Health and Development (MF, TO); Department of Laboratory Medicine (KH) and Pediatrics (TH), Keio University School of Medicine, Tokyo, Japan

Cytochrome P450 oxidoreductase (POR) is an electron donor of all microsomal P450 enzymes. Homozygous or compound heterozygous mutations of the *POR* gene cause an autosomal recessive multi-system disorder, Antley-Bixler syndrome (ABS). The classical manifestations of ABS comprise a distinctive facial appearance (craniosynostosis with a pear-shaped nose), skeletal abnormalities (arachnodactyly and joint fusion/contracture), and endocrinological abnormalities due to multiple enzyme (CYP21A2, CYP17A1, and CYP19A1) deficiencies for steroidogenesis (stress-induced adrenal insufficiency, poor masculinization in males, virilization and poor pubertal development in females, and maternal virilization during pregnancy). However, recent investigations have shown a wide range of phenotypic consequences of *POR* mutations. We report here on the genotype/phenotype correlation of *POR* mutations in 22 families (28 affected individuals).

Based on physical examination, we divided affected individuals into the mild phenotype (3 males and 8 females) and severe phenotype (9 males and 8 females). The former group was characterized by minor facial dysmorphism and mild arachnodactyly with interphalangeal joint contracture; however, two affected boys did not show the skeletal changes but only facial dysmorphism. The latter showed overt craniofacial dysmorphism, apparent arachnodactyly with undertubulatiuon of the short tubular bones and interphalangeal joint contracture. Contracture and/or fusion of the elbow joints and craniosynostosis were found variably in severity among patients. The former group was attributed to R457H (the common mutation)/R457H (8 families) or R457H/E580Q (1 family), while the latter to compound heterozygosity of R457H/a variety of mutations, such as premature termination codon mutations and splicing mutations (12 families), or Y578C/I444fsX449 (one family). From the endocrinological viewpoint, stress-induced adrenal insufficiency and male poor masculinization tended to be severer in the former than in the latter, while female virilization and maternal virilization were almost identical between both groups. The ambiguous endocrinological distinction between both groups is attributable to the complexity of impaired steroidogenesis in POR deficiency, including counterbalance between CYP21A2 and CYP17A1 deficiencies and the presence of placental steroidogenesis and an altenative pathway (termed the backdoor pathway) for synthesis of DHT.

Affected individuals with the mild skeletal phenotype were often misdiagnosed as having non-classical 21-hydroxylase (CYP 21A2) deficiency or aromatase (CYP19A1) deficiency. However, all of them showed an abnormal facial appearance, and most showed mild skeletal and/or articular changes of the hand. Meticulous attention should be paid to these subtle physical and radiological changes to make a diagnosis of mild ABS patients.

SOX9, CAMPOMELIC AND ACAMPOMELIC DYSPLASIA: A MOLECULAR AND CLINICAL UPDATE

Gerd Scherer, Elke Bausch, Wenjun Jin, Christine Zeschnigk, and Sheila Unger

Institute of Human Genetics and Anthropology, University of Freiburg, Freiburg, Germany

Campomelic dysplasia (CD; OMIM 114290) is a skeletal malformation syndrome with characteristic shortening and bowing of the long bones, especially the lower limbs. Additional features include hypolastic scapulae, a bell-shaped thorax, 11 pairs of ribs, undermineralized thoracic pedicles, narrow iliac wings, clubbed feet, typical facial features, Robin sequence, tracheomalacia, and XY sex reversal. Campomelia is only a facultative feature absent in about 10% of cases, defining a subgroup of acampomelic CD (ACD). CD/ACD are caused by missense, nonsense, frameshift or splice mutations in the *SOX9* gene, by chromosomal rearrangements (translocations and inversions) close to the *SOX9* locus, or by deletions of SO*X*9. The translocation/inversion breakpoints are distributed over more than 1 Mb upstream of *SOX9*, likely affecting the action of *cis*-regulatory elements (enhancers). Several of these long-range enhancers, which control a subset of the *SOX9* expression domains, have now been identified. Unpublished work from our laboratory involving quantitative PCR shows that *SOX9* micro-deletions of a few kb or macro-deletions up to several Mb are more frequent than previously thought.

Clear genotype/phenotype correlations with respect to disease severity or the presence or absence of campomelia or XY sex reversal do not exist. However, it has been noted that ACD cases are more prevalent among the long-term survivors, result from missense mutations that allow for residual SOX9 activity more frequently than is the case for CD cases, and are overrepresented in the group of translocation cases. This trend still holds. In fact, of 15 translocation/inversion breakpoints mapped in detail, the four most distal breakpoints at 789 to 932 kb from *SOX9* are all from ACD cases, including 2 familial cases with Robin sequence as a major clinical feature. Very recent studies also implicate *SOX9* in isolated Robin sequence.

AN UPDATE ON THE SPECTRUM OF *LEMD3* MUTATIONS IN PATIENTS WITH OSTEOPOIKILOSIS, BUSCHKE-OLLENDORFF SYNDROME AND MELORHEOSTOSIS

Jan Hellemans, Björn Menten, Karen Buysse, Paul Coucke, Frank Speleman, Geert R Mortier

Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

Osteopoikilosis, Buschke-Ollendorff syndrome (BOS) and melorheostosis constitute a group of rare skeletal dysplasias characterized by increased bone density. A genome-wide linkage analysis in three families with osteopoikilosis and associated BOS or melorheostosis lesions, allowed us to map the causal gene to 12q12–q14.3. Sequencing of candidate genes within the linkage interval led to the identification of heterozygous *LEMD3* mutations in all three families. The LEMD3 gene encodes an inner nuclear membrane protein that was shown to antagonize both the BMP and TGFβ signalling pathways in human cells. To further explore the allelic heterogeneity within this group of hyperostotic bone disorders, a series of 51 patients was screened for *LEMD3* mutations.

Patients were classified in four different phenotypical groups:

A. osteopoikilosis associated with short stature and mental retardation (n=3)
B. osteopoikilosis or Buschke-Ollendorff syndrome (without additional abnormalities) (n=19)
C. melorheostosis occurring within an osteopoikilosis or BOS family (n=4)
D. sporadic melorheostosis (n=25)

All patients in group A were found to have a microdeletion encompassing the *LEMD3* gene on chromosome band 12q14. The size of the interstitial deletion varied between 3.44 and 6 Mb with a 3.44 Mb common deleted region. The deleted interval was not flanked by low-copy repeats or segmental duplications. All three unrelated patients had a similar phenotype characterized by osteopoikilosis, proportionate short stature and mental retardation, suggesting a new microdeletion syndrome. A total of 21 heterozygous *LEMD3* mutations were identified in the probands from groups B, C and D. All mutations were predicted to result in a loss-of-function of the protein. The identification of a *LEMD3* mutation in 16/19 patients from group B confirms that osteopoikilosis and BOS are caused by LEMD3 haploinsufficiency. Similar germline *LEMD3* mutations were also found in the 4 probands from group C. In contrast, only in one patient from group D a heterozygous inactivating *LEMD3* mutation was identified. In addition we did not find evidence for a somatic *LEMD3* mutation in available bone samples from 2 patients of group D. The possibility of somatic mutations in other genes within the LEMD3 regulated pathways remains open and is currently investigated.

GENOTYPE-PHENOTYPE STUDY IN 240 MO PATIENTS

Pedrini E, Capponcelli S, Mordenti M, Maini V, Sgariglia F, Parra A, Donati I, **Sangiorgi L**

Genetic Unit, Rizzoli Orthopaedic Institute, Italy.

Multiple osteochondromas (MO) is an autosomal dominant hereditary disorder characterized by the presence of multiple cartilage-capped (exostoses), tipically located at the meta-epiphyseal areas of the long bones. The great variability in size and number of exostoses reflects the clinical heterogeneity and variable severity of MO, which is characterized by pain, abnormal skeletal growth (resulting sometimes in short stature), decreased range of motion, deformities and nerve compression. In a small percentage of cases (2-5%) an osteochondroma undergoes malignant transformation to a chondrosarcoma.

To evaluate if the severity of disease and the risk of malignant transformation are related with any genetic alteration, we performed a genotype-phenotype correlation study using a new clinical classification based on deformity and functional limitations. We investigated 240 patients, with clinical and radiographic diagnosis of MO, for the presence of mutations in either *EXT1* (8q24) or *EXT2* (11p11-12) genes, using a DHPLC analysis and subsequent direct sequencing of all samples with abnormal elution profile. In negative patients, all EXT1 and EXT2 exons and splice-site junctions were directly sequenced. Mutational analyses showed 162 mutations in EXT1 (67,5%) and 55 in EXT2 (22,9%) with a mutation frequency of 90,4%. The majority are responsible of EXT1/EXT2 protein truncation.

The most severe clinical presentations were associated with EXT1 mutations and seems also to be related with men rather than women. It has been found also the important role of the association of proband and parents gender which could increase or reduce the risk of developing a mild or severe forms; ingravescence of disease is more frequently observed in the mother-son transmission. Patients without EXT mutations seem to be related to mild phenotypes whereas the most of sporadic cases is related to more severe forms. Malignant transformation of osteochondroma is not related with either the severity of disease or EXT1/EXT2 mutations.

Due to the great number of patients analyzed, it has been possible to obtain relevant information about MO which may provide an useful tool both in predicting patient outcome and in defining the right follow-up program (increasing clinical examination for patients with higher risk to belong to class III). The absence of any prognostic marker in malignant transformation requires a regular screening for every patients with MO.

THE MOLECULAR GENETICS OF SCHEUERMANN DISEASE

Melita Irving[1,2], Jane Bleasel[3], Oliver Sisson[4], Melanie Bahlo[4], Ravi Savarirayan[2], John Bateman[1] Shireen Lamandé[1]

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Scheuermann disease (SD) is a common condition causing progressive thoracolumbar kyphosis with adolescent onset[1-3]. Vertebral bodies become wedge shaped with irregularity of the fibrocartilaginous end-plate, Schmorl's nodes and narrowing of the disc spaces. At the histological and electron microscopic levels it has been shown that the deformed vertebral bodies are the consequence of an irregular arrangement of collagen fibrils with herniation of disc material through the resulting defects[4]. Numerous families with multiple affected individuals have been described, indicating that in some instances the disease follows autosomal dominant inheritance with reduced penetrance[2,3].

The aim of the study was to characterise the underlying molecular mechanisms associated with SD, thereby contributing to existing knowledge of the development and normal functioning of the cartilaginous vertebral end plate, its role in this and other types spondylar dysplasia and providing potential opportunities for disease modification. We have collected DNA samples and clinical information from a three generation family with multiple affected individuals and undertaken genotyping using Affymetrix 10K SNP chips. Pair-wise analysis was used to generate genome-wide S-Pair scores through nonparametric pedigree approximation[5]. Two genomic regions have been identified as likely to habour the disease causing gene. A positional candidate gene approach in combination with cartilage protein expression data has been employed to prioritise genes for sequencing and the results will be presented.

References

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MOLECULAR ANALYSIS OF THE CUL7 GENE IN 58 PATIENTS WITH 3 M SYNDROME

Céline Huber[1], Anne-Lise Delezoide[2], Clarisse Bauman[2], Valérie Malan[1], Arnold Munnich[1], Valérie Cormier-Daire[1] and The international Collaborative Group on 3M syndrome

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3M syndrome is an autosomal recessive condition characterized by pre- and post-natal growth retardation, facial dysmorphism, large head circumference, normal intelligence and skeletal changes including long slender tubular bones and tall vertebral bodies. Studying a series of 29 families, we have mapped the disease locus gene on chromosome 6p21.1, and then identified mutations in the CUL7 gene.

Following this initial study, we have collected the samples of 29 additional 3 M families and identified CUL7 mutations in 16/ 29 comprising 18 novel mutations. This series included one terminated pregnancy at 33 weeks of gestation. The fetus presented with severe growth retardation, normal head circumference, facial features, prominent heels and long slender tubular bones suggestive of 3 M syndrome. By direct sequencing, we first identified a CUL7 splice site mutation (c.1215+1G>A), inherited from the father. In addition we found no maternal contribution but a complete isodisomy of the chromosome 6 of paternal origin. Histological study of the femoral growth plate from this case showed an increase in the chondrocyte density and size in the resting and proliferative zones but no major abnormalities in the prehypertrophic and hypertrophic zones, suggesting that CUL7 is mainly involved in the chondrocyte proliferation but not in their differentiation.

We conclude that CUL7 is the major gene responsible for 3 M syndrome accounting for 77.6 % of our cases (45/ 58). The absence of any mutation in 13 patients and the exclusion of the 6p21.1 locus in 5 consanguineous families argue in favor of a genetic heterogeneity.

CZECH DYSPLASIA METATARSAL TYPE: ANOTHER TYPE II COLLAGEN DISORDER

Hoornaert Kristien [1], Marik Ivo[2], Kozlowski Kazimierz[3], Cole Trevor[4], Le Merrer Martine[5], Leroy Jules G[1], Coucke Paul J[1], Sillence David[6], **Mortier Geert**[1]

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Background: Czech dysplasia metatarsal type is an autosomal dominant disorder characterized by an early-onset, progressive spondyloarthropathy with normal stature. Shortness of 3rd and/or 4th toes is a frequently observed clinical feature. Similarities between individuals with this dysplasia and patients with an R275C mutation in the COL2A1 gene, prompted us to analyze the COL2A1 gene in the original families reported with Czech dysplasia.

Methods: Targeted sequencing of exon 13 of the COL2A1 gene was performed, followed by sequencing of the remaining exons in case the R275C mutation was not identified.

Results: We identified the R275C substitution in two of the original patients reported with Czech dysplasia and three additional patients. All affected individuals had a similar phenotype characterized by normal height, spondyloarthropathy, shortening of the postaxial toes and absence of ocular and orofacial anomalies. The R275C mutation was excluded in a third patient reported with Czech dysplasia. However, the identification of the Y1391C mutation in the latter patient with disproportionate short stature made the diagnosis of spondyloperipheral dysplasia (SPD) more likely. The Y1391C mutation is located in the carboxy-propeptide of the procollagen chain and has been reported before in a patient with the Torrance type of lethal platyspondylic skeletal dysplasia (PLSD-T). Our observation of the same Y1391 mutation in an additional unrelated patient with SPD further supports the evidence that PLSD-T and SPD represent a phenotypic continuum.

Conclusions: Czech dysplasia metatarsal type can now be considered as a new member of the type II collagenopathy family.

COUNTERING EXCESSIVE FGFR3 SIGNALS IN ACHONDROPLASIA

William Horton

COMPLEXITY OF FGF SIGNALING IN CHONDROCYTES

William R. Wilcox and Pavel Krejci

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FGFR1 and FGFR3 are both expressed in cartilage and activating mutations in either receptor cause human dwarfism. The FGFR ligands present in the human growth plate are FGF1, 2, 17, and 19. In contrast to most other cells, FGF signaling in chondrocytes paradoxically leads to growth arrest as well as alterations in differentiation and matrix synthesis and degradation. The molecular mechanisms underlying these effects are slowly being defined. We and others have shown the essential role of prolonged FGFR signaling via Erk MAPK in these effects, as well as ability of C-natriuretic peptide signaling to counteract many of the FGFR actions on chondrocytes.

FGFR signaling in chondrocytes is more complicated than originally anticipated. We have shown that in addition to the canonical adapter Frs2, FGFR3 uses Gab1 and Shc to transmit signal to Ras and thence to Erk in chondrocytes. Furthermore, an atypical protein kinase C is required for recruitment of Shp2, an inhibitor of Ras-GAP, to the FGFR signaling complex, allowing FGFR to activate the Erk pathway.

Based on limited data from human samples and murine models, it is believed that FGF signaling inhibits chondrocyte growth via activation of several Stat proteins, although the exact mechanism of both Stat activation and Stat-mediated inhibition of chondrocyte growth is unclear. Using RCS chondrocytes, we show that FGFR3 interacts directly with Stat1 and Stat3 and can, in an *in vitro* kinase assay, directly phosphorylate Stat1 but not Stat3. In cells, however, FGF does not activate Stat1 or Stat3 even though there is potent growth arrest. Moreover, activation of Stat1 and/or Stat3 does not sensitize chondrocytes to FGF-mediated growth arrest. Since FGF-mediated growth arrest can be rescued by siRNA-mediated down-regulation of Erk MAPK but not Stat1 or Stat3, we conclude that Stats are not required for FGF-mediated growth arrest.

In contrast to acute FGF treatment, chronic FGF signaling can inhibit canonical Stat signaling in chondrocytes. Chronic FGF stimulation leads to accumulation of Stat1, 3, 5 and 6 proteins in both *in vitro* RCS cells and murine limb explant cultures. This accumulation is only partially due to increased transcription. Despite the accumulation, both endogenous and cytokine-induced activation of Stat1 and Stat3 is impaired by chronic FGF stimulation. FGF inhibits the common receptor for the IL6-family of cytokines, gp130, through induction or modulation of at least three known gp130 inhibitors, PTP1B, Socs1 and Shp2. Since the IL6-family of cytokines represent important regulators of cartilage growth, the inhibition of their signaling may contribute to the effects of FGF signaling on endochondral bone growth.

The effects and pathways of even normal FGFR signaling in chondrocytes are clearly much more complicated than suggested by initial studies on human samples and murine models. Additional investigations using *in vitro* systems and new murine models are needed to define the complicated mechanisms and effects of FGF actions on endochondral bone growth.

WISP1 IS EXPRESSED DURING CARTILAGE DEVELOPMENT

Peter Kannu[1,2,3], Daniele Belluoccio[1,2], Bianca C Bernardo[1,2], Ravi Savarirayan[1,2,3], John F Bateman[1,2]

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Mature articular cartilage is maintained through the production of key matrix molecules, and destroyed by diseases such as arthritis. Wnt 1 inducible secreted protein (WISP 1, chromosome locus 8q24.1-3) is a member of the connective tissue growth factor family, which are extracellular matrix associated proteins. WNT signalling is recognised as one of the key players in chondrogenesis and WNT genes are critical for a variety of cell fates and functions including the regulation of chondrogenesis and the chondrocyte cell cycle. Overexpression of Wisp 1 leads to accelerated cell growth and Wisp 1 also activates antiapoptotic signalling pathways following DNA damage. While mutations in WISP 3 are found in Progressive Pseudorheumatoid Dysplasia (PPD), little is understood about the role and expression of WISP 1 in cartilage. To investigate the role of Wisp 1 in cartilage biology, its expression was analysed at several developmental time points in mouse cartilage. We detected Wisp1 RNA expression in cartilage by in situ hybridisation and quantitative PCR (Q-PCR). Q-PCR shows a modest difference in expression between mouse articular and growth plate cartilage. We have also demonstrated Wisp 1 expression in mouse articular cartilage at the protein level by immunohistochemistry. Functional experiments on Wisp 1 using a cartilage degradation model are currently being undertaken.

NEW SKELETAL DYSPLASIA CANDIDATE GENES IDENTIFIED IN A GENOME-SCALE ANALYSIS OF CARTILAGE-SELECTIVE GENE EXPRESSION

Vincent A. Funari, Allen Day, Deborah Krakow, Zachary A. Cohn, Zugen Chen, Stanley F. Nelson and **Daniel H. Cohn**

Medical Genetics Institute, Cedars-Sinai Medical Center and David Geffen School of Medicine at UCLA, Los angeles, USA.

Cartilage plays a fundamental role in the development, function and maintenance of the human skeleton and mutations in many genes selectively expressed in cartilage are associated with skeletal dysplasia phenotypes. To identify additional cartilage-selective candidate genes for the skeletal dysplasias and to more broadly define the transcriptional profile of developing cartilage, a genome-scale analysis of fetal cartilage gene expression was carried out. Gene expression in 18-22 week human distal femur cartilage was compared with gene expression in a panel of 38 normal human tissues comprising 265 microarrays.

Two-way hierarchical clustering identified a core set of 64 genes with coordinately higher expression in cartilage, indicating that a subset of the cartilage transcriptome is not generally expressed in the other tissues. Many of the genes encoded well-known cartilage-selective markers including the cartilage collagen genes, aggrecan and COMP. More broadly, there were 1720 genes with at least three-fold higher expression in cartilage relative to non-cartilage tissues, including genes selectively expressed in each of the zones of the growth plate, as well as articular cartilage. These data were validated using an independent dataset requiring a more stringent 5 fold higher expression in cartilage as compared with non-cartilage tissues. From this validation the genes were ranked, favoring genes with the least variation in gene expression among the non-cartilage tissues. This analysis yielded 161 cartilage-selective genes, including 25 genes associated with skeletal dysplasia phenotypes in humans and/or mice. Quantitative RT-PCR using a subset of these genes replicated and validated the cartilage selective gene expression pattern observed by comparative microarray analysis.

Many of the cartilage-selective genes not have not been associated with skeletal dysplasias and do not have established roles in cartilage, including 28 unannotated genes. A cartilage-selective expression pattern suggests that the product of each identified gene may have a functional role in the development of the skeleton, a hypothesis that can be tested by knocking out the orthologous genes in mice. These genes may also represent expression candidates for skeletal dysplasias in which the disease gene has yet to be identified. As new skeletal dysplasia loci are defined, coincidence between a locus and a cartilage-selective gene may promote rapid identification of the disease gene. This may be particularly important for rare phenotypes in small families where linked genomic intervals may be large.

The cartilage gene expression data also provide a platform for exploring altered gene expression in skeletal disorders, facilitating mechanistic dissection of the expression pathways disrupted in selected disorders, as well as the description of gene expression networks in cartilage. Overall the data suggest that fetal cartilage is a complex and transcriptionally active tissue and demonstrate that the set of genes selectively expressed in the tissue has been greatly underestimated.

CONSEQUENCES OF CHONDRODYSPLASIA-ASSOCIATED POINT MUTATIONS IN COLLAGEN II AT THE STRUCTURAL AND CELLULAR LEVEL

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Introduction: Collagen II is the major cartilage collagen and is a fibrillar molecule that consists of homotrimers with Gly-X-Y repeats in the triple helical region. Due to its complex structure collagen II is highly susceptible to mutations leading to a variety of diseases including chondrodysplasias. In the present study, we have investigated patient-derived and artificial arginine to cysteine exchanges within the triple helical region of collagen II. The mutations were selected based on the caused clinical phenotypes (Stickler syndrome and SEDC) and their position within the Gly-X-Y repeat. The present study attempts to understand the effects of these mutations at the structural and cellular level.

Material and Methods: Human collagen type II cDNA was used for site directed mutagenesis and cloned into pCEP-Pu with an N-terminal His-Myc-tag and transfected into HT1080, 293-EBNA cells and primary bovine chondrocytes. Recombinant wildtype (wt) and mutant protein variants (R75C, R134C, R704C, R740C and R879C) were purified from 293-EBNA cell culture supernatants and used for analysis of triple helix stability by trypsin digestion. Further, structural integrity was analysed by CD spectroscopy and electron microscopy. Morphological changes and intracellular events after transfection were analysed by immunofluorescence staining and induction of ER stress and apoptosis was monitored.

Results and Discussion: Successful mutagenesis was confirmed by sequencing. Analyses of purified proteins by SDS-PAGE indicated a shift in the mobility of the mutant R789C compared to all other mutants and the wildtype protein. The mutations R740C and R789C located close to the C-terminal end of the triple helix were more susceptible to trypsin digestion. In contrast, all other mutants were trypsin-resistant indicating a stable triple helix formation. Significant abnormalities in the structure were also visible in electron micrographs where fibrillar structures were completely absent in case of R789C. CD spectra confirmed a severe triple helical structural instability and melting temperatures were significantly lower in R740C and R789C. Morphologically, HT1080 cells and primary chondrocytes expressing the mutants R740C and R789C were abnormally rounded as compared to cells transfected with other constructs. Further, retention of mutants R740C and R789C in the endoplasmis reticulum (ER) was observed whereas other mutants were secreted without any signs of compromised protein trafficking. The ER retention resulted in increased expression of the chaperone BIP indicating an induction of an unfolded protein response. This was accompanied by specific splicing of Xbp-1. In addition, activation of caspase-3 and fragmentation of DNA was detected suggesting that ER stress eventually resulted in apoptotic cell death.

Conclusion: The resulting cellular phenotype depends on the exact localization of the mutation. Coming from the N- to the C-terminal end of the triple helical region, we have found a gradual increase in the severity of all effects.

STRUCTURAL AND FUNCTIONAL CHARACTERISATION OF MATRILIN-3 AND ITS IMPLICATION FOR HUMAN CHONDRODYSPLASIAS

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Multiple epiphyseal dysplasia (MED) is a genetically heterogeneous chondrodysplasia that can result from mutations in the genes encoding matrilin-3, type IX collagen and cartilage oligomeric matrix protein (*COMP*). Many of the mutations in these genes cluster in distinct regions of the protein and usually affect residues that are important for the structure and/or function of the relevant gene products. However, the non-allelic genetic heterogeneity of MED has not been fully determined. Matrilin-3 is the third member of a family of extracellular matrix (ECM) proteins; matrilin-1 and matrilin-3 are primarily expressed in cartilaginous tissues whilst matrilin-2 and matrilin-4 have a wider pattern of expression in a variety of extracellular matrices including non-skeletal tissues. Matrilin-3 consists of a single von Willebrand Factor A-like domain (A-domain), four EGF-like motifs and a coiled-coil oligomerization domain. Matrilin-3 can form hetero-oligomers with matrilin-1 and has been shown to bind to COMP and collagen types II and IX *in vitro*. Mutations in the A-domain of matrilin-3 have been shown to result in multiple epiphyseal dysplasia (MED). With a few exceptions, the majority of disease-causing mutations are located within the single β-sheet of the A-domain, suggesting that they may disrupt the structure and/or function of this important domain.

To characterize the interactions of matrilin-3, binding studies were performed by BIAcore using various type IX collagen molecules and also COMP. These studies confirm that the matrilin-3 A-domain binds to type IX collagen and also to COMP in a cation-dependent manner. Moreover, we have specifically shown that the A-domain of matrilin-3 interacts with the COL3 domain of type IX collagen and that this interaction is abolished when the type IX collagen molecules harbours an in-frame deletion that is comparable to that caused by the skipping of exon 3 of *COL9A3* (i.e. a mutation that is known to cause MED). Overall these data provide a rationale for the non-allelic genetic heterogeneity seen in MED.

HIGH-DEFINITION IMAGING INFRARED MICRO-SPECTROSCOPY OF CARTILAGE IN MICE WITH NORMAL AND IMPAIRED DIASTROPHIC DISPLASIA SULFATE TRANSPORTER

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We report quantitative, 5-μm resolution distributions of major extra-cellular matrix components across femur head cartilage of wild type (WT) and mutant newborn mice. We analyze sulfate-deficient mice with a knocked-in homozygous mutation in SLC26A2 sulfate/chloride antiporter and discuss implications of discovered abnormalities for cartilage function in diastrophic dysplasia. We developed high-definition infrared micro-spectroscopy for label-free imaging of thin, solvated tissue sections with significantly increased chemical resolution and spectral reproducibility. This new technique resolves different GAG types and the extent of their sulfation and distinguishes between collagen and other proteins. We found that the extent of GAG sulfation increased toward the femur head center both in the mutant and WT. In the mutant, the GAGs were 2.3-times undersulfated at the articular surface, but nearly normal in the head center. This normalization may be caused by faster degradation of undersulfated GAGs, increased intracellular sulfate due to GAG catabolism or slower rate of GAG synthesis. The mutation also affected the concentrations and spatial distributions of other extra-cellular matrix components. Sugar groups were nearly uniformly distributed in WT, but depleted near the articular surface in the mutant. Concentration of non-collagenous proteins was 1.8 times lower in the mutant. It gradually decreased (1.5 fold) from the articular surface toward the femur head center in both genotypes. Collagen concentration in WT also gradually decreased (2 fold) toward the femur head center, but remained nearly uniform across the mutant's femur head probably due to delayed development. At the articular surface, collagen concentration in the mutant was about 1.5 times lower than in WT. The lower densities of collagen, GAGs and sugar sulfate may be responsible for lowering mutant cartilage elasticity and increasing its permeability to synovial enzymes, contributing to the observed cartilage degradation in diastrophic dysplasia.
This work was supported in part by Telethon-Italy, grant #GGP06076.

NOGGIN MUTATIONS DEREGULATE BMP SIGNALING DURING LIMB DEVELOPMENT AND LEAD TO JOINT FUSIONS AND BRACHYDACTYLY

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NOGGIN (NOG) is one of the best characterized BONE MORPHOGENETIC PROTEIN (BMP) antagonists and several mutations with a predicted loss of function are reported to be associated with human disorders like proximal symphalangism (SYM1), multiple synostosis syndrome (SYNS1) or tarsal carpal coalition (TCC) syndrome. We identified six different point mutations in NOG (P35A, P35S, A36P, E48K, R167G, P187S) in patients affected by brachydactyly type B (BDB) with additional SYM1 and TCC. 3D-modelling of the mutations in a dimeric GDF5-NOG complex revealed that the mutations are widespread distributed all over NOG. Functional analysis in the chicken limb bud micromass culture system indicated that the newly identified BDB-mutations are not characterized by a major loss of function. They are expected to alter only slightly the ability of NOG to bind to BMPs and thus disturbing the intricate balance of BMP signaling. Interestingly, this phenotype resembles BDB1 caused by mutations in the orphan receptor ROR2, a speculated BMP-Co-receptor. The phenotypic overlap argues for a functional connection between BMP- and ROR2 signaling in vivo.

ORTHOPEDIC MANAGEMENT OF BONE DYSPLASIAS IN PAEDIATRIC PATIENTS

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Orthopaedic treatments are an important part of the management of bone dysplasias.
-In dysplasias with spine involvement, clinical examination, X ray with dynamic studies, TDM and MRI must be done systematically and before general anaesthesia. C1/C2, instability, stenosis of the foramen magnus and vertebral malformations, with potential risk of neurological damage must be searched. Stenosis of the vertebral canal is also a frequent complication. Preventing in young patients the onset of spine deformities is important to reduce the neurological risk in adult patients. The treatment of vertebral stenosis is difficult and conservative management has its limits. The principles of surgery are always the same: liberation of the compression and stabilisation by vertebral fusion.
-The dysplasic and abnormal epiphyses have a delayed ossification and are fragile. The mechanical stress in the growing child will induce progressive deformations. A surgical correction of architectural disorders can improve mechanical conditions and reduce the stress on the epiphysis. Surgery enables to prevent, in an effective manner, an alteration of the hips and the knees. For the hips acetabular osteotomy of Chiari seems a very useful procedure in MED and similar disease.
-In achondroplasia, the stenosis of the foramen magnus in young patients, especially with respiratory deficiencies, must be searched and a systematic MRI must be done before the age of 6 months. Compressions of the upper part of the medulla require a surgical decompression by occipital craniectomy and a laminectomy of C1.
The prevention of spine deformity and hip retraction by bracing and physiotherapy seems very important in children to avoid the onset of stiff deformations. These deformities become quickly rigid and during adulthood worsen the spine stenosis and make its treatment more difficult. For older patients, with rigid and important kyphosis, a surgical treatment can be necessary. Pre-operative halo-cranial traction can result in a progressive reduction of the kyphosis. Stabilisation is obtained by anterior (with vertebral corporectomy if necessary) and posterior fusion associated with laminectomies.
Lumbar stenosis is quite rare in paediatric patients but this complication is frequent in adults, conservative treatment is not always sufficient and surgery with laminectomies can be necessary. These procedures are difficult with the risk of neurological complications
Correction of leg bowing in achondroplasia by tibial and fibular osteotomies is generally performed after the age of six years. The main difficulty is the important laxity of the knee. The frontal correction of the varus must be associated with a flexion to reduce the recurvatum and to have a stable knee in standing position. In young patients, under the age of 9/10 years old, an epiphysiodesis of the proximal growth cartilage of the fibula can be performed.
- In multiple exostosis (ME), indication for surgery is quite rare before bone maturity in a growing child since the risk of recurrence is high. The vertebral localisations are often undiagnosed and must be searched for systematically. The voluminous exostosis of the proximal fibula can be removed by total resection in young patients with no risk of recurrence. This surgery is recommended to avoid fibular nerve compression and before a tibial osteotomy.
Valgus deformity of the ankle can be treated in a simple manner by an internal epiphysiodesis of the distal epiphysis of the tibia.
Asymmetrical growth of the radius and the ulna must be corrected before the onset of a radial head dislocation. The lengthening of the ulna is a difficult procedure and we generally prefer a simple osteotomy to straighten and shorten the diaphysis of the radius and we remove at the same time the exostosis of the wrist.
At bone maturity, it becomes possible to perform more extensive surgeries for functional and/or esthetical reasons.
-Surgical lengthening of lower limbs on patients with epiphyseal involvement and/or joint laxity (like in pseudoachondroplasia) can induce very severe complications and is contraindicated. Furthermore, this surgery for micromelia requires multiple operations, the immobilisation of the patient is long, complications are frequent, the financial cost is very high and the benefice is not obvious.

DYNAMIC CERIVOMEDULLARY CORD COMPRESSION AND ALTERATIONS IN CEREBROSPINAL FLUID DYNAMICS IN CHILDREN WITH ACHONDROPLASIA

Moise Danielpour, Bill Wilcox, Yasemin Alanay, Barry Pressman and **David Rimoin**

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Common abnormalities of the cervicomedullary junction in infants and children with achondroplasia include stenotic foramen magnum and cervical spine canal. Compression at the cervicomedullary junction can result in myelopathy, hypotonia, sleep apnea and even sudden death. However, the frequency of these symptoms and percentage of patients undergoing surgical decompression have varied widely among different skeletal dysplasia centers. The majority of children with achondroplasia who do not suffer from severe neurological symptoms will gain normal motor and intellectual development, are not at risk for sudden death, and do not require surgical intervention. Other infants with some symptoms and signs can gain normal function with time, since the foramen appears to grow faster than the spinal cord and they recover spontaneously, without requiring surgery.

There have been several reports on prospective assessment of achondroplastic children in order to estimate the frequency of clinical and laboratory features referable to abnormalities of the craniocervical junction that can be the best predictors of the need for surgical decompression. At our center we have incorporated MRI cerebrospinal fluid (CSF) flow studies in assessing children with cervicomedullary junction compression. Recently we have identified a number of symptomatic children with MRI and flow studies within the normal range in neutral position, but complete blockage of CSF flow on flexion and more dramatic posterior cervicomedullary compression on extension studies. Their symptoms ranged from severe neurological abnormalities and sleep apnea to others who just developed headaches and/or apnea episodes when sleeping or in a car seat. These children underwent decompressive surgery with dramatic improvement or resolution of signs and symptoms, which have persisted for up to 18 months of follow-up. We propose that there is an increased risk for dynamic cord compression in achondroplasia that can only be detected with MRI's in both flexion and extension and which can constitute an indication for surgical decompression at the cervicomedullary junction.

THE RESTRICTED GROWTH EXPERIENCE, QUALITY OF LIFE AND BARRIERS TO PARTICIPATION

Wright MJ [1,2], Thompson S[3], Shakespeare TW[3]

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Much of the existing literature about adults with skeletal dysplasias describes diagnosis specific complications and/or is based on the experiences of individuals attending hospital clinics or drawn from the membership of support organisations. This project was a collaborative exercise between a research team, comprising a clinical geneticist and two sociologists, and the Restricted Growth Association, the largest support group for individuals with skeletal dysplasias in the UK.

The project aimed to contact every adult with a skeletal dysplasia in a defined geographical area in the North of England. 81 respondents ultimately completed a structured questionnaire and a sub group of 50 individuals agreed to be interviewed by one of the authors (ST). A proportion of these respondents kept diaries in which they described their symptoms and general life experiences.

The majority of participants (57%) had achondroplasia however 19% had never been given a specific diagnosis other than being told they had a form of dwarfism. There was evidence of reduced mobility (78%) and regular pain (84%) in most respondents, in many cases this had begun in childhood and adolescence rather than in adulthood. Pain management was a major concern and it was clear that in many cases it was poor. 27% of respondents had symptoms suggestive of sleep apnoea using a standard questionnaire. This was largely unrecognised by the individuals concerned prior to the study. Obesity was a major concern for this group however 34 of the 42 individuals with achondroplasia reported weights within the published normal range for their height.

The educational attainment of the respondents was similar to the general UK population. Many individuals however left school at the earliest opportunity to take up employment and there was an increased proportion of people in unskilled and semi-skilled occupations despite good qualifications.

The majority of individuals felt that they lived normal lives most of the time however 96% had experienced staring or pointing, 77% had been verbally abused and 12% had been the victims of physical violence directly as a result of their stature. Adults of restricted growth were twice as likely as the general population to live alone. Despite this a standard quality of life measure (SF36) suggested that respondents had mental component scores at or above those for the general population whilst physical component scores were reduced.

A series of recommendations for healthcare providers, legislators, support organisations and individuals of restricted growth have been derived from this study and will be presented.

OBSTETRICS AND OBSTETRICAL ANESTHESIA ISSUES IN WOMEN WITH DWARFISM

JE Hoover-Fong[1], G Oswald[1], D Miller[1], J Leadroot[1], H Barnes[1], J Rossiter[1,2], D Penning[3], I Berkowitz[1], D Krakow[4]

1 McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, 2 St. Joseph Medical Center, Baltimore, MD, 3 University of Miami Miller School of Medicine, Miami, FL, 4 Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Objective: To assess current clinical practice, opinion and training of obstetrical anesthesiologists for dwarf women, and survey the direct obstetrical experiences and opinions of this patient population. Dissemination of information about pregnancy and delivery in dwarf women is needed.

Study design: Part 1: A comprehensive survey of the Society of Obstetrical Anesthesia and Perinatology (SOAP) members regarding formal training, clinical practice and opinions about 3 hypothetical case scenarios concerning anesthesia for pregnant dwarfs. Part 2: A retrospective cohort study of LPs with $\geq$ 1 prior conception, regarding pregnancy and delivery experience, physical status pre- and post-partum, and general opinions about pregnancy in LPs.

Results: Part 1:149 SOAP members completed the survey (99 male, mean 48.7 yrs; 50 female, mean 46.3 yrs) with 3765 average deliveries/yr at primary hospital sites.134 are board certified in general anesthesia or related field. Career contact with dwarf women for OB anesthesia: none (3.5%), <5(79.7%), 5-10(11.4%), 11-20(3.4%) and >20(2%). 15% received specific instructions regarding OB anesthesia for LPs while in training. Part 2: To date, 61 women representing 128 pregnancies (including one twin set) with 13 skeletal dysplasias have completed the study: achon (36), pseudo (6), SED variants (5), hypo (3), DD (3), and other (7). 93 liveborn infants were delivered via C-section (49 general anesthesia-GA, 44 spinal and/or epidural), 24 miscarriages, 4 terminations, and 2 currently pregnant. 5 liveborn infants were delivered vaginally; 3 without regional anesthesia, 2 with epidural. 46.7% received genetic counseling for a pregnancy and 28.9% had genetic testing for a skeletal dysplasia. 24.4% were told she should not carry a pregnancy. 40% believe LP women should have GA for all deliveries; 28.9% regional. 4.4% regret carrying a pregnancy and 20% believe carrying the pregnancy damaged health overall.

Conclusions: There is no evidence of increased fetal loss or maternal pregnancy complications due to dwarfism thus far. Most LP women will require C-section due to cephalopelvic disproportion, yet vaginal delivery is found in dysplasias with minimal truncal or pelvic disproportion. Many LPs have carried successful pregnancies and delivered with adequate pain control with general and regional anesthesia, despite the lack of medical literature and formal training in obstetrical anesthesia for this population. We neither promote nor discourage childbearing in dwarf women, yet more published data is needed for those who choose to have children and those who provide their medical care.

SUNDAY JULY 22

9h-10h30……CLINICAL CHARACTERIZATION
Moderators: Sarah Smithson, Ravi Savarirayan.

9h00……**Angulated femurs and the skeletal dysplasias.**
Y. Alanay. Clinical Genetics Unit, Department of Pediatrics, Faculty of Medecine, Hacettepe Unversity, Ankara, Turkey.

9h10……**Cerebro-osseous-digital syndrome - Clinical and radiological phenotype with histological findings.**
C.M. Hall, Department of Radiology, Great Ormond Street Hospital for Children, London, UK.

9h20…….. **Delineation of a new syndrome with syn-/oligodactyly, urogenital malformations and anal atresia.**
S. Unger, Institute for Human Genetics, University of Freiburg, Germany.

9h30……**Complex skeletal phenotype in a patient with a double insertional translocation between 7q and 10q and deletion of the TRPS1 gene on 8q24.**
R. Mendoza, Division of Clinical and Metabolic Genetics, Hospital for Sick Children, Toronto, Canada.

9h40…….. **Adams-Oliver syndrome: clinical variability in a four-generation family.**
CA. Bacino. Department of Molecular and Human Genetics, Baylor College of Medecine, Houston, USA.

9h50……**Foetal translucent bones associated with massive perivillous fibrin deposition in the placenta (gitte/infarct/ maternal floor infarct).**
PGJ. Nikkels. Department of Pathology, University Medical Centre Utrecht. Utrecht, the Netherlands.

10h00……. **Cervical spine defects in Menkes disease, a new finding potentially confused with evidence of child abuse.**
S. Hill, Warren Grant Magnuson, Clinical Center, Diagnostic Radiology, Bethesda, USA.

10h10……. **Transforming the International Nosology of Constitutional disorders of Bone into a web accessible knowledge base.**
A. Zankl. Genetic Health Queensland, Royal Children's hospital, Brisbane, Australia.

10h20-11h00…..BREAK

11h-12h30……..NEW PERSPECTIVES / TREATMENT
Moderators: Martine Le Merrer, William Wilcox.

11h00**……. Growth hormone (GH) treatment of children with SHOX deficiency is effective and does not adversely affect body proportions: Two-year results of a randomized, controlled, multi-center trial.**
M. Rosilio, Eli Lilly and Company, Suresnes, France.

11h10……. **Nomenclature of OI syndromes**
D. Sillence, Department of Genetics, The Children's Hospital at Westmead, Australia.

11h25……. **Complications of Bisphosphonates**
G. Finidori, Service d'orthopédie infantile, hôpital Necker-Enfants Malades, Paris, France.

11h35……. **Penicillamine therapy results in symptomatic and radiological remission in diaphyseal dysplasia.**
D. Sillence, Department of Genetics, The Children's Hospital at Westmead, Australia.

11h45……. **Perindropil reduces large artery stiffness and aortic root diameter in a randomised double blind study of patients with Marfan syndrome**
R. Savarirayan. Genetic Health Victoria, Murdoch Childrens Research Institute, Melbourne, Australia.

11h55…… **MAROTEAUX – LAMY SYNDROME: E. KAKKIS**

12h10 ..... PERSPECTIVES- ISDS 2009

12h30…… LUNCH (*HOTEL D'ORLEANS)*

14h30 …..... END OF THE MEETING

ANGULATED FEMURS AND THE SKELETAL DYSPLASIAS. EXPERIENCE OF THE INTERNATIONAL SKELETAL DYSPLASIA REGISTRY (1988-2006)

Yasemin Alanay[1,2] Deborah Krakow[2,3,5] David L. Rimoin[2,3,4,6] Ralph S. Lachman[2,3,6,7]

1 Clinical Genetics Unit, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey, 2 Medical Genetics Institute, Cedars-Sinai Medical Center, and Departments of, 3 Human Genetics, 4 Internal Medicine, 5 Obstetrics and Gynecology and 6 Pediatrics, and 7 Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, USA.

Angulated or bent femur (isolated or associated with other long bone bowing) in the fetus or newborn is relatively common when evaluating patients with skeletal dysplasias. To determine the extent and heterogeneity of disorders associated with angulated or bent femurs, we analyzed cases in the radiographic database (1998-2006) of the International Skeletal Dysplasia Registry (ISDR) and determined which established skeletal dysplasias and genetic syndromes are associated wtih this finding. The results show that more than 40 distinct disorders with varying frequency (very rare to more commonly-occuring disorders) can be associated with bowed/bent/angulated femurs. Sixty-six percent of the cases with angulated femurs belonged to three well described groups of disorders; campomelic disorders (24.4 %), thanatophoric dysplasia (23.9 %) and finally osteogenesis imperfecta (OI) (18.1 %). With specific emphasis on these, this cross-sectional cohort provides discussion of data on other rare disorders associated with angulated femurs and the importance of the finding relative to its occurrence within a diagnostic group. This study aims to provide differential diagnosis of entities to be considered when a fetus or newborn is found to have congenital bowing/angulation of the femur.

CEREBRO-OSSEOUS-DIGITAL SYNDROME - CLINICAL AND RADIOLOGICAL PHENOTYPE WITH HISTOLOGICAL FINDINGS

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1 Department of Radiology, Great Ormond Street Hospital for Children, London, UK, 2 Department of Pathology, Birmingham Women's Health Care Trust.

Introduction : We report the eighth and ninth cases of cerebro-osseous-digital syndrome. Four cases were described by Elliot et al in 2002 and two earlier cases by Scott et al in 1981. One case, illustrated by Spranger and Maroteaux in Lethal Osteochondrodysplasias (1990), is described as 'toothpick dysplasia' There are similarities to cerebro-arthro-digital syndrome reported by Spranger in 1980. All the previously reported cases have been sporadic with no known consanguinity, although case 2 of Scott et al had three earlier undocumented miscarriages.

Case reports : The affected fetuses were born to healthy black African parents. There was no known consanguinity. There are two healthy unaffected daughters.
Fetus1, a female, was terminated at 21 weeks gestation for short limbs. No major internal organ anomalies were identified at post mortem.
The clinical findings include severe micromelia with oedematous limbs and short digits, contractures, bilateral talipes, relative macrocephaly, marked proptosis and hypoplastic or absent eyelids, bluish sclerae, low set almost absent external ears, a small mouth, depressed nasal bridge and a short neck.

Radiologically the long bones are under-tubulated (stick-like), with wide, sclerotic diaphyses and absent medullary cavities. The hips show posterior dislocation and there are dislocated elbows and possible humero-radial synostoses. There is absent ossification of the hands and feet. The skull vault is relatively large, the thorax broad and short with wide ribs and the pelvis shows wide sacro-sciatic notches. The ischia and pubic bones are unossified. In the spine there is absent ossification of the sacrum and vertebral bodies in the cervical region. The thoracic and lumbar vertebral bodies have saggital clefting and the pedicles in the lumbar region are absent. The clavicles are long and the scapulae disproportionately large with absent glenoid fossae.

Bone histology was relatively non-specific and showed a normal growth plate, resting cartilage and columnar zone with an elongated proliferative cartilage zone.
Fetus 2, a male and the sibling of fetus 1 was terminated at 17 weeks gestation and showed virtually identical clinical and radiological findings.

Comment: This is the first report of a recurrence of cerebro-osseous-digital syndrome and raises the possibility of autosomal recessive inheritance.

Reference:
Elliot AM, Gonzales M, Hoeffel JC, Le Merrer M, Maroteaux P, Encha-Razavi F, Joye N, Berchel C, Fliegel C, Aughton DJ, Beaudry-Rodgers K, Hasteh F, Nerlich AG, Wilcox WR, Rimoin DL, Lachman RS, Freisinger P. Cerebro-osseous-digital syndrome. Am J Med Genet 2002;109:139-148.

DELINEATION OF A NEW SYNDROME WITH SYN-/OLIGODACTYLY, UROGENITAL MALFORMATIONS AND ANAL ATRESIA

Sheila Unger[1,2], Boehm Detlef [3], Wictor Borozodin[1,3], Bernhard Zabel[1,2], Kristi Borowski[4], Kim Keppler-Noreuil[4], Albert Schinzel[5], Geert Mortier[6], Bernhard Steiner[5], Andrea Superti-Furga[2], Jürgen Kohlhase[1,3]

1: Institute for Human Genetics, University of Freiburg, Freiburg, Germany 2: Centre for Pediatrics and Adolescent Medicine, University of Freiburg, Freiburg, Germany 3: Center for Human Genetics, Freiburg, Germany 4: University of Iowa, USA 5: Institute of Medical Genetics, Zurich, Switzerland 6: Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

In 1996, Green et al., reported a mother and daughter with syndactyly, anogenital and renal malformations. We report four unrelated children from different parts of the world with a strikingly similar constellation of congenital malformations. All four children came to medical attention at birth because of anal atresia and significant cutaneous syndactyly of the feet. They shared similar dysmorphic features with telecanthus and abnormal ears being the most prominent. Renal/urinary tract anomalies, abnormalities of the genitalia, and minor heart malformations were present as well. Chromosome analysis was performed on all four probands and gave normal results. *SALL1* and *SALL4* were sequenced as mutations in these genes have been associated with anal atresia in Townes-Brocks and Okihiro syndromes respectively but no mutations were found. Also, as the children had pronounced fifth finger clinodactyly, in addition to the syndactyly of the toes, Feingold syndrome was considered but sequencing of the *MYCN* gene excluded this possibility. The strong degree of consistency between these four patients and the mother-daughter pair reported by Green, along with the lack of *SALL1*, *SALL4*, or *MYCN* gene mutations, suggest that this represents a distinct, possibly dominant syndrome.

COMPLEX SKELETAL PHENOTYPE IN A PPATIENT WITH A DOUBLE INSERTIONAL TRANSLOCATION BETWEEN 7q AND 10q DELETION OF THE TRPS1 GENE ON 8q24

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Split hand/split hand malformation (SHFM) is a genetically heterogeneous human limb malformation characterized by absent central digital rays, deep median cleft, and syndactyly of the remaining digits. SHFM may be isolated or syndromic; five candidate loci have been mapped including SHFM1 on chromosome 7q21, SHFM2 on Xq26, SHFM3 on 10q24, SHFM4 on 3q27 and SHFM5 on 2q31. Tricho-rhino-phalangeal syndrome type 1(TRPS1) is a malformation syndrome characterized by distinctive facial features, sparse hair and skeletal abnormalities. TRPS1 is caused by haploinsuficiency for the *TRPS1* gene located on 8q24. We report a patient with overlapping features of SHFM and TRPS1. The patient presented as a newborn with SHFM of the hands and feet, and developed short stature and mildly dysmorphic features. Cytogenetic analysis revealed a double insertional translocation involving insertion of two segments of chromosome 7 (7q31.31-7q22.2 and 7q22.1-7q21.3) into two different regions of one chromosome 10 (10p22.3 and 10q26.12). There was no apparent chromosomal deletion. FISH with probes mapping to the critical SHFM1 region demonstrated that one of the breakpoints mapped to this locus. Array CGH was used to investigate further the possibility of deletions or duplications of 7q or 10q. Although this analysis did not detect any DNA copy number changes on 7q or 10q, array CGH detected a deletion of the TRPS1 locus on 8q24. We hypothesize that our patient's SHFM is the result of a position effect involving the SHFM1 region. To our knowledge this is the first report of a patient with overlapping features of SHFM and TRPS1, due to independent cytogenetic abnormalities.

ADAMS-OLIVIER SYNDROME : CLINICAL VARIABILITY IN A FOUR-GENERATION FAMILY

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Adams-Oliver syndrome (MIM 100300) is a rare disorder characterized by congenital scalp defects, terminal transverse limb defects and cutis marmorata telangiectatica. Limb abnormalities are typically limb truncation defects affecting the distal phalanges, entire digits and/or distal limbs. Cardiac and vascular malformations have also been frequently reported in this disorder. Autosomal dominant inheritance is the most frequently reported mode of inheritance for Adams-Oliver syndrome, although autosomal recessive inheritance has also been suggested.

We report a new family of Mexican ancestry with Adams-Oliver syndrome with multiple affected individuals in four generations that segregates in an autosomal dominant fashion. The affected members exhibit significant phenotypic variability ranging from distal phalangeal involvement to severe limb reduction defects. The absence of congenital scalp defects in some family member suggests that this feature is not an invariably finding in Adams-Oliver syndrome patients. The etiopathogenesis of this disorder remains unclear, but genes involved in vasculogenesis/angiogenesis during limb development have been proposed as possible candidates for this disorder. We will describe the clinical findings and variability. Linkage studies on this large family are underway to identify the gene responsible for Adams-Oliver syndrome.

FOETAL TRANSLUCENT BONES ASSOCIATED WITH MASSIVE PERIVILLOUS FIBRIN DEPOSITION IN THE PLACENTA (GITTER INFARCT/MATERNAL FLOOR INFARCT)

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Introduction: the formation of bones in utero is dependent on many different factors; delivery of nutrients via the placenta is one of the important factors. A normal vitamin D, calcium and phosphate metabolism is essential for normal bone development and the placenta and kidneys are key organs for this metabolism. The placenta decidual cells can form active vitamin D (1,25-dihydroxy vitamin D) necessary for increased absorption of calcium and phosphate and enhance the effect of parathyroid hormone on bone resorption and calcium retention by the kidneys. Three cases are presented in which an association was observed between the occurrence of translucent osteopenic bones and massive perivillous fibrin deposition in the placenta.

Material & results: during the period from 2001-2006 187 foetuses with a lethal skeletal dysplasia were sent for consultation to the Dutch Skeletal Dysplasia Registry and in three of them remarkable translucent bones were observed without other skeletal abnormalities and in all three cases the placenta showed massive perivillous fibrin depositions. One case was born after 32 weeks gestational age (GA) with severe IUGR and maceration, the foetus died 2-4 weeks before birth, with a body weight of 690 gram and the placental weight was 400 gram. The second case was born after 20 weeks GA and also showed IUGR and was severely macerated. The third case was born after 30 weeks GA and ultrasound showed severe IUGR from 20 weeks onwards. This foetus was born alive with severe asymmetrically IUGR but died very shortly after birth due to severe asphyxia and cardio-repiratory failure. Histology of the long bones showed rachitis like abnormalities with expansion of chondroid matrix and chondrocytes from the epiphysis within the adjacent primary trabeculae. The live born foetus showed renal abnormalities associated with sever chronic hypoxia and/or hypoperfusion: i.e. partial loss of the nefrogenic zone, small tubulo-glomerular cysts and loss of proximal tubuli. A similar lesion has also been observed in the donor of twin-transfusion syndrome. The maceration of the two other foetuses was too advanced to evaluate renal histology.

Discussion and conclusion: the association of translucent bones and massive perivillous fibrin deposition is very rare; there is one other series of 3 cases published in the literature. During the same period several other placentas with massive perivillous fibrin deposition and IUFD were seen without bony abnormalities. Both the placenta abnormalities as well as the renal abnormality observed in the life born foetus might be responsible for the skeletal abnormalities. The histological abnormalities of the bones are reminiscent of rachitis and can also be observed in cases with severe hypophosphatasia. This suggests an abnormality in calcium and phosphate metabolism. A possibility is that due to the placental abnormality the formation of active vitamin D is hampered or that the placental uptake of calcium, phosphate and/or active vitamin D is diminished. However, a disturbed calcium and phosphate metabolism could also be caused by the renal tubular malformation with loss of proximal tubules due to the severe chronic ischaemia and hypoperfusion caused by the placental abnormality. So far the precise mechanism that causes these skeletal abnormalities is not known and further research is necessary to get more insight into this intriguing association.

CERVICAL DEFECTS IN MENKES DISEASE; A NEW FINDING POTENTIALLY CONFUSED WITH EVIDENCE OF CHILD ABUSE

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Menkes disease (MD) or trichopoliodystrophy is an infantile onset, X-linked, neurodegenerative and connective tissue disorder caused by deficiency of a copper transporting ATPase and associated with mutations of the ATP7A gene. Previously described radiographic features include two groups of findings. Members of the first are attributable to bone and vascular dysplasia (i.e. Wormian bones, flared clavicles, deformed elbows, occipital horns, pectus deformities, dolechoectatic changes of extra and intracranial vessels.). Members of the second are attributable to weakening of bone and may be confused with the results of non-accidental trauma (i.e. fractures of the skull, long bones or ribs and metaphyseal corner changes and cupping simulating fractures). In this poster, we illustrate these previously-described features and a new additional abnormality noted in 3 of a series of 27 patients we reviewed: bony defects of the pedicles of C2 . Since this bone abnormality potentially mimicks a hangman's fracture, this observation adds to those previously associated with Menkes disease that may be confused with evidence of child abuse.

TRANFORMING THE INTERNATIONAL NOSOLOGY OF CONSTITUTIONAL DISORDERS OF BONE INTO A WEB-ACCESSIBLE KNOWLEDGE BASE

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For the last 30 years, the International Nosology of Constitutional Disorders of Bone has provided much needed guidance in the classification of skeletal dysplasias. However, over the last years several shortcomings have become apparent: As our knowledge of the pathogenetic mechanisms underlying skeletal dysplasias increased, the Nosology evolved from a purely clinical-radiological classification to a hybrid scheme that also tries to accommodate the relationships at the molecular level. The growing complexity of the classification system along with the surging number of recognized entities has made the Nosology increasingly unwieldy. Due to the fast pace of research in the field, the printed Nosology also becomes quickly out of date. In addition, the limited ability to provide additional information for each entry (such as clinical descriptions, typical radiographs, links, key publications) makes the Nosology in its printed form of little practical value as a diagnostic aid.

To overcome these limitations we propose to transform the Nosology into a web-accessible knowledge base. Each entry will be represented by a web page that contains an abstract describing the condition, digital radiographs of typical cases, a commented bibliography with links to the original publications, links to related databases (e.g. OMIM, UniProt) and other features. Instead of being forced into a rigid classification scheme, each skeletal dysplasia will be annotated with a controlled vocabulary that describes the condition in many dimensions (clinical features, radiographic features, underlying molecular mechanism etc.), which allows to search or sort the database in a very flexible manner.

As a proof of concept, we have created a simple web-accessible database and have populated it with the abstracts, digital radiographs and associated annotation from REAMS (Radiological electronic atlas of malformation syndromes and skeletal dysplasias, Oxford University Press, 1999). This database can be searched and sorted in a traditional way, e.g. by searching for specific conditions or radiographic features. In addition, we demonstrate a radically different approach to searching the database using a software tool that displays radiographic images associated with each condition in a three-dimensional space based on user-selected descriptors. This allows to visually group disorders that share certain characteristics and allows the user to explore the radiographs in a group of related disorders. For example, the user can literally "zoom in" on the relevant part of the Nosology by specifying a few radiographic characteristics to compare the radiographic examples with the radiographs of a patient to be diagnosed.

Should the prototype be successful, we plan to transform the complete Nosology into the proposed multi-dimensional model under the curatorship of the International Skeletal Dysplasia Society Nosology Group.

GROWTH HORMONE (GH) TREATMENT OF CHILDREN WITH SHOX DEFICIENCY IS EFFECTIVE AND DOES NOT ADVERSELY AFFECT BODY PROPORTIONS: TWO-YEAR RESULTS OF A RANDOMIZED, CONTROLLED, MULTI-CENTER TRIAL

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Patients (pts) with haploinsufficiency of the Short Stature Homeobox-containing (*SHOX*) gene (including those with Turner syndrome [TS]) have variable degrees of growth impairment, with or without a spectrum of skeletal anomalies consistent with mesomelic skeletal dysplasia.

This study aimed to determine the efficacy of GH in treating short stature associated with SHOX deficiency (SHOX-D) and to assess the effect of GH treatment on body proportions. Prepubertal pts (n=52, 24 M, 28 F; age 3-12.3y) with molecularly-proven SHOX-D and height (Ht) <3rd %ile (or Ht <10th %ile and Ht velocity [HV] <25th %ile) were randomized to either a GH-treatment (GH-Tx) group (Humatrope® 0.05 mg/kg/d; n=27) or an untreated (Un-Tx) control group (n=25) for 2y. To compare GH-Tx effect between patients with SHOX-D and TS, the 3rd study group comprised 26 pts with TS (4.5-11.8y) who received GH (GH-Tx TS). Between-group comparisons of 1st-y and 2nd-y HV, Ht standard deviation scores (SDS) and Ht gain (cm) were performed using ANCOVA, accounting for diagnosis, sex and baseline age. Anthropometric measurements to assess body proportions were performed at baseline and 2yr. Between-group comparisons were assessed by ANOVA.

GH-Tx SHOX-D pts had significantly greater 1st-y HV than Un-Tx pts (8.7±1.6 vs. 5.2±1.1 cm/y [mean±SD]; p<0.001) and similar 1st-y HV to GH-Tx TS pts (8.9±2.0 cm/y, p=0.592). GH-Tx pts also had significantly greater 2nd-y HV (7.3±1.1 vs. 5.4±1.2 cm/y, p<0.001), 2nd-y Ht SDS (-2.1±1.0 vs. -3.0±0.9, p<0.001) and 2-y Ht gain (16.4±2.0 vs. 10.5±1.9 cm, p<0.001) than Un-Tx pts.

GH-treated pts (SHOX-D and TS) had significant (P<0.001) baseline-to-2yr changes in SDS values for Ht, sitting Ht (SHt) and arm span (AS), whereas UnTx pts had not (table). There was a significant decrease in the SHt/Ht ratio for both SHOX-D groups and a significant increase in the AS/Ht ratio in all groups corresponding to approximately 20% better growth of the legs and arms (i.e. long bones) than total Ht. However, there were no significant between-group differences in changes of measures of body proportion (SHt/Ht, AS/Ht).

Table. Baseline-to-2yr changes for anthropometric measurements.

	Un-Tx SHOX-D	GH-Tx SHOX-D	GH-Tx TS
Ht SDS	0.2(0.5)	1.2(0.7)*	1.2(0.7)*
SHt SDS	0.2(0.6)	1.2(0.9)*	1.0(1.4)**
AS SDS	0.0(0.5)	0.8(0.7)*	1.0(0.6)*
SHt / Ht (%)	-0.8(1.3)	-1.1(2.2)	-1.3(3.9)
AS / Ht (%)	1.1(1.5)	1.2(2.6)	1.6(2.1)

Mean(SD); *P<0.001 or **P=0.018 vs. Un-Tx SHOX-D.

This study, the first large scale, randomized, multi-center clinical trial in pts with SHOX-D, demonstrates marked, highly significant, GH-stimulated increases in HV and Ht SDS, with similar efficacy of GH-Tx between pts with SHOX-D and TS, a not unexpected finding given that SHOX-D accounts for a major portion of the short stature of TS. We conclude that two-yr GH treatment of children with SHOX-D improves linear growth without adversely affecting body proportions.

NOMENCLATURE OF OI SYNDROMES

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The discovery of the importance of prolyl 3-hydroxylation of collagens and the demonstration of mutations responsible for types of OI in the loci for Cartilage Associated Protein (CRTAP) and Leprecan (P3H1/Lepre1) whose proteins contribute to the P3H1 complex has occasioned a relook at the Nomenclature of OI syndromes.

The numerical nomenclature proposed in the 1978 was based on a population study of Osteogenesis Imperfecta (OI) in Victoria Australia. It resulted in the observation that there were at least 4 groups of disorders which could be distinguished on the basis of clinical, radiographic, histological findings and patterns of inheritance. The existence of recessive cases resulting in 2 of the 4 phenotypes delineated was argued at the time to support the possibility of further genetic heterogeneity within each phenotypic category.

In 2007 the genes known to result in "OI" include COL1A1, COL1A2, PLOD2, CRTAP, P3H1/Lepre1 and LRP5. At least 4 disorders, OI type V, VI, Spondylo-ocular dysplasia and Bruck type I await a molecular defect. Some loci e.g. cyclophilin B whose protein contributes to the P3H1 complex await further study of their role in OI. Like many other heritable disorders of connective tissue, the phenotype/genotype correlation, despite its imperfections has stood the test of time. However molecular findings indicate far more complexity.

A molecular nosology has been proposed. Despite the intellectual attractiveness of a molecular nosology, the phenotypes which result from mutations in each of the phenotypic groups is due to the complete range of known mutational mechanisms each of which results in a variable phenotype. Furthermore the factors regulating the expression of mutations at each locus are not completely understood. We have shown previously that some mutations are differentially expressed in fibroblast versus bone. The factors which regulate expression in neural crest mesoderm versus somatic mesoderm are still incompletely understood.

A revised nomenclature of the OI syndromes will be presented.

ORTHOPEDIC MANAGEMENT OF OSTEOGENESIS IMPERFECTA AND SIDE EFFECTS OF BISPHOSPHONATES TREATMENTS IN OI PAEDIATRIE PATIENTS

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O.I. is a constitutional disease, which can be dramatically worsen by secondary accidents: bone deformities, fractures and immobilisations will increase the osteoporosis and the severity of the pathology. Medical treatment and physiotherapy are very effective. Surgery is very useful and central medullary osteosynthesis are largely used. According to our experience, Bailey and Dubow telescopic nails are a very efficient solution to protect the femurs. It is now possible to perform osteotomies, realignment and nailing with with minimal surgical approach or percutaneously. The main problem is to avoid a varus position of the femoral neck during the nailing.

For the humerus, the forearm and the tibia, telescopic wiring generally done percuteaneously is a quite simple, non-invasive and effective procedure.

The onset of a severe scoliosis or kyphoscoliosis is very frequent in severe forms of O.I. Bracing is poorly efficient. The lack of spine growth, the shortness and deformity of the trunk induce a severe respiratory insufficiency, which is the main cause of premature death in O.I. adult patients.
Vertebral posterior arthrodesis is an effective treatment. Surgery must be performed on young patients, without taking bone maturity into account, before the onset of an important and rigid deviation, especially in kyphosis, and. when there is no more growth of the trunk and no amelioration or regression of the respiratory functions. A progressive halo-cranial reduction during the pre operative period can induce an important correction of the angulations and can enable an improvement of the size of the trunk and of the respiratory functions. Posterior arthrodesis gives stable results if it is done on a spine with mild deformities. Therefore, surgery must not be performed too late.

Many, if not all, O.I. patients we see now for the first time have received long and "over dosed" treatments with bisphosphonates. These treatments seem to induce new and severe complications.
According to our experience, there is no exact correlation between the increase of bone density and the mechanical strength of the bone. The density of the structure of the bone can be increased but it will remain fragile, with bowing and fractures. Remodelling and consolidation seem also severely impaired by bisphosphonates, which seem to have long-term effects.
We now see many O.I. patients with thick, dense bones who seem to have osteopetrosis with diaphyseal bowing and pseudathrosis.

It seems urgent and necessary to inform physicians of this new type of complication due to bisphosphonates. These drugs must be used only on patients suffering from severe forms of O.I. with multiple fractures, platispondylia and who undergo long immobilisations periods.
Bisphosphonates administration protocols must be properly defined.

PENICILLAMINE THERAPY RESULTS IN SYMPTOMATIC AND RADIOLOGICAL REMISSION IN DIAPHYSEAL DYSPLASIA

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A nine year old with a severe form of Diaphyseal Dysplasia (Camurati-Engelmann) developed linear scleroderma and was treated with Penicillamine with a satisfactory clinical response. Within weeks of commencing treatment with Penicillamine, the patient had a remarkable remission of symptoms of Diaphyseal Dysplasia. Long bone pain and limb girdle weakness improved significantly. Oral Penicillamine was commenced as per management of linear scleroderma beginning at a dose of 62.5 mg daily. Her Penicillamine was changed to 125 mg alternate days. There was a complete radiological remission of the diaphyseal sclerosis during the period of treatment. Attempts to cease Penicillamine have resulted in relapse of the classic symptomatology of Camurati-Engelmann disease.

The subject is unusual in that she was diagnosed with progressive Diaphyseal Dysplasia at 25 months of age (Bye A and Kozlowski K. Pediatric Radiology 1998, 18:340). She had previously had an episode of immune nephritis at 13 months of age. At 9 years of age she developed linear scleroderma..

No mutation has been detected in the coding region of TGF Beta. However a functional assay for TGF Beta protein indicates that she does not produce TGF Beta. A long term remission of autoimmune complications has been achieved with daily oral colostrum 400 mg BD (which is a rich source of TGF Beta). Because of worsening renal function, a renal transplant was performed. Her Diaphyseal Sclerosis remains in remission 15 years after commencing therapy with Penicillamine.

PERINDOPRIL REDUCES LARGE ARTERY STIFFNESS AND AORTIC ROOT DIAMETER IN A RANDOMISED DOUBLE BLIND STUDY OF PATIENTS WITH MARFAN SYNDROME

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Background: Aortic stiffness is elevated in Marfan syndrome (MFS) contributing to aortic dilatation and rupture, the major cause of premature death in this condition. Given the known beneficial effects of angiotensin converting enzyme inhibitors (ACEI) on arterial stiffness, we hypothesised that perindopril therapy would reduce aortic stiffness and attenuate aortic dilatation in MFS patients.

Methods: 17 MFS patients (all fulfilling Ghent criteria, aged 33±6yr) on standard β-blocker therapy were randomised to receive either add-on perindopril (10 mg/day, n=10) or placebo (n=7) for 24 weeks in a randomised, double blind study. Indices of arterial stiffness were assessed globally via systemic arterial compliance and augmentation index, and regionally via carotid-femoral (PWVc) and femoral-dorsalis pedis (PWVp) pulse wave velocity. Aortic root diameter was assessed via transthoracic echocardiogram. Data are expressed as percent or absolute change from baseline for the placebo and perindopril groups.

Results: Perindopril reduced arterial stiffness as indicated by increased systemic arterial compliance (perindopril 62±11% vs placebo -4.30±1%, p<0.0001), reduced augmentation index (perindopril -23.50±3% vs placebo 3±1%, p<0.0001), reduced PWVc (perindopril -21±2% vs placebo 5±2%, p<0.0001) and PWVp (perindopril -20±2% vs placebo 2±1%, p<0.0001). In addition, perindopril significantly reduced aortic root diameter (perindopril -0.28±0.04cm vs placebo 0.11±0.03cm, p<0.0001). While perindopril marginally reduced mean blood pressure (perindopril -3.5±0.5mmHg vs placebo 1.1±0.7mmHg, p<0.001), the observed changes in both arterial stiffness (p=0.01-0.03) and aortic diameter (p<0.01) remained significant when mean blood pressure was included as a covariate.

Conclusion : Perindopril reduces both aortic stiffness and aortic root diameter in MFS patients and might decrease the incidence of aortic rupture, even in patients on standard β-blocker therapy.

POSTERS

ANTENATAL PRESENTATION OF SKELETAL DYSPLASIA

1- **D.P.Cavalcanti**: Lethal short-rib polydactyly dysplasia with Elejalde syndrome clinical phenotype: a variant form of Beemer Langer syndrome or new type of SRP dysplasia?
2- **P. Sarda**: Variable phenotype in three sibs with short-rib dysplasia and polydactyly.
3- **P. Kannu**: Skeletal pathology in a lethal case of metatropic dysplasia.
4- **DP. Cavalcanti**: Skeletal dysplasia associated with malformations recurring in sibs – a lethal form of Desbusquois dysplasia-.
5- **E.M. Carter, MS**: Case report and literature review: twins with thanatophoric dysplasia.
6- **SB. Sousa**: Tetra-amelia and lung agenesis syndrome-case report.
7- **AL. Delezoide**: IUGR-osteopenia-oliganamnios – placental massive fibrin deposition: a "new"recurrent fetal phenotype for an "old" placenta pathology.

MOLECULAR CHARACTERIZATION

8- **S. M. Nikkel**: Autosomal recessive osteopetrosis, malignant infantile form due to OSTM1: a novel mutation.
9- **L. Garavelli**: The homozygous deletion of the 3' enhanger of the SHOX gene causes langer mesomelic dysplasia.
10- **H.G. Dos Santos**: A case of Smith-Mccort syndrome caused by a new mutation in the dymeclin (FLJ20071) gene.
11- **H.G. Dos Santos:** Clinical and molecular diagnosis of bone disorders associates with mutations in the gene that codifies for the fibroblast growth factor receptor 3 (FGFR3) – A Portuguese experience.
12- **N. Dagoneau**: Overlap of Crisponi syndrome with Stüve-Wiedemann syndrome (SWS).
13- **S. Heuertz**: Chondrodysplasias series: Achondroplasia, Hypochondroplasia, Thanatophoric Dysplasia : FGFR3 mutations and update
14- **J. Martinovic**: Thanatophoric dysplasia caused by two missense FGFR3 mutations.
15- **H. Kayserili**: Homozygous c.2763delT (p.P425Pfx62) in COLL11A2 gene causes no-mRNA decay in otospondylomegaepiphyseal dysplasia (OSMED).

CLINICAL DELINEATION OF NEW AND OLD SYNDROMES

17- **S.Wallace:** Distal phalanx and nail hypoplasia associated with osteopetrosis: report of an affected mother and son.
18- **P.Sarda**: Severe spondyloepimetaphyseal dysplasia with profound mental retardation: a new autosomal recessive MCA/MR syndrome?
19- **R. Rupps**: A novel malformations syndrome with skeletal abnormalities complicated by moyamoya.
20- **R Ortiz De Luna** : Casamassima-Morton-Nance syndrome with 47,XYY. Case report.
21- **M. Simon**: Spondylo-megaepiphyseal-metaphyseal dysplasia in two sibs: prenatal presentation and follow-up to adulthood.
22- **A. Dieux-Coëslier**: Unusual epiphyseal and metaphyseal dysplasia associated with major advanced bone maturation and severe asymetric lower limbs deformation.
23- **C.M. Hall:** Spondylometaphyseal dyspalsia with cone-rod dystrophy.
24- **M. Simon**: Anisospondyly as an unusual hallmark of a new form of chondrodysplasia punctata.
25- **S. B. Sousa**: Alkaline phosphatase and skeletal dysplasia –3 different diagnoses-.

26- **R. S. Lachman MD**: Radiographic imaging of the mucopolysaccharidoses.
27- **N. Brunetti-Pierri**: Electron microscopy studies on skin fibroblasts is a useful and reliable adjuvant tool for the diagnosis of geleophysic dysplasia.

NETWORK AND MANAGEMENT

28- **J. Taylor**: The European Skeletal Dysplasia Network.
29- **G. Baujat** : The « centre de référence des maladies osseuses constitutionnelles ». A challenge for public health, a necessity for patient diagnosis and care.
30- **V. Fano:** Skeletal dysplasia in a referral pediatric hospital in Argentina.
31- **K. Ok-Hwa**: Spinal manifestations in Winchester syndrome : atlantoaxial subluxation and dural ectasia.
32- **D. Sillence**: Health supervision for children with spondyloepiphyseal dysplasia congenita and related disorders.
33- **E. Okenfuss**: Multiple epiphyseal dysplasia (MED) with cervical spine instability in family.
34- **E. M. Carter, MS**: Case report: first reported custom total hip replacement in a 14-year-old male with mucopolysaccharidosis type IH (MPS IH, or Hurler syndrome) post bone marrow transplant.
35- **J.E. Hoover-Fong**: Age-appropriate body mass index (BMI) and height velocity in children with achondroplasia.

TREATMENT

36- **D. Earl**: A patient with opsismodysplasia treated with pamidronate.
37- **S. Bellais**: Gentamicin mediates readthrough of premature termination codon in Stüve-Wiedemann syndrome.
38- **V. Valayannopoulos**: Experience with laronidase treatment in 5 MPS I patients with various phenotypes and indications.
39- **David Silence**: Nomenclature of OI syndromes. (See oral presentation)

1- LETHAL SHORT-RIB-POLYDACTYLY DYSPLASIA WITH ELEJALDE SYNDROME CLINICAL PHENOTYPE: A VARIANT FORM OF BEEMER-LANGER SYNDROME OR NEW TYPE OF SRP DYSPLASIA?

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SRP type IV or Beemer-Langer syndrome is a lethal skeletal dysplasia usually associated with non-skeletal defects. Elejalde syndrome or acrocephalopolydactyly dysplasia is a rare condiction caractherized by short neck with redundant skin folds, short limb with post-axial polydactyly, and craniosynostosis. The purpose of this presentation is reporting a male infant presenting features of both syndromes. The propositus, first child of a young - she 20 and he 26 years old - and non-consanguineous parents, was born by vaginal delivery at 30 weeks, weighting 2360 g, length 40 cm, head circumference 33.5 cm and arm span of 22,5 cm. The family history was unremarkable except for two cases of hydrocephalus from paternal side. During pregnancy an ultrasound examination at 12 weeks showed an increased nuchal transluscence (3.0 mm). Posterior examinations showed a nuchal folding of 8.0 mm at 17 weeks, diffuse oedema, short long bones, short ribs and postaxial polydactyly on hands. Malformations of non-skeletal structures were not described. The baby died some minutes after birth and physical examination showed: hydrops, short thick neck with a large soft tissue mass around all the neck, turribrachycephaly, small low-set dysmorphic ears, accessory frenulum, large protuberant trunk, mamilar hypertelorism, short limbs, curved upper limbs, generalized brachydactyly, postaxial polydactyly on hands and syndactyly between 4^{th}-5^{th} toes. This clinical appearance of Elejalde syndrome was soon discarded by radiological examination that revelead: very short horizontally oriented ribs, highly placed clavicles, small scapulae, small ilia, short tubular bones with smooth metaphyseal margins except distal margins of radius and fibulae, tibiae longer than fibula, bowed radii and more slightly ulna, femora and tibiae, duplicated calcaneous, supranumerary digits not ossified, and premature closure of cranial sutures. Unfortunately necropsy was not carried out. Although radiological findings in the present case are strongly suggestive of SRP-IV, craniosynostosis and clinical aspect prompted two diagnostic possibilities – a variant form of this one or a new subtype of SRP. However, in the absence of a known genetic basis of lethal forms of SRP the two diagnostic hypothesis seem probable.

2- VARIABLE PHENOTYPE IN THREE SIBS WITH SHORT-RIB DYSPLASIA AND POLYDACTYLY

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Short-rib and polydactyly dysplasias are a group of well known autosomal recessive skeletal dysplasias, including lethal short rib-polydactyly, Ellis-Van Creveld and Jeune syndromes. We present a peculiar family with autosomal recessive MCA syndrome including short-rib and polydactyly dysplasia in three sibs.
The three sibs were born of young consanguineous Turkish parents. The mother is gravida 7 para 5.

The first sib, a 27 weeks' gestation female fœtus, presented a severe lethal phenotype including corpus callosum agenesis, polymicrogyria, cleft of right lip and palate, abdominal and thoracic situs inversus and horseshoe kidneys. Skeletal X-rays revealed a very narrow thorax with short ribs, short rhizomelic long bones, malformation of the 8th dorsal vertebral body and sciatic notch spurs.

The second child, a eutrophic boy born at term, presented respiratory distress due to thoracic dysplasia associated with post axial polydactyly of the right foot. No other malformation (cerebral, thoracic or abdominal) was noted. X-ray revealed a small thorax with short ribs, short rhizomelic long bones and dysmorphic iliac bones with sciatic notch spurs. The child died from respiratory distress at 45 days of life.
The third child, a eutrophic girl, presented isolated omphalocele and had a normal development after surgical correction.

For the fifth pregnancy, severe short rib-polydactyly was detected, early at 13 weeks of gestation, and termination of pregnancy was performed at 14 weeks of gestation. The fœtus presented cervical hygroma, abdominal and thoracic situs inversus, polysplenia but no polydactyly. Skeletal X-rays confirmed a very small thorax with short ribs, short long bones and sciatic notch spurs.

Three sibs present no anomalies and have normal follow-up.
In this family, three sibs present a syndrome combining osteochondrodysplasia, short-rib and polydactyly. For the first sib, the MCA with major thoracic dysplasia without polydactyly is characteristic of lethal short rib-polydactyly syndromes. The second child with less severe thoracic dysplasia and post axial polydactyly is more suggestive of Ellis-Van Creveld or Jeune syndrome but seems to be different from these two diagnosies. The third sib presents severe thoracic dysplasia with heterotaxia but no polydactyly.
We do not know how to interpret the significance of isolated omphalocele in the girl with normal development.

The extreme variability noted in the phenotype of these three sibs poses the question of a possible oligogenic mode of inheritance for the group of skeletal dysplasias with short-rib and polydactyly.

3- SKELETAL PATHOLOGY IN A LETHAL CASE OF METATROPIC DYSPLASIA

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Metatropic dysplasia is a rare spondylo-epi-metaphyseal dysplasia characterised by short limbs, joint enlargement and a progressive kyphoscoliosis. We describe the pathological findings in a stillborn infant delivered at 31 weeks of gestation following an antenatal diagnosis of a severe skeletal dysplasia. Antenatal ultrasound showed shortening of long bones, thickening of the end of femur, flexed elbows with absent movements, bilateral talipes and bunching together of fingers with absent movements. The post mortem skeletal survey was consistent with Metatropic Dysplasia and disclosed the following changes: severe platyspondyly, short and slender ribs, narrow thorax, vertical and broad ischia, and short long bones with metaphyseal widening. An early ossification of tarsal bones was observed. The karyotype was normal. Sections from the femoral end showed metaphyseal enlargement and an increased number of large cartilage canals. There was poor columnisation of the growth plate, irregularity of chondroosseous junction, focal clumping and irregularity of chondrocytes and irregular vascular invasion of cartilaginous matrix which has been observed in other studies. Unusual broad spicules of non calcified cartilage matrix were seen in the primary spongiosa indicating retardation in ossification. These are all generalised bone architectural abnormalities which in some way may contribute to the progressive scoliosis typical of this entity. Surprisingly, sections from vertebrae showed normal appearing cartilage. Metatropic dysplasia remains an enigma from a molecular perspective. We believe that the putative gene must be important in the regulation of skeletal and cartilage development and hope that anatomical pathology data from this and previous reports will contribute to the prioritisation of candidate genes.

4- SKELETAL DYSPLASIA ASSOCIATED WITH MALFORMATIONS RECURRING IN SIBS - A LETHAL FORM OF DESBUQUOIS DYSPLASIA -

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Prenatal short limb skeletal dysplasia (SD), especially when associated with non-skeletal malformations, could be a lethal condition. Clinical heterogeneity is common in a number of cases making a difficult task to obtaining a conclusive diagnosis. In this report we present a lethal short limb SD in sibs. The 1st child, from youthful and non consanguineous parents, was born by cesarean section at 37 weeks, weighting 2250 g and 36 cm height. Prenatal ultrasonography examinations showed polyhydramnios, omphalocele, shortened long bones without polydactyly and short thorax. The baby died soon after the birth and the physical examination revealed the following features: hydrops, brachycephaly, large palpebral fissures, round flat face with low nasal bridge, microretrognathia, U-shaped cleft palate, short neck, prominent abdomen with intact omphalocele, short limbs, medial displacement of thumbs, dislocations of fingers with wide spaced 2nd and 3rd ones, short adducted haluces and tibial deviation of toes. Karyotype was normal - 46,XY. Skeletal X-rays showed: shortening of long bones, slightly broad metaphyses, enlargement of lesser trochanter, broad thumb's 1st phalange and 1st metatarsal, accessory ossification centers between the 2nd and 3rd metacarpals, reduced interpedicular distance in thoracic vertebrae, marked lumbar lordosis and advanced carpal bone age. The autopsy findings revealed pulmonary hypoplasia, VSD, omphalocele, ureterohydronephrosis and large proliferative layer and reduced hypertrophic zone of growth plate at the microscopic examination. A couple of years later a second child, also a male infant, was born presenting the same clinical and radiological picture except for omphalocele that was absent. This baby died soon after the birth and autopsy findings showed coarctation of the aorta and pulmonary hypoplasia. Although some similarity with Catel-Manzke syndrome could be found, the present cases are suggestive to be a skeletal dysplasia rather a malformative syndrome. In conclusion we suggest a lethal form of Desbuquois Dysplasia.

5- CASE REPORT AND LITERATURE REVIEW: TWINS WITH THANATOPHORIC DYSPLASIA

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Background Thanatophoric dysplasia (MIM 187600, 187601, 151210) is a perinatally-lethal osteochondrodysplasia that occurs in approximately 1.68 per 100,000 births. Major clinical findings include disproportionate dwarfism with very short extremities, relatively normal trunk length, a narrow thorax, and a disproportionately large head with depressed nasal bridge, prominent forehead, and protruding eyes. Detection in utero is possible through sonography on the basis of short limbs and a narrow thorax. Death occurs in early infancy secondary to respiratory insufficiency. We describe twins with thanatophoric dysplasia and review previously-described twins with thanatophoric dysplasia.

Case The twins were the second pregnancy for a non-consanguinous 36 year old father and 32 year old G_3P_1 mother. At 27 week ultrasound findings at an outside hospital were suggestive of bone dysplasia. At 30 weeks gestation sonogram showed severe micromelia, small chest circumference, macrocephaly with mild ventriculomegaly, normal skull and spine, and polyhydramnios. Twin girls were delivered by Caesarean section at 37 weeks gestation, were placed on ventilation, and complete skeletal x-rays were obtained. Radiographic findings were consistent with a diagnosis of thanatophoric dysplasia, including bowing and severe shortness of long bones, short ribs, and flat vertebrae. Cord blood was sent for fibroblast growth factor type 3 (FGFR3) analysis. Both twins were found to have a R248C mutation in FGFR3, consistent with a diagnosis of thanatophoric dysplasia type 1. The family elected to remove care given the poor prognosis and the infants expired.

Literature review Twins have a risk of congenital anomalies three-fold higher than that of singletons. Thanatophoric dysplasia occurs in approximately 1.68 per 100,000 births, and its occurrence in multiple pregnancies is even less common. Family and twin studies play a role in implicating the presence of a hereditary component in disease. Six other sets of twins with thanatophoric dysplasia (TD) have been described (Bouvet JP et al. 1974, Sato D. et al. 1981, Horton WA et al. 1983, Serville F. et al. 1984, Young ID et al. 1989, and Corsello G. et al 1992). Clinical, radiographic, and histologic manifestations of thanatophoric dysplasia are well defined. Horton (1983) and Corsello (1992) described variable expression of the cloverleaf skull finding in two sets of monozygotic twins with TD. In each case, the twins were concordant for histopathologic and other radiographic findings. It is now accepted that thanatophoric dysplasia is caused by autosomal dominant mutations in the FGFR3 gene, with a high new mutation rate. All cases described to date have been the result of new mutation; gonadal mosaicism is possible but has not been reported.

6- TETRA-AMELIA AND LUNG AGENESIS SYNDROME-CASE REPORT

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Tetra-amelia (MIM 273395, 301090 and 273390) is a rare malformation characterized by the complete absence of the four limbs. It may be associated with other anomalies and it usually has an autossomal recessive transmission.

We describe the first pregnancy of a young non consanguineous couple, not surveyed until 20 weeks and without known teratogen exposure. The ultrasonographic evaluation at 20 weeks identified: tetra-amelia, bilateral cleft lip and palate and a hyperecogenic focus at the right ventricle. Pregnancy termination ocurred at 22 weeks. The pathological study further revealed bilateral lung agenesis, without other anomalies. Karyotype in amniocytes was normal (46,XX) having been excluded Roberts syndrome cytogenetic abnormalities. *WNT3* molecular analysis was normal. Molecular analysis of the *HS6ST1* and *HS6ST3* genes is being performed.

Niemann *et al.,* in 2004, identified a homozygous mutation in the *WNT3* gene (17q21) in 4 foetuses with tetra-amelia associated with craniofacial and urogenital anomalies from a consanguineous family. The specific association of tetra-amelia, lung agenesis/hypoplasia and, inconsistently, cleft lip/palate, was reported for the first time in 1991 by Rosenak *et al*. (MIM 273395). In 2005, Krahn *et al.* excluded mutations in *WNT3*, *FGF10*, *HS6ST1* and *HS6ST3* genes and the existence of an abnormal FGFR2 isoform, in 2 affected foetus with this pattern of malformation and propose its classification as a distinct syndrome, with no identified gene.

The reported case is suggestive of the syndrome tetra-amelia and lung agenesis. Molecular studies are important to clarify its pathogenesis, to confirm the genetic heterogeneity and to improve the classification of entities with tetra-amelia. At the moment, genetic counselling for this couple implies a 25% risk of recurrence, being crucial the precocious ultrasonographic diagnosis.

7- IUGR – OSTEOPENIA – OLIGOANAMNIOS – PLACENTAL MASSIVE FIBRIN DEPOSITION : A "NEW" RECURRENT FETAL PHENOTYPE FOR AN "OLD" PLACENTAL PATHOLOGY ?

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We report a cohort of 26 fetuses (2 isolated cases, 24 cases from 17 families), presenting with a new, often letal phenotype,defined by a constant association of four criteria : 1) precocious (2d trimester) and severe IUGR, 2) precocious oligoanamnios, 3) hypocalvaria and diffuse hypomineralization of the skeleton, 4) hypotrophic placenta with massive perivillous fibrinoid deposition.

Pregnancies were terminated between 14 and 31 weeks of gestation, by spontaneous per partum or intra-uterine death (IUD) (10 cases), or following medical induction on indications of IUGR and anamnios (16 cases). Antenatal history was also marked by an elevated level of foetoprotein in maternal serum (8 on 8 recorded) and maternal associated auto-immune pathology (4/7). Uterine dopplers were often normal (14/17).

Fetopathological examination performed in all cases, revealed severe IUGR, with relative macrocrania, unvarying facial dysmorphia including bulging forehead and depressed nasal bridge, both related to hypocalvaria, Potter deformations due to anamnios, and occasional slight angulation of the thighs. Internal exam found renal meduller fibrosis (constant) or lesions suggesting acquired tubular dysgenesis (8/24) and usual manifestations of chronic fetal hypoxia (meconial ileus, splenic and thymic lymphoid depletion) or prolonged exposition to anamnios (pulmonary hypoplasia). Osseous lesions were characterized by diffuse demineralization of the skeleton, leading to some per partum fractures : histologic examination revealed anomalies of the growth plate, particularly increased lenght of the hypertrophic zone, and increased remodelling of the primary osseous trabeculae leading to severe osteopenia. Hematopoiesis was poor in the endostic spaces, which were mainly occupied by fibrous tissue. This aspect has suggested fetal hyperparathyroidism, which was confirmed by cord blood analysis in one cases. Placentas were characterized by hypoplasia, thickness, and massive fibrin deposits, which were often associated with villitis and intervillositis, with predominant CD 68+ macrophages and CD 45+ lymphocytes.

In 15 families out of 17, the pathology appeared at the first or at the second pregnancy and was recurrent in all subsequent pregnancies; in two families, recurrence suggested an autosomal recessive pathology.

Massive perivillous fibrin deposition (MFD) is a placental lesion known to be associated with recurrent IUGR and fetal loss, or repeated spontaneous abortions. Associations with maternal pathologies such as phlebitis, thrombophilia or auto-immune diseases have been described; but most of the cases remain unexplained. We define here a peculiar phenotype of hypotrophic fetuses, characterized by skeletal and renal lesions reminiscent of that observed in acquired renal tubular dysgenesis, which appears specifically related to placental MFD. The causes of this syndrome seem to be heterogenous, with, mostly, recurrent environnemental factors suggesting materno-fetal disease, but also, in a few cases, genetic diseases. The pathogenic mechanism binding mothers, placental lesions, fetal parathyroid, kidneys and bone remains to be further elucidated.

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8- AUTOSOMAL RECESSIVE OSTEOPETROSIS, MALIGNANT INFANTILE FORM DUE TO *OSTM1*: A NOVEL MUTATION

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Autosomal recessive osteopetrosis is a rare condition seen in approximately one in 300,000 births. Bone marrow transplantation is the treatment of choice. Three genes have been reported to date to be responsible for the malignant infantile form: *TCIRG1*, accounting for approximately 55-60%; *CLCN7*, accounting for 10-15 percent; and *OSTM1* (grey lethal), accounting for an estimated 1-5% of cases. Other genes are presumed to exist as not all families have been found to have mutations in one of these three genes. There are few reported cases of individuals with *OSTM1* mutations. Along with the classical bone and haematological findings, a neurodegenerative phenotype has been identified which makes transplantation contraindicated. We report a further patient with infantile osteopetrosis born to non-consanguineous Pakistani parents who was found to be homozygous for a novel IVS5+1G>A mutation in the *OSTM1* gene. At almost 6 months of age, he has had a worsening clinical course with profound hypotonia, little spontaneous movement and suspected onset of seizures. This case illustrates the importance of defining the genotype in individuals with malignant infantile osteopetrosis prior to undergoing transplantation.

9- THE HOMOZYGOUS DELETION OF THE 3' ENHANCER OF THE SHOX GENE CAUSES LANGER MESOMELIC DYSPLASIA

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A disturbance in the long-range regulation of gene expression has been proposed as the cause of a number of diseases, in which the disruption of the transcriptional control results in a loss of function and in phenotypes identical to those caused by inactivating mutations in the coding region of the gene. Deletions in cis-acting enhancer elements of some developmental regulator genes, such as *PAX6* or *SOX9*, cause the typical phenotypes of aniridia and campomelic dysplasia. Also for the *SHOX* gene, heterozygous deletions in two different hotspots downstream the coding region have been shown to result in the phenotype of the Leri-Weill Syndrome,and a similar mechanism has been suggested for the homozygous form of LWS, Langer Mesomelic Dysplasia (LMD, MIM 249700), a rare dwarfism with a shortening of the middle segment of the limbs, associated with hypoplasia of the ulna and the fibula: recently, a compound heterozygote has been described, associating a deletion in the 3' *SHOX* flanking region in one allele with the loss of the entire SHOX gene in the other, resulting in a "mild" LMD phenotype. In the present report we characterize the first case of "pure" homozygous deletion of the enhancer region in LMD, and we confirm this mechanism as a possible cause of the SHOXpathies.

Materials and methods: A couple, first cousins affected by LWS, was referred to us for prenatal counselling after a previous 22-week therapeutical abortion for the ultrasonographic diagnosis of LMD. The diagnosis was also confirmed by the pathological examination of the fetus, showing a severe hypoplasia of the ulna and fibula, a thickened and curved radius and tibia, ulnar deviation of the hands and hypoplasia of the mandible. In the two parents, *SHOX* gene mutation analysis by direct sequencing of exons 2 to 6a and deletion analysis with 3 microsatellites failed to detect any mutation, although the markers DXYS233 and DXYS234, located respectively 250 and 700 Kb downstream of *SHOX* showed only one allele: this non informative result could not be further tested due to the unavailability of DNA from their parents. In the absence of a known familial mutation, prenatal diagnosis was not performed and the follow-up was only ultrasonographical. A boy of 48 cm of length was born at term. Also two years after a girl of 47 cm of length was born at term. After the publication of the articles showing the involvement of SHOX 3' enhancer region in the pathogenesis of the LWS, the family was re-examined. Deletion analysis of *SHOX* and the PAR1 was carried out by multiplex ligationdependent probe amplification (MLPA), using the *SHOX* salsa P018B kit (MRCHolland, Amsterdam, The Netherlands), containing 27 probes covering the whole PAR1 region (including three probes for the enhancer) and 18 control probes. The analysis was implemented by using microsatellites, including the known markers located directly distal to *SHOX* (DYS290, DXYS10093, DXYS233, DXYS234, DXYS228) plus two additional ones, newly identified through the program Tandem Repeat Finder, one intragenic and one 3' flanking the gene (submitted to the GDB Human Genome Database, http://www.gdb.org/gdb/).

Results and discussion: A large heterozygous deletion extending from exon 6b of the *SHOX* gene downstream for 1.1 Mb up to include the IL3RA gene, encompassing the enhancer, was detected in the two LWS parents by MLPA ; the same deletion in a homozygous form was found in the DNA from the previously aborted LMD fetus . In the other son and daughter of the couple, no deletion in the PAR1 region was found by MLPA. Microsatellite analysis confirmed the results by showing heterozygosity for the markers CA SHOX (located approximately 15 kb upstream of *SHOX*) and for DXYS228, (located 2Mb downstream of *SHOX*), whereas the remaining 5 markers revealed only one allele in both the parents and the absence of any amplification product in the LMD fetus. The reported case is the first description of a homozygous deletion in a regulatory region causing disease in humans: through the typical phenotype of the LMD-affected fetus, it was possible to demonstrate how enhancer deletions can completely abolish the gene function to the same extent of a loss-of-function intragenic mutation. The fact that the reported deletion encompasses also exon 6b of the *SHOX* gene coding region should not affect our conclusions, since no causative mutation in exon 6b, encoding for 20 aminoacids in the COOH terminal of the protein, has ever been described for the pathogenesis of the SHOXpathies . The present report clears the doubts raised by the previous LMD description about the possibility of a residual gene function and of a milder phenotype when caused by the enhancer deletion and confirms this latter as a possible mechanism of *SHOX* gene silencing.

10- A CASE OF SMITH-MCCORT SYNDROME CAUSED BY A NEW MUTATION IN THE *DYMECLIN* (*FLJ20071*) GENE

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Dyggve-Melchior-Clausen (DMC) and Smith-McCort (SMC) are rare autosomal recessive allelic spondyloepimetaphyseal disorders caused by mutations in the *Dymeclin / FLG20071* gene (Cohn et al., *2003;* El Ghouzzi et al., *2003*). Clinical identical features of both disorders are short limbs and trunk, a barrel shaped chest, progressive kyphoscoliosis, varus and valgus deformity of the knees, limitation in joint movement and brachydactyly. The two osteochondrodysplasias are only distinguished by the presence in the DMC patients of important development delay or mental retardation (Spranger et al, 1976). Radiological features include platyspondyly, metaphyseal and epiphyseal irregularities and a patognomonic lacy appearance of the iliac crests. Here we describe a case of Smith-McCort of a 6 years girl from a consanguineous family from Madeira Island. This affected girl presents the main clinical and radiological features of this disorder not revealing any development delay. Molecular analysis of the all entire coding region of *Dymeclin* gene was performed. A novel missense variant was identified in exon 15, C542R, in homozygosity. In order to clarify its clinical significance, additional studies were carried out. The comparison of the *Dymeclin* protein sequence and homologous proteins in other species showed that this amino acid residue is evolutionary conserved. This variant was also excluded in 50 Portuguese healthy individuals screened (100 chromossomes), which strongly supporting a pathogenic role. Therefore, we believe that the homozygous C542R mutation is responsible for the Smith-McCort phenotype.

To date, at least 23 different *Dym* gene mutations have been described in 29 unrelated families, which represent 45 affected patients with founder effects in Morocco, Lebanon, Spain and Guam Island (Paupe et al 2004, Pogue et al 2005). Two DMC Portuguese origin patients were also previously identified. Consanguinity was reported in the vast majority of these families. An interesting suggestion of the possibility that the exon-skipping mutation and the haplotype from Argentina, Chile and Guam Island were originated in *Spain or in a closely related population* was emphasized by Pogue et al 2005. This might be due to the Spanish and Portuguese cincumnavigation trip in 16th century.

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11- CLINICAL AND MOLECULAR DIAGNOSIS OF BONE DISORDERS ASSOCIATED WITH MUTATIONS IN THE GENE THAT CODIFIES FOR THE FIBROBLAST GROWTH FACTOR RECEPTOR 3 (FGFR3) – A PORTUGUESE EXPERIENCE

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Background: Achondroplasia (Ach), Hypochondroplasia (Hch), Muenke craniosynostosis (MS) and Tanatophoric dysplasia (TD) are autosomal-dominant skeletal disorders caused by heterozygous mutations in different regions of the *FGFR3* gene. In Ach virtually all patients have localised point mutations at codon 380, located within the transmembrane domain. Hch mutations are spreadout in *FGFR3*, with a hotspot in the tyrosine kinase domain at codon 540. TD also results from several mutations in the extracellular and tyrosine kinase domains. MS is characterized by a heterozygous missense mutation in the extracellular domain at codon 250. In addition, mutations in this gene have been identified in patients with LADD syndrome and more recently in a patient with CATSHL syndrome, a mutation has been identified at codon 62. Clinical and radiographic features of these bone dysplasias are typical and to the most of the cases the molecular diagnosis appeared to confirm the clinical diagnosis. However, recently it has been reported an increasing number of cases in which the molecular analysis was crucial to perform an accurate diagnosis, which is well illustrated in the present study.

Population: We studied 105 Portuguese subjects with the clinical diagnosis of Ach (21 cases), Hch (40 cases), Muenke craniosynostosis (41), TD (2 cases) and LADD syndrome (1 case) based in the clinical and radiographic features.

Methods: Clinical questionnaires were taken from all patients. The patients first referred to Ach with no mutations found were also tested to Hch and *vice versus*. The mutation search was performed on the *FGFR3* gene and involved exons 9 and 10 for Ach, exons 13 and 15 for Hch, exon 7 for Muenke syndrome, exons 7, 10, 15, 19 for TD and exon 13 for LADD, since these are the exons in which the most common mutations for these chondrodysplasias are present. To the LADD case, exon 16 and exon 1 of *FGFR2* and *FGF10* genes, respectively, were screened. The mutation search was performed by direct sequencing the PCR amplification exons using an automated sequencer ABI PRISM^{R} 3100-Avant.
Results: Nine different pathogenic mutations were identified, G380R (19 cases), G380K (2 cases), N540K (9 cases), P250R (8 cases), R200C (1 case), E360K (3 cases), R248C (1 case) and X807W (1 case). Two of these nine mutations were novel (G380K and E360K). The two TD cases were identified with R248C and X807W mutations.

Conclusions: Genetic heterogeneity is present in Portuguese patients with 9 different mutations identified, 2 of which were novel. These results demonstrated that to the patients with a clinical diagnosis of Ach or Hch, it is worthwhile to perform the molecular analysis of both disorders. To the cases with a clinical diagnosis of Ach and Hch, lacking the most common mutations, a complete screening of *FGFR3* is recommended whenever the final clinical re-avaliation confirmed the first diagnosis.

12- OVERLAP OF CRISPONI SYNDROME WITH STÜVE-WIEDEMANN SYNDROME (SWS)

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Stüve-Wiedemann syndrome (SWS) is a severe autosomal recessive condition characterized by bowing of the long bones, with internal cortical thickening, flared metaphyses with coarse trabecular pattern, camptodactyly, respiratory distress and hyperthermic episodes responsible for early lethality. Studying a series of 19 SWS families, we have mapped the disease gene to chromosome 5p13.1 and then identified null mutations in *LIFR* (Leukemia Inhibitory Factor Receptor). We have also shown that the *LIFR* mutations are responsible for an impairment of the JAK/STAT signalling pathway in patient cells.

Since this first study, we have collected the samples of 26 additional SWS families. Among them, we have identified *LIFR* mutations in 17 families (at the homozygote or compound heterozygote state) including 11 novel mutations responsible either for a premature stop codon or for the change of conserved aminoacids. In the 9 other families, the absence of any *LIFR* mutation prompted us to perform a linkage analysis in the 4 consanguineous families and we have excluded the 5p13 locus as the disease causing locus. In addition, we have tested the activation of the JAK/STAT3 pathway in the skin fibroblasts from 4 patients without any *LIFR* gene mutation and observed a normal activation of the pathway in response to LIF.

On the other hand, Crisponi syndrome [MIM 601378] is an autosomal recessive disorder characterized by congenital contractions of facial muscles with trismus, dysmorphic features, camptodactyly, feeding and respiratory difficulties with access of hyperthermia leading to death in the first months of life. The overlap with SWS is striking. However, congenital bowing of the lower limbs, which is a cardinal feature of SWS, has never been reported in Crisponi syndrome.

We first excluded *LIFR* as the disease causing gene in four children from three families with Crisponi syndrome. We then considered the Cytokine Receptor-Like Factor 1 (*CRLF1*) gene as a candidate gene based on the identification of *CRLF1* mutations in cold-induced sweating syndrome. By direct sequencing, we identified *CRLF1* mutations in the four children. Following this initial study, we identified homozygote *CRLF1* mutations (G60S) in two sibs from Morocco with Crisponi syndrome.

The combination of our data allows us to suggest a key role of the CNTFR pathway in the function of the autonomic nervous system while the specific impairment of the LIFR pathway is presumably involved in the bone manifestations characteristic of SWS.

13- CHONDRODYSPLASIAS SERIES: ACHONDROPLASIA, HYPOCHONDROPLASIA, THANATOPHORIC DYSPLASIA: FGFR3 MUTATIONS AND UPDATE

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Achondroplasia (ACH), hypochondroplasia (HCH), thanatophoric dysplasia (TDI, TDII) are skeletal disorders caused by missense FGFR3 mutations in various domains of the receptor.
More than 98% of achondroplasia cases are caused by one mutation in the FGFR3 gene, which results in a specific amino acid substitution, G380R. A common mutation (N540K) in the tyrosine kinase domain of the receptor is detected in only 60-65% of hypochondroplasia cases and the thanatophoric dysplasia fetuses are associated with mutations located in different domains of the receptor.
Here, we studied 177 cases with the clinical diagnosis of HCH (85), ACH (30) and TD (62). Eighteen exons of the FGFR3 gene were entirely sequenced in a cohort of patients in whom common mutations had been excluded.

For achondroplasia: we identified the G380R mutation (26 cases), G375C (1 case), Y278C (1 case), Y279C (1 case) and one novel mutation G295C (1 case).
Radiographs for each patient were re-examined and ACH clinical and radiological features were found. No mutations were detected in 4 patients clinically diagnosed with mild achondroplasia.
Hypochondroplasia : we identified the N540K mutation (27 cases), K650Q (1 case), S84L (1 case), N262H (1 case), R200C (1 case), V381E (1 case), G268C (1 case) and three novel mutations S351C (1 case), N328I (1 case), E360K (1 case). For each HCH patient radiographs were re-examined: we observed that mutations creating cysteine residues cause severe forms of hypochondroplasia. No mutations were detected in 48 clinically diagnosed HCH patients.

Thanatophoric dysplasia: we identified the R248C (24 cases), Y373C (10 cases), S249C (6 cases), G370C (4 cases), S371C (1 case), K650E (3 cases), K650M (1 case), X807C (1 case), X807G (1 case) and the X807S (1 case). The substitution of lys650 by methionine (K650M) can give rise to a less severe phenotype called severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN). In our series, the fetus with the K650M mutation had the clinical and radiological TD I phenotype.

This study demonstrates that the complete screening of the FGFR3 gene is necessary for patients with a clinical diagnosis of achondroplasia and hypochondroplasia in the absence of the most common associated mutation. Finally, our data emphasize the possibility of genetic heterogeneity of hypochondroplasia.

14- THANATOPHORIC DYSPLASIA CAUSED BY TWO MISSENSE FGFR3 MUTATIONS

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Thanatophoric dysplasia (TD) is the most frequent form of neonatal lethal skeletal dysplasia. In this report we studied a fetus, showing severe shortness of limbs, large head, frontal bossing, flat vertebral bodies (platyspondyly), narrow thoracic cage, polyhydramnios without cloverleaf skull. Cerebral cortex malformation was characterized by a combination of abnormalities, which affect the temporal lobe most severely, and consists of temporal lobe polymicrogyria, and histologicaly abnormalities of the hippocampus and heterotopic neuroglial tissue within the meninges.

The common TDI mutations (R248C, Y373C, X807S) were excluded. The entire *FGFR3* gene was sequenced. We identified the common hypochondroplasia mutation at position 540, an asparagine-to-lysine substitution (N540K) and one heterozygous mutation at residue 485 a glutamine to arginine substitution (Q485R).
Here we describe the first TD I fetus with a clinical and radiological thanatophoric dysplasia phenotype due to two missense mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene.

15- HOMOZYGOUS C.2763DELT (p.P425Pfx62) IN COLL11A2 GENE CAUSES NO-MRNA DECAY IN OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA (OSMED)

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Keyword: otospondylomegaepiphyseal dysplasia (OSMED), mutation, collagens, no-mRNA decay.

Otospondylomegaepiphyseal dysplasia (OSMED) is a rare genetic disorder of bone growth that results in disproportionate shortness of the limbs with abnormally large knees and elbows, severe hearing loss, and distinctive facial features presenting mid-face hypoplasia, depressed nasal bridge with anteverted nares. Cleft palate and micrognathia are also the common findings (Insley & Astley 1974; Giedion et al. 1982; Käärinäinen et al. 1993). The phenotype is very similar to non-ophthalmic Stickler or Stickler Type III (MIM #184840) which displays more subtle signs. Autosomal recessive mutations on collagen peptide coding gene COL11A2 are responsible of OSMED while dominant mutations are associated with Stickler type III. First implication of COL11A2 gene with osteochondrodysplasia was shown by the identification of a homozygous missense mutation in one OSMED patient in 1995 (Vikkula et al. 1995). Presently, more mutations in OSMED and in other similar phenotypes like cleft palate, Robin sequences, micrognathia, and non-ophthalmic Stickler syndrome are described which adds up to a total of 20 different mutations altogether in *COL11A2* gene (Pihlajamaa et al. 1998; Sirko-Osadsa et al. 1998; Melkoniemi et al. 2000; Melkoniemi et al. 2003; Vuoristo et al. 2004)

In this study, two cousins with OSMED were clinically assessed and the cDNA of COL11A2 was sequenced to define the causative mutation. Analysis showed a novel homozygous c.2763delT (P425Pfx62) in exon 38 which causes frameshift stop in exon 40. This deletion was not found in 200 ethnically matched control chromosomes. Successful sequencing covering 66 exons including portions of 3' and 5' UTR regions showed that this mutation does not cause mRNA decay.

16- SKELETAL AND CARDIOVASCULAR ABNORMALITIES IN PATIENTS WITH JUVENILE POLYPOSIS OF INFANCY ASSOCIATED WITH MICRODELETIONS INVOLVING THE *BMPR1A* AND *PTEN* GENES

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Juvenile polyposis of infancy is characterized by the presence of generalized polyposis of the gastrointestinal tract that presents in the first 2 years of life. The phenotype has recently been found to be due to deletions involving the *BMPR1A* and *PTEN* genes on chromosome 10q23. We present the unique skeletal and cardiovascular phenotype in a patient with a microdeletion involving the *BMPR1A* and *PTEN* genes and a review of the literature with focus on these aspects of the phenotype. Our patient presented at three months of age with generalized polyposis. On examination at 7 years of age she had significant dysmorphic features including macrocephaly, high, broad forehead, flat facial profile, broad nasal bridge, and shallow orbits. Her palate was high arched with dental crowding and delayed shedding of deciduous dentition. She had significant hypermobility and broad thumbs and first toes. Echocardiogram revealed a perimembranous VSD, mitral stenosis, subaortic ridge and severely dilated left atrium. She was found to have an apparently balanced de novo translocation: 46,XX,t(2;10)(q31;p15). Serial microsatellite typings and semiquantitative PCR for *PTEN* and the surrounding genomic region indicated a deletion of at least 1.2 Mb that included the full coding sequence for *BMPR1A* and *PTEN*. To our knowledge this is the oldest reported patient with a hemizygous deletion of *BMPR1A* and *PTEN*. It has been proposed that deletions of both *BMPR1A* and *PTEN* act synergistically and lead to very early development of polyps. However, little information is available on the extracolonic phenotype of such patients. In addition to its role during colonic epithelium development, *BMPR1A* is also crucial during the craniofacial, skeletal and heart development. Haploinsufficiency for this protein may explain some of the phenotypic manifestations in patients with this microdeletion and suggests that the deletion of these two genes results in a distinctive phenotype with features of juvenile polyposis of infancy, Cowden syndrome, cardiovascular and skeletal manifestations.

17- DISTAL PHALANX AND NAIL HYPOPLASIA ASSOCIATED WITH OSTEOPETROSIS; REPORT OF AN AFFECTED MOTHER AND SON

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A mother and her 4-year-old son presented with skull hyperostosis, short distal phalanges and hypoplastic nails. The pregnancy was complicated by hydrops fetalis. Amniocentesis showed a normal 46,XY karyotype. The boy has recurrent otitis media, recurrent sinusitis and speech delay and was diagnosed with bilateral profound sensorineural hearing loss. He underwent a cochlear implant. His mother has adult onset hearing loss, tinnitus, vertigo, and chronic sinusitis. Both mother and son have retrognathia, short digits and hypoplastic nails. Growth parameters were normal. Neither mother nor son had dental abnormalities, skin abnormalities, anemia or an increased propensity to fracture. Radiographs showed hyperostosis of the base of the skull and distal hypoplasia of the phalanges. The long bones were normal.

18- SEVERE SPONDYLOEPIMETAPHYSEAL DYSPLASIA WITH PROFOUND MENTAL RETARDATION: A NEW AUTOSOMAL RECESSIVE MCA/MR SYNDROME ?

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We report four sibs born of non consanguineous parents and presenting an unusual syndrome including severe spodyloepimetaphyseal dysplasia and profound mental retardation in the surviving boy.

After the birth of a normal boy, the couple's second pregnancy with monozygotic female twins was terminated at 34WG because hydrocephaly and cerebral calcifications were detected in both fetuses. One fetus presented flat dysplastic acetabulae on skeletal X-rays.
Subsequently, the third pregnancy was also terminated at 25WG because of corpus callosum agenesis and ventriculomegaly in a male fetus. Flat dysplastic acetabulae were also present on skeletal X-rays.

The couple's fourth pregnancy was normal. At birth, the apparently healthy boy had a normal cerebral ultrasound. Hypotonia and psychomotor retardation developed at 7 months. Chromosome studies and metabolic tests were normal, but we were not able to obtain lymphocyte cultures for lysosomal deficiency studies. The child presented severe osteochondrodysplasia evidenced on X-rays which showed platyspondyly, dysplastic iliae with a lacey border of iliac crests, irregular metaphysis, extreme brachydactyly and highly dysplastic carpal and tarsal bones. Cerebral MRI revealed cerebral atrophy with ventriculomegaly. At the age of 8 years, there is severe mental retardation with no language and total hypotonia. In addition, the boy has convultions and required tracheotomy because of major respiratory distress due to impaired swallowing mechanism.
Hypotheses:

A new MCA/MR syndrome combining cerebral anomalies and spondyloepimetaphyseal dysplasia with variable expressivity, This syndrome can become manifest in the prenatal or postnatal period.

19- A NOVEL MALFORMATION SYNDROME WITH SKELETAL ABNORMALITIES COMPLICATED BY MOYAMOYA

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We report a 12-year-old boy with growth delay, osteopenia, and fractures following minimal trauma. A skeletal survey revealed delayed bone age, gracile ribs, tubulated long bones, and increased long bone cortical density. He was born with an atrial septal defect, branch pulmonary stenosis, intestinal non-rotation and anal stenosis. At age 2-1/2 years, he presented with symptomatic seizures and a right-sided hemiplegia. Cranial imaging and angiography demonstrated moyamoya phenomenon. The patient was managed surgically with an internal carotid bypass graft and subsequently, because of progressive cerebral ischemia, had an encephaloduroangiomyosynangiosis (EDAMS) procedure. His additional features include nonprogressive sensorineural hearing loss, livedo reticularis, growth delay, severe headaches, and diffuse arteriosclerosis causing intestinal ischemia, renal artery stenosis and hypertension. Extensive biochemical and molecular analyses have not identified an underlying abnormality. Microarray comparative genomic hybridization (CGH) and *ABCC6* mutation analysis are in progress. To the best of our knowledge, this pattern of skeletal abnormalities, congenital malformations, and the progressive arteriosclerosis with moyamoya define a novel osteochondrodysplasia or genetic syndrome. To understand better the underlying pathophysiology and phenotypic spectrum, we seek other patients with this disorder.

20- CASAMASSIMA-MORTON-NANCE SYNDROME WITH 47,XYY. CASE REPORT

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Introduction. The Casamassima-Morton-Nance Syndrome (CMNS) is characterized by spondylocostal dysostosis with anal atresia and urogenital anomalies, just a few cases of this association have been reported in the literature. We describe a patient who besides fulfilling the clinical criteria for CMNS also had a chromosomal anomaly 47, XYY.

Case report. The patient was a male newborn, product of the second pregnancy and only child of a young, not related couple. The pregnancy was complicated by a placental hematoma diagnosed at the 5th month. He was delivered at term by cesarean section due to no labor delivery progression and umbilical cord around the neck. The weight was 3200grs, height 48cm, Apgar 6/8. The clinical exploration showed: imbrication of craneal sutures, telecantus, high ojival palate, preauricular left tag. Short neck and thorax, congenital cardiopathy, anorectal malformation with fistula, male genitals with thick medial rafe and short penis. The extremities were symetrical with big hands and feet. The radiographic analysis demostrated right lung atelectasia, spinal cord with costal fusion of the 3rd and 4th costal bones in both left and right hemithorax, vertebral dysplasia. The Ultrasound analysis showed renal ectasia. To complete the clinical assesment a chromosomal analysis was carried out which demonstrated a 47,XYY karyotype. The patient died at 4 moths 24 days of age, due to penumoniae and respiratory distress, an autopsy was not performed.

Discussion. In this patient there was a combination of spondylocostal dysostosis with a chromosomal anomaly. The CMNS is an autosomic recessive entity which has the anal atresia and urogenital anomalies shown in our patient. Among the few reported cases there was at least one with a chromosomal anomaly, a (6;9) balanced translocation. In our case although there was a chromosomal anomaly it was numeric as a 47,XYY karyotype was found, this is a well known anomaly which is not usually seen in spondylocostal dysostosis neither has especific characteristics in the newborn period. Therefore we consider this case as a CMNS with a chromosomal numeric anomaly, an association not previously described in the literature.

21- SPONDYLO-MEGAEPIPHYSEAL-METAPHYSEAL DYSPLASIA IN TWO SIBS: PRENATAL PRESENTATION AND FOLLOW-UP TO ADULTHOOD

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Spondylo-megaepiphyseal-metaphyseal dysplasia (SMMD) is a rare skeletal dysplasia with autosomal recessive inheritance and yet unknown genetic defect. The most characteristic radiographic findings include severe ossification defects of the vertebral bodies and the presence of large, rounded epiphyses with wide growth plates. To date, only 9 cases have been reported. We report two affected sibs and discuss the characteristic clinical and radiographic features of this condition at different ages.

The proband was born as the third child of healthy, consanguineous parents. At birth, the diagnosis of hypochondrogenesis was suspected because of absent vertebral ossification in the sacral and cervical spine. At 13 years of age, the boy developed pyramidal symptoms and progressive hydrocephalus due to a stenosis of the cervical spinal canal, for which he underwent laminectomy and ventriculoperitoneal drainage. Evaluation at the genetics unit at the age of 20 years revealed a disproportionate short stature (height: 130 cm) with short trunk, pigeon chest and severe kyphoscoliosis for which he had a corset. His fingers were slender with camptodactyly and some were disproportionately long. He was disabled and could not walk long distances.

Radiographs taken at 10 months of age showed enlarged, almost perfect spherical epiphyses with wide growth plates at the shoulders, hips, knees and ankles. The pelvis was abnormal with large sacrosciatic notches, small iliac wings and absent ossification of the pubic bones. The thorax had eleven pairs of ribs showing metaphyseal widening and irregular calcifications at their anterior ends. Remarkable was the absent ossification of the cervical and sacral vertebrae and abnormal ossification of the thoracolumbar vertebrae with both sagittal and coronal clefts that persisted during childhood. On further follow-up, the ossification of the vertebral bodies improved but reduced ossification of the vertebral bodies was still visible on a MRI of the spine taken at the age of 20 years. Radiographs of the hands taken at the age of 20 years revealed small carpal bones, shortening of the 4^{th} and 5^{th} metacarpals with slender diaphyses, and shortening of several phalanges.

Prenatal ultrasound in a next pregnancy of the mother revealed absent ossification of the vertebral bodies at 19 weeks gestation, indicating the recurrence of this skeletal dysplasia in this child. Fetal radiographs after termination confirmed the absent ossification of all vertebral bodies with small pedicles and widened costovertebral junctions. They also showed a small pelvis with round iliac bones and absent ossification of the ischial bones. The mild shortening of the tubular bones in the limbs differentiated this dysplasia from the different forms of achondrogenesis.

In conclusion, our report adds further evidence for an autosomal recessive inheritance pattern in SMMD and highlights the characteristic radiographic abnormalities of this skeletal dysplasia that deserves inclusion in the next Nosology of Constitutional Disorders of Bone.

22- UNUSUAL EPIPHYSEAL AND METAPHYSEAL DYSPLASIA ASSOCIATED WITH MAJOR ADVANCED BONE MATURATION AND SEVERE ASYMETRIC LOWER LIMBS DEFORMATION

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We describe an 8-year-old girl, followed since neonatal period, initially presenting with short stature of prenatal onset and micromelia. There was no familial history, no parental consanguinity.

Clinical course was marked by moderate short stature with progressive deceleration of the growth curve from 3 years of age (height is now -3SD), but severe and progressive asymmetric lower limbs deformation, which required surgery (left distal tibial osteotomy at 4 ½ years and left femoral osteotomy at 7 years). Limitation of elbows extension, second left finger clinodactyly and high arched palate were noticed. She had no sensorial disorder and normal milestones.

Radiological findings included flared and irregular metaphyses, associated with precocious and irregular mineralization of the epiphyses of long bones, especially of the lower limbs, and major advanced carpal bones maturation. Epiphyses are now very enlarged and deformed, leading to recurrent varus deformity of the lower limbs despite surgery. Skull and spine radiographs were normal.

Biochemical findings showed normal calcium homeostasis. Because of radiological similarities in bone structure with Jansen type metapyhseal dysplasia, analysis of PTHR1 gene was performed, but no mutation was found. Electronic microscopy of the growth plate revealed unusual anomalies.

23- SPONDYLOMETAPHYSEAL DYSPLASIA WITH CONE-ROD DYSTROPHY

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Introduction
The spondylometaphyseal dysplasias (SMD) are a rare, heterogeneous group of disorders of which three have been clearly identified - SMD type Kozlowski, SMD type Sutcliffe (corner fracture type) and the congenital and severe SMD Sedaghatian type. In 2004 Walters et al identified a further group, which was characterised by a cone-rod dystrophy and specific radiological features, which progressed with age. They described eight patients and suggested autosomal recessive inheritance on the basis of three affected siblings with normal parents and one set of consanguineous parents.
We report the clinical findings of a further patient with this rare disorder and illustrate the progression of radiological findings up to the age of fifteen years.

Case report
There is no relevant family history. He presented in infancy because of short limbs. In early childhood he was diagnosed as having retinitis pigmentosa. At the age of 15 he has normal intellect and marked rhizomelic shortening with femoral bowing.
Radiologically there is marked flaring, irregularity, flocculation, cupping and some sclerosis of the metaphyses. The adjacent epiphyses are large and rounded. The femora are short and bowed with coxa vara and the fibulae disproportionately long. There is platyspondyly with anterior wedging, wide intervertebral spaces and a mild double curve scoliosis. The hands show mild brachydactyly and multiple ivory epiphyses. The metaphyseal changes, femoral bowing and platyspondyly have all progressed with age.

Reference
Walters BA, Raff ML, Ver Hoeve J, Tesser R, Langer LO, France TD, Glass IA, Pauli RM. Spondylometaphyseal dysplasia with cone-rod dystrophy. Am J Med Genet 2004;129A:265-276.

24- ANISOSPONDYLY AS AN UNUSUAL HALLMARK OF A NEW FORM OF CHONDRODYSPLASIA PUNCTATA

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Chondrodysplasia punctata (CDP) is a heterogenous group of disorders characterized by small calcifications (puncta) in the cartilaginous epiphyses of the axial and appendicular skeleton. The puncta are usually present at birth and generally disappear during the first years of life. Growth of the affected bones is often retarded, which can result in limb shortening, delayed ossification, bone deformities, and/or vertebral anomalies. We report on a girl with an unclassifiable form of CDP.

The proband was born at term to consanguineous parents of Arab-Berber origin. The pregnancy was uncomplicated. The healthy mother did not report any significant illnesses or use of medication. Birth weight was 3700g and length 45 cm (<P3). After birth bilateral hip dislocation was noted and treated conservatively. Skin lesions were not present in the postnatal period.

From the age of 15 months the girl was followed because of growth retardation and progressive scoliosis. Clinical evaluation at the age of 3 years revealed a short stature with short trunk, scoliosis, and a lower limb length discrepancy. Clinical signs reminiscent of CDP (midface hypoplasia, low nasal bridge, skin lesions, joint contractures) were not present. Ophthalmologic examination was also normal.

Radiographic evaluation at the age of 1 year revealed multiple small calcifications around the sacral spine and in the tarsal region. Several tarsal bones were fragmented and tarsal ossification in the left foot was retarded. There was also an asymmetry in the lower limbs with delayed epiphyseal ossification in the right leg and shortening of the right tibia. Radiographs of the spine showed thoracolumbar scoliosis and remarkable anisospondyly as can be seen in dyssegmental dysplasia.

The phenotype of our patient is compatible with CDP but does not fit with any of the well-delineated types of CDP. The rhizomelic type, brachytelephalangic type, and tibia-metacarpal type of CDP can be easily excluded based upon the clinical and radiographic features. Asymmetric limb shortening is characteristic for the Conradi-Hünermann type of CDP. However, other features of this disorder such as skin lesions, cataracts, and midface hypoplasia were absent in our patient. Sterol analysis and plasmalogen levels were normal and no mutations were identified in the *EBP* gene. Anisospondyly is a hallmark of dyssegmental dysplasia. Other skeletal anomalies of dyssegmental dysplasia, like micromelia, dumbbell-shaped tubular bones, and a narrow chest, were not observed in our patient. Dysplastic vertebral bodies have been reported in chondrodysplasia punctata, and are attributed to asymmetric calcification and ossification defects of the vertebral bodies. Anisospondyly to a degree as is observed in our patient has to our knowledge never been reported in CDP. We therefore believe that our patient may have a new form of chondrodysplasia punctata.

25- ALKALINE PHOSPHATASE AND SKELETAL DYSPLASIA - 3 DIFFERENT DIAGNOSES -

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Serum tissue non-specific alkaline phosphatase (ALP) activity abnormalities are found in a restricted number of skeletal dysplasias, characteristically associated with bone density interference and possible fracture risk. The authors report 3 clinical cases as examples of 3 different diagnoses in this context.

The Case 1 is a 7 years old girl who developed since the age of 2 years: bowing deformity, bone fractures after small trauma, symmetrical thickening and mild pain in her lower limbs. Growth and psychomotor development were normal and she had no dysmorphisms. Radiologically, there was an irregular diaphyseal dysplasia, long bone bowing and cranium involvement. ALP activity was consistently elevated. Diagnosis of Juvenil Paget's Disease ou Familial Hyperphosphatasia (MIM#239000) was made at the age of 3 years and confirmed by *TNFRSF11B* molecular analysis which identified the homozygous mutation c.349T>C, p.Phe117Leu, afterwards described as the "Iberian mutation". She has bilateral moderate sensorineural deafness with hearing aids since the age of 6 years. The clinical and biochemical response to pamidronate treatment was good.

The Case 2 is a 29 years old woman with short stature, osteopenia, short bilateral 4th metatarsal, ostheoarticular pain and swelling episodes since childhood, coccyx fracture and numerous dental infections. Levels of serum ALP are consistently subnormal. The diagnosis of Hypophosphatasia (MIM#241500) was considered. *TNSALP* molecular analysis revealed a heterozygous mutation c.1426G>A, pE476K, previously associated with lethal hypophosphatasia in homozygosity. Familial studies are being performed in order to clarify the situation.

The Case 3 is a 10 year old boy with obesity, normal stature, macrocefaly, history of large fontanelles, dentition retardation, *coxa vara* surgically corrected, osteopenia and femur pseudarthrosis. There was reduced serum ALP activity. The clinical observation and radiological findings at the age of 9 years were suggestive of Cleidocraneal Dysplasia (CCD, MIM#119600), in accordance with the identification of an unpublished heterozygous mutation c.392G>A, pArg131His in *RUNX2* gene. Features of hypophosfatasia is a known secondary effect of *RUNX2* mutations, found in a subset of patient with severe CCD. No fractures occurred until the moment.

26- RADIOGRAPHIC IMAGING OF THE MUCOPOLYSACCHARIDOSES

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BioMarin Pharmaceutical Inc.

A new era in the treatment of the mucopolysaccharidoses (MPS) has occurred with the advent of enzyme therapy. A case in point is the new treatment Naglazyme® (galsulfase), introduced in 2005 by BioMarin Pharmaceutical Inc, specifically for the treatment of MPS VI. It is apparent that the earlier this therapy is initiated the better the expected results. Therefore it becomes imperative that the clinician (geneticist, pediatrician, radiologist etc.) determines the diagnosis as early as possible. It is also suspected that perhaps certain mildly affected individuals go through life symptomatic but undiagnosed. The diagnosis is usually suggested by a combination of "clinical" and radiographic features. The radiological manifestations play an extremely important role.

The mucopolysaccharidoses have in common a quite specific radiological expression, which is termed "dysostosis multiplex". All types of MPS disease exhibit these findings to a greater or lesser degree. The role of the radiologist and other clinicians is to recognize any of these diverse changes on radiographs so that the patient can be tested to ascertain which MPS disease is present for treatment, genetic counseling and management. Dysostosis multiplex changes are widespread in the skeletal system involving many different bones. At times even the "routine" chest film will reveal changes suggesting the diagnosis of possible MPS disease. This poster presentation will cover the entire skeletal system to show the spectrum of dysostosis multiplex changes suggesting the presence of MPS disease in the individual. Also several previously unreported dysostosis multiplex findings will be shown. Hopefully, our awareness of these findings will result in earlier and even more frequently accurate diagnoses within this group of disorders.

27- ELECTRON MICROSCOPY STUDIES ON SKIN FIBROBLASTS IS A USEFUL AND RELIABLE ADJUVANT TOOL FOR THE DIAGNOSIS OF GELEOPHYSIC DYSPLASIA

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Geleophysic dysplasia (MIM 231050) is a rare autosomal recessive disorder characterized by short-limbed dwarfism, brachydactyly and a "happy-looking" facial appearance. Geleophysic dysplasia is frequently associated with cardiac valvular disease although the incidence of heart complications remains unknown. Infiltration of liver and cardiac leaflets has been reported in some patients. Based on the clinical picture of these patients and the detection of lysosome-like inclusions in different tissues, the underlying cause of the condition is considered to be a generalized lysosomal storage defect. We report the clinical and radiological features of four further cases of geleophysic dysplasia confirmed by the presence of skin fibroblast inclusions on electron microscopy analysis. Two of the four cases are siblings and exhibited significant variability especially with regards to the cardiac involvement. Short stature and brachydactyly were present in all four patients, while laryngeal stenosis was present in two patients and Perthes disease in one patient. Taken together, these findings show a significant interfamilial and intrafamilial clinical variability and are consistent with a broad disease spectrum. No gene is currently known for this disorder and the diagnosis of geleophysic dysplasia is often difficult and mostly based on clinical and radiological findings. We provide evidence that electron microscopy of cultured skin fibroblasts is a useful and reliable tool for the confirmation of the diagnosis until further biochemical or molecular studies become available as a definitive diagnosis for this disorder.

28- THE EUROPEAN SKELETAL DYSPLASIA NETWORK

Jacky Taylor and the European Skeletal Dysplasia Network

Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, Michael Smith Building, Oxford Road, Manchester, M13 9PT, UK.

www.ESDN.org

The European Skeletal Dysplasia Network (ESDN) was established in January 2002 with a grant from the European Commission and with a remit to develop an integrated research and diagnostic network for skeletal dysplasias. Skeletal dysplasias are a diverse and complex group of rare genetic disorders affecting the development of the skeleton. Over 200 different conditions have been described, ranging in severity from mild to lethal. The overall prevalance of these conditions is at least 4 per 10,000, suggesting that at least 180,000 people in the 25 EU member states suffer from these bone diseases.

ESDN continues to link centres of excellence involved in specialist research and/or diagnosis of skeletal dysplasias; Michael Briggs & Rob Elles (Manchester, UK); Geert Mortier (Ghent, Belgium); Michael Wright & Judith Goodship (Newcastle, UK); Valerie Cormier-Daire, Martine Le Merrer & Laurence Legeai-Mallet (Paris, France); Leena Ala-Kokko & Minna Mannikko, (Oulu, Finland); Juergen Spranger & Gabriele Wildhardt (Mainz, Germany); Andrea Superti-Furga, Bernhard Zabel & Sheila Unger (Freiburg, Germany) Luisa Bonafé, (Lausanne, Switzerland), Andreas Zankl (Brisbane, Australia) and Christine Hall (London, UK).

Since January 2002, ESDN has received approximately 2500 patient referrals and performed over 2000 molecular diagnostic tests. From September 2003 over 600 cases have been referred using the ESDN Case Manager; a secure web-based case management system that allows clinicians to submit cases directly to ESDN from anywhere in the world thereby enabling access to expert advice.

In summary, ESDN has successfully demonstrated it can act as a “virtual European centre of reference” for skeletal dysplasias by linking a multi-disciplinary group of clinicians, radiologists and scientists.

29- THE « CENTRE DE REFERENCE DES MALADIES OSSEUSES CONSTITUTIONNELLES », A CHALLENGE FOR PUBLIC HEALTH, A NECESSITY FOR PATIENT'S DIAGNOSIS AND CARE

Geneviève Baujat [(1)], Valérie Cormier-Daire [(1)], Veronique Forin [(2)], Christian Roux [(3)], Marie-Christine de Vernejoul [(4)], Martine Le Merrer [(1)]

*For the contributors to the Center of Reference of skeletal dysplasia **
**Centre de Référence des Maladies Osseuses Constitutionnelles, Hôpitaux, 1 Necker-Enfants Malades, 2 Trousseau, 3 Cochin, 4 Lariboisière, Paris, France*

A disease is considered rare if less than one person out of 2000 is affected, but rare diseases still represent 6-8% of the world population. Insufficient knowledge of the majority of rare disease by health professionals underlies diagnosis errors, a great source of suffering for patients and their families and delayed care provision, which can sometimes be prejudicial.

France launched the National Plan for Rare Disease in November 2004, affected from 2005 to 2008. The plan included the creation of national centres of reference (CR), to improve the somewhat unstructured care situation which previously existed. Criteria for CR, intended for university hospitals, were focused on their provision of expertise and provision of direct care. The CRs have to establish and coordonate a network of expert clinics centers (competence centers) with the intention of increasing the geographic coverage of the CR.

In this aim was labelled in 2004 the center of reference of skeletal dysplasia, coordinated by Dr M. Le Merrer, Paris, and including 2 paediatric sites (Necker-Enfants Malades Hospital and Trousseau Hospital) and 2 adult sites (Cochin Hospital and Lariboisière Hospital). The missions of the CR, currently in progress, include:

- To increase knowledge of the epidemiology of rare diseases through a specific rare disease database, named CEMARA, to better appreciate natural history and evaluation of the needs.
- To be an expert diagnostic center and to improve the organisation of screening and access to diagnostic tests
- To organize the global management of the patients including orthopaedic, rhumatologic, endocrinologic, neurosurgical, genetic, and general follow up for each osteochondrodysplasia ; establishment of specific practice guildlines in collaboration with the "Haute Autorité de Santé" (High Health Authority).
- To facilitate the transition between paediatric and adult teams in charge of the follow-up, by specific multidisciplinary clinics "de transition" for young adult patients.
- To improve specific accompaniement resources (in terms of educational, familial, and social aspects) for people suffering from these rare diseases.
- To provide psychological care for patients and their families, especially when diagnosis annoucement takes place.
- To teach and diffuse among the country knowledge about skeletal dysplasia.
- And to participate to specific research programs (clinical, therapeutic, social studies) on unknown skeletal dysplasia especially with european and international partnerships and with patients associations.

Up to date, the clinical activity, shared between the 4 sites of the CR, includes the diagnosis of 600 new patients a year and 3000 patients with a regular follow up trough clinics, day or traditional hospitalisations. These results and realizations will be evaluated by an independant expert commission at half- and end course of the National Plan.

30- SKELETAL DYSPLASIAS IN A REFERRAL PEDIATRIC HOSPITAL IN ARGENTINA

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Skeletal dysplasias (SD) is a heterogeneous group of genetic diseases affecting bone development, and associated to a great variety of clinical problems, such as short stature, skeletal deformities, and social integration difficulties. In Buenos Aires, our multidisciplinary group provides continuous health care to this group of patients ever since the hospital foundation, in 1987. The team is composed of geneticists, paediatricians, orthopaedic surgeons, auxologists, physical therapists, and experts in symptomatic treatment; it works with the support of a laboratory of precision anthropometrics and of molecular genetics. The team also develops teaching and research activities. The out patient clinic on SD is attended by an average of 120 patients per month, referred from all over the country. Up to the present time, the following number of patients have been registered: Achondroplasia: 176, Osteogenesis Imperfecta: 197 ,Hipochondroplasia 41,Metaphyseal Dysplasias: 38, MED 37 ,Multiple Exostosis 30,Pseudoachondroplasia 25 , MPS 21 and other conditions (Total : 1091)

Due to the position of the hospital within the national public health network, we estimate indirectly that these figures represent approximately 40 % of all SD patients in the country.

31- SPINAL MANIFESTATIONS IN WINCHESTER SYNDROME: ATLANTOAXIAL SUBLUXATION AND DURAL ECTASIA

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Winchester syndrome is an inherited osteolysis syndrome characterized by multicentric osteolysis and other connective tissue abnormalities, such as subcutaneous nodules and corneal opacities. Spinal manifestations in the syndrome have attracted very little attention, other than osteoporosis and compression fractures. The aim of this presentation is to discuss unique and new findings shown at the spine MRI in a patient confirmed as having Winchester syndrome.

The patient is a 31-year-old Korean woman born to a nonconsanguineous marriage, presenting with extreme shortening of the trunk and limbs with fixed flexion of the elbows and wrists, and stiff knees. All fingers and toes were telescoping. Skeletal survey revealed severe generalized osteoporosis with destruction and resorption of the phalangeal and carpotarsal bones, and ankylosis in the elbows, hip and knee joints. The vertebrae showed osteoporosis, mild compression fractures, and scalloping of the vertebral body posteriorly in the lumbar spine. She complained of back pain and tingling sensation on the upper extremity. Spine MR imaging showed osteolysis of the odontoid process with atlantoaxial subluxation. Furthermore, the thoracolumbar spine showed apparent dural ectasia, more severely affected in the lumbar spine. Both atlantoaxial subluxation and dural ectasia have not been described in the literature. A molecular analysis for this patient confirmed a missense homozygous mutation in *MMP2* (Gly406Asp).

Recently *MMP2* has been shown to play a specific role in elastolysis, and its activity is considered to be important in the maintenance and remodeling of connective tissue contents. In this context, we also briefly comment probable interaction between defective *MMP2* and degradation in collagen content of the dura resulting in development of dural ectasia in Winchester syndrome.

32- HEALTH SUPERVISION FOR CHILDREN WITH SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA AND RELATED DISORDERS

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The Spondyloepiphyseal Dysplasias (SED's) are a diverse group of disorders which collectively have a frequency similar to Achondroplasia. This group of disorders share potential musculo-skeletal complications which may be managed expectantly to prevent long term disability. There are key periods (windows of opportunity) to prevent disabling or life threatening complication. We have prepared draft health supervision guidelines for SED congenita and other SED's. Anticipatory management can prevent or eliminate these potentially disabling complications. We seek the endorsement of the ISDS for a working group to establish guidelines on an international basis.

Cervical instability
This is a progressive feature in the SED's which are characterized by odontoid hypoplasia. It is aggravated by joint hypermobility, a variable feature of SED congenita (Spranger-Wiedemann) but present in many other forms of SED including SED with joint laxity. Dislocation is rare in Pseudoachondroplasia. Avoidance of activities which are at high risk of neck injury and special care when anaesthetized is advised. Early occipito-cervical fusion may be necessary. In our Centre this has been necessary from 18 months of age in an occasional patient.

Hip dysplasia
The SED's are complicated by progressive varus of the femoral neck. Management is compounded by the extreme delay in ossification of the proximal femoral epiphyses in most SED disorders. In our Centre virtually all subjects with SEDC have surgical correction of hip varus in late childhood.

Myopia
While usually mild, many subjects with SED's have myopia. A high morbidity is associated with myopia in Kniest dysplasia. Two patients in our experience have developed retinal detachment at an early age.

33- MULTIPLE EPIPHYSEAL DYSPLASIA (MED) WITH CERVICAL SPINE INSTABILITY IN A FAMILY

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Multiple epiphyseal dysplasia (MED) is a group of skeletal dysplasias with mild short stature and earlier than usual onset large joint arthropathy. Radiographically, the epiphyses are the most significantly affected – small, irregular, late-ossifying. There can be mild degenerative changes in the spine – mild irregularity of the end plates of the vertebrae, and Schmorl nodes in the second and third decades. Unlike many of the other skeletal dysplasias (including pseudoachondroplasia), cervical spine instability has not been reported with this condition.

We report a family with 3 generations of individuals manifesting MED in which multiple members have been noted to have cervical spine instability. Our proband is a 16 year old, African-American female with MED and the commonly associated avascular necrosis of the capital femoral epiphysis and significant chronic hip pain. Family history revealed the following members to be affected with MED: mother, 2 maternal aunts, maternal uncle, maternal grandmother, great uncle and multiple cousins.

In 2005, the family informed us that the patient's maternal uncle with MED had required a cervical spine fusion. Subsequent imaging of the proband showed gross instability at the C1-C2 vertebrae levels with significant narrowing of the neural canal on flexion views and an ossiculum terminale of the odontoid. Cervical fusion has been recommended by our clinic team, but refused by the family. Review of the affected mother's cervical spine films show a hypoplastic odontoid, but no instability. The family reports that in addition to the maternal uncle the maternal grandmother and great uncle also have cervical spine instability. The clinic has not yet received radiographic images to confirm this history.

To date, the family has not yet had molecular testing. Based on the radiographic findings in this autosomal dominant family, a mutation in COL9A1 or Matrillin is thought to be more likely than a mutation in COMP.

Discussion: Cervical spine instability is a feature of many of the skeletal dysplasias. MED is a group of disorders, some of which have COL9 defects, matrillin defects and even a small number with COMP defects, which are all autosomal dominant conditions. More recently, an autosomal recessive form of MED has been described with a DTSDT molecular defect (diastrophic dysplasia gene abnormality). Although the radiographic features of this family are more like those seen in MED due to COL9 defects, we will be testing this family for defects in all AD associated gene defects (COMP, COL9, MATN) realizing that pseudoachondroplasia which is caused by defects in the COMP gene has associated cervical spine instability.

This appears to be the first reported family with cervical spine instability in MED patients. We would welcome information from anyone who has seen this rare combination.

34- REPORT: FIRST REPORTED CUSTOM TOTAL HIP REPLACEMENT IN A 14 – YEAR-OLD MALE WITH MUCOPOLYSACCHARIDOSIS TYPE IH (MPS IH, OR HURLER SYNDROME) POST BONE MARROW TRANSPLANT

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Purpose Mucopolysaccharidosis type IH (MPS IH), also known as Hurler syndrome (OMIM 607014), is an autosomal recessive progressive lysosomal storage disorder caused by deficiency of the enzyme α-L-iduronidase. This enzyme is responsible for normal degradation of the glycosaminoglycans (GAGs) heparan and dermatan sulfate, long chains of complex sugars with structural roles in connective tissue, cartilage, and the extracellular matrix of our tissues. Lysosomal accumulation of GAGs results in progressive organ dysfunction, widespread tissue damage, and physical and mental disability. Individuals with untreated Hurler syndrome present with progressive developmental delay, corneal clouding, airway obstructions, cardiac disease, hepatospelnomegaly, and dysostosis multiplex. Most die in the first decade of life from infections, aspiration, or cardiac failure. Bone marrow transplantation (BMT) performed before 24 months of age can ameliorate visceral and soft-tissue manifestations, halt cognitive deterioration, and increase life expectancy, but has no effect on skeletal manifestations. We present a 14 year-old male who was diagnosed with Hurler syndrome at 10 months of age by enzymatic testing and subsequently underwent an allogenic bone marrow transplant at age 16 months. Surgical history includes corneal transplant, tonsillectomy and adenoidectomy, trigger digit releases, bilateral femoral and pelvic osteotomies, lumbar spine fusion 2002 (L1-L4), laminectomy with decompressive diskectomy, and epiphyseal stapling of bilateral lower extremities for valgus deformity. Other pertinent history includes mitral valve prolapse, unilateral corneal clouding, and irritable bowel syndrome. He attends regular 9th grade classes at school. Until recently he ambulated on his own, but had been using a wheelchair and walker prior to surgery due to pain. He presented with low back pain, bilateral hip pain which markedly increased over the prior 9 months and marked right hip dysplasia.

Methods Patient underwent custom right total hip replacement with custom cemented stem and acetabular cup. The right femoral head, approximately 4.1 cm in diameter with approximately 2 cm of neck attached was sectioned and stored in EtOH (Fourier Transform Infrared studies pending), electron microscopy fixative, formalin, and formalin-cetylpyridinium chloride (for light microscopy studies).

Results The right femoral head, approximately 4.1 cm in diameter with approximately 2 cm of neck attached was sectioned and stored in EtOH (Fourier Transform Infrared studies pending), electron microscopy fixative, formalin, and formalin-cetylpyridinium chloride (for light microscopy studies). Examination of these articular bone and synovium samples show a thoroughly degenerate, dysplastic joint. The articular surface shows irregular nodular proliferation of the cartilage, which was mostly smooth, interspersed with regions of deep fissuring and loss of the articular cartilage. No osteophytes were present. The attached synovium was generally smooth and semi-gelatinous. Articular cartilage in cut section was bluish white and ranged in thickness up to 3 mm. Subarticular bone showed residual growth plate cartilage and disruption beneath the exposed surfaces. Bone marrow reamings were stored in formalin. Hematopoietic bone marrow showed trilineage maturation with no sign of excess GAG accumulation. No excess plasma cells or granulomas were present. It is not clear whether the described histopathologic changes are primary to the disorder or secondary to degenerative arthritis.

Conclusion The first successful bone marrow transplant in a patient with Hurler syndrome was completed in 1981. As this patient population ages beyond the life expectancy for untreated patients with Hurler syndrome, we expect an increased need for orthopaedic intervention to preserve quality of life and independence in activities of daily living for these patients. Previous studies have identified progressive hip deformity in these patients, in some cases requiring surgical containment procedures. Our patient's clinical phenotype is consistent with bony manifestations of Hurler syndrome. It appears that bone marrow transplant does offer some protection based on lack of GAG accumulation in the samples studied. It is not clear whether the described histopathologic changes are primary to the disorder or secondary to degenerative arthritis. **Significance** We present the first reported total hip replacement in a patient with Hurler syndrome.

35- AGE-APPROPRIATE BODY MASS INDEX (BMI) AND HEIGHT VELOCITY IN CHILDREN WITH ACHONDROPLASIA

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Objective : To examine body mass index (BMI) in relation to indices of height, develop age-appropriate BMI charts for clinical use, and quantify height velocity from birth through 16 years in individuals with achondroplasia.

Methods : An anthropometry database was created from longitudinal, retrospective, single observer data extracted from clinical records of 334 individuals with achondroplasia from birth through 16 years of age. BMI was calculated (weight, kg/height, m^2) at every point at which a simultaneous weight and length/height was available. Growth velocity was calculated as the change in height over the time interval between every two consecutive height values, provided the time interval was >2 months but <18 months. Velocity was plotted at the midpoint of the age interval between the two height measurements.

Results : Data were analyzed from 241 and 236 subjects contributing 1935 BMI and 1846 height velocity datapoints, respectively. Percentiles (5, 50, 95th) were estimated across the age continuum by gender, using a one month window ($\pm$ 0.5 months) around each time point of interest. Percentiles were smoothed by a quadratic smoothing algorithm. BMI and height velocity data from the achondroplasia cohort are compared to that of age- and gender-matched average stature children. From 2 through 8-9 years of age, the entire BMI distribution (5-95%ile) of achondroplasia individuals lies above the 95th percentile of their average-stature peers. Up to 16 years of age thereafter, the lower half of the achondroplasia BMI distribution (ie. up to the 50th percentile) overlaps the upper half of the average stature BMI distribution (ie. beyond the 50th percentile). A BMI peak in infancy and nadir in childhood are not observed in achondroplasia as in average stature children. While length at birth is not substantially different between achondroplasia and average stature norms, height velocity in achondroplasia individuals is dramatically compromised during infancy. Similarly, height velocity is compromised in achondroplasia from late childhood through age 16 years, while comparable to average stature norms in mid-childhood.

Conclusions : In the current era of obesity awareness, average stature BMI curves overestimate the body fatness of individuals with achondroplasia due to the decreased contribution of lower extremity length to this measurement, and thus average stature BMI norms cannot be applied to the achondroplasia population. Height velocity in individuals with achondroplasia is most compromised during infancy and in the peripubertal period, with birth length and mid-childhood height velocity comparable to that of average stature peers.

36- A PATIENT WITH OPSISMODYSPLASIA TREATEDWITH PAMIDRONATE

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Opsismodysplasia is a rare chondrodysplasia characterized clinically by micromelia, brachydactyly and the development of respiratory failure during the first few years of life. The primary radiologic manifestations include severe platyspondyly, significantly delayed skeletal ossification and metaphyseal irregularity with cupping. Autosomal recessive inheritance has been suggested. The molecular etiology of opsismodysplasia is not known.

We present a 4 ½ year old boy with features of opsismodysplasia who has been treated with pamidronate therapy for 10 months. He is the only child to his consanguineous parents. He has disproportionate short stature with micromelia and a small chest. He requires mechanical ventilation secondary to respiratory failure. He has relative microcephaly, an enlarged anterior fontanel, prominent forehead and short nose with depressed nasal bridge. His motor skills are delayed. His radiographs show diffuse demineralization with relative sparing of the skull and mandible, marked platyspondyly, short tubular bones with diffuse cortical thinning, severe metaphyseal irregularity and cupping and absent secondary ossification centers. He has hypophosphatemia and mildly elevated parathyroid hormone and alkaline phosphatase. His normal laboratory studies include total calcium, vitamin D level, 1-25 dihdroxy vitamin D, karyotype, PTH/PTHrP and PHEX sequencing, 8(9) cholestenol, very long chain fatty acids, plasmalogen and type I and III procollagen analyses. He was initiated on pamidronate therapy at 3 years 8 months. His bone mineral density improved 26.9% to his lumbar spine following 3 months of treatment. After 7 months of treatment his radiographs revealed improved bone mineralization and the progressive development of secondary ossification centers.

37- GENTAMICIN MEDIATES READTHROUGH OF PREMATURE TERMINATION CODON IN STÜVE-WIIDEMANN SYNDROME

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Stüve-Wiedemann syndrome (SWS) is a severe autosomal recessive disorder characterized by bowing of the lower limbs, camptodactyly and dysautonomia symptoms often responsible for death in the first years of life. Studying a large series of SWS families, we have identified the LIFR gene as the causative gene for SWS. Binding of LIF to the LIFR complex is known to induce the activation of the JAK/STAT3 pathway and we have previously shown that the LIFR mutations are responsible for an impairment of the JAK/STAT3 pathway. Up till now, we have identified LIFR mutations in 45 SWS patients including 25 distinct mutations. Among these mutations, six are non sense mutations.

In the last several years, aminoglycosides have been shown to induce mammalian ribosomes to readthrough premature termination codons (PTC). We have therefore decided to test the restoration of full length LIFR protein synthesis in the presence of gentamicin in fibroblasts from SWS patients with premature stop codons. Fibroblasts from three different patients and controls have been cultured in presence of gentamicin during 48H. They have been then incubated in serum free medium for 12 H and stimulated with 20 ng/ml of LIF during 15 minutes. The restoration of the LIFR function has been finally tested by Western blot analysis of the activation of STAT3 using an antiphospho (tyr 705)-STAT3 antibody. We have found a partial JAK/STAT3 pathway restoration after 48H treatment with 200 or 500 µg/ml of gentamicin. This restoration was estimated up to approximately 5 % of control fibroblast STAT3-P signal when cells were cultured with 500 µg/ml of gentamicin. Furthermore, we have tested the stability of LIFR mRNA of patient fibroblasts treated with or without 200 µg/ml of gentamicin. Quantitative RT-PCR analysis revealed that this aminoglycoside was able to stabilize mRNA containing UGA premature termination codon with a 3-fold stabilization factor in the fibroblasts from two SWS patients. The present *in vitro* study is a prerequisite for future clinical trials using aminoglycosides or other less toxic molecules in this severe disorder.

39- EXPERIENCE WITH LARONIDASE TREATMENT IN 5 MPS I PATIENTS WITH VARIOUS PHENOTYPES AND INDICATIONS

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Patients: patients 1, 2 and 3 (14, 11, and 3 years old) presented with an attenuated Scheie phenotype. Patient 1 suffered visual loss due to optic nerve compression. Patient 4, a 2 years old boy with a severe Hurler phenotype presented with an impaired psychomotor development. ERT has been proposed while waiting for bone marrow transplantation (BMT). Patient 5, 15 years old, Hurler patient underwent successful BMT at age of 5, but displayed a severe progressive pulmonary disease with life threatening pulmonary hypertension and poor general condition.

Methods: All patients have been treated by a weekly infusion of laronidase. Clinical outcome was assessed according a detailed protocol.

Results: At this stage of treatment (30, 26 and 21 months for patients 1, 2 and 3; 9 months for patients 4 and 5), no adverse effects occurred. Urinary GAG levels were high and decreased for all patients except for patient 5 who had low GAG before treatment. Patients 1, 2 and 3 showed improved joint mobility and better exertion tolerance. Eyesight improved dramatically for patient 1. Patient 4 continued to decline neurologically. Patient 5 showed a better joint mobility and was able to stand and walk. Pulmonary hypertension improved. No efficacy has been observed in bone deformities.

Conclusion: our data are in line with the reported efficacy of ERT in patients with the mild (Scheie) phenotype. Further follow-up is needed for assessment of ERT in the severe Hurler patients with neurological impairment and in transplanted patients with progressive symptoms in which ERT may have a positive effect.

ADRESSES

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