Welcome to Los Angeles!

This conference is the 3rd of the International Skeletal Dysplasia Meetings. The first meeting was organized by Andrew Poznanski in Chicago in 1993 and the second meeting was organized by Pierre Maroteaux in Versailles in 1995. We hope that this tradition will continue with the meetings occurring every two years.

This year's meeting has been divided into three separate sections. Thursday's program is devoted to clinical aspects of the skeletal dysplasias, Friday's session to biochemical and molecular aspects and Saturday morning's session to treatment and complications of the skeletal dysplasias. In addition, there is an unknown case session at the end of the Thursday afternoon program.

The posters will be available for display throughout the meeting. They will be displayed in a special tent in the tennis court area of the hotel. Each of the poster's authors have been assigned a half hour between 5:00 and 7:00 p.m. on Thursday, August 7th to be standing by their posters. Unknown cases that were submitted for presentation but not included in the platform presentation, will be displayed as posters as well. In addition, there will be a table containing a slide projector and x-ray view box for informal consultations on individual cases.

On Thursday evening during the 5:00-7:00 p.m. poster session, there will be wine and cheese available. On Friday evening, there will be a special reception at the Hollywood Bowl, one of Los Angeles' great venues. Buses will leave from the hotel at 5:15 p.m. for the Hollywood Bowl where there will be a reception and dinner in their patio area. At 8:30 p.m., the program will begin with San Francisco's Ballet production of Swan Lake, Act II followed by Tchaikovsky's Overture - Fantasy, Romeo and Juliet and 1812 Overture with fireworks and marching band. The dress is casual, but the evening may be cool, so bring a jacket. The reception is included in the general registration cost, but any accompanying members must buy an individual ticket to the reception which are limited in number.

We would like to thank Bari Laner, Sue Lane and Maryann Priore for all their hard work in organizing this meeting.

We hope this will be a most informative and interactive conference.

David L. Rimoin, M.D., Ph.D.

Ralph S. Lachman, M.D.

WE GRATEFULLY ACKNOWLEDGE

MARCH OF DIMES

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IN SUPPORT OF THIS MEETING

PROGRAM

THURSDAY, AUGUST 7, 1997
CLINICAL STUDIES

8:30-10:30 a.m.	MODERATOR – DAVID RIMOIN	
8:30	The New International Nomenclature	David Rimoin
9:00	Diagnosing Skeletal Dysplasias	Christine Hall
9:30	The Same and Not The Same - Cone Epiphyses	Andres Giedion
10:00	Oculo-Facio-Cardio-Dental (OFCD) Syndrome, Otodental Syndrome and Lobodontia - Dental Disorders of Interest to the Pediatric Radiologist	Robert Gorlin
10:30	COFFEE BREAK	
10:45-12:00 Noon	MODERATOR – RALPH LACHMAN	
10:45	Regressive Metaphyseal Dysplasias: Further Delineation	Martine Le Merrer
11:15	Congenital Osteolysis Syndromes	Andrew Poznanski
11:45	Natural History of Cervical Kyphosis in Diastrophic Dysplasia	Ville Remes
12:00 Noon-1:30 p.m.	LUNCH	
1:30-3:30 p.m.	MODERATOR – ANDREW POZNANSKI	
1:30	Progressive Craniocervical Deformation in Osteogenesis Imperfecta	David Sillence

(cont'd Thursday)

2:00	Clinical Care for Skeletal Dysplasias in the Managed Care Environment	Judith Hall
2:30	Diaphyseal Medullary Stenosis with Bone Malignancy	Karen Norton
2:45	Spondyloepimetaphyseal Dysplasia with Flocky Epiphyseal Calcification, Advanced Carpal Ossification, and Congenital Hydrocephalus	Gen Nishimura
3:00	Five Cases of Stüve-Wiedemann Syndrome	Valerie Cormier-Daire
3:15	Radiographic Features of Genotyped Achondroplasia and Hypochondroplasia Patients	Yoshito Matsui
3:30	COFFEE BREAK	
4:00-5:00	Unknown Cases for Diagnosis and Workup	
	MODERATOR – RALPH LACHMAN Panelists	 Andres Giedion Christine Hall Andrew Poznanski
5:00-7:00	Poster Session with Wine & Cheese Reception	
	Posters 1-18	5:00-5:30 p.m.
	Posters 19-37	5:30-6:00 p.m.
	Posters 38-57	6:00-6:30 p.m.
	Posters 58-74	6:30-7:00 p.m.

FRIDAY, AUGUST 8, 1997
BIOCHEMICAL AND MOLECULAR STUDIES

8:00-10:30 a.m.	MODERATOR – DANIEL COHN	
8:00	Experimental Approaches to Studying Achondroplasia	William Horton
8:30	A Splice Site Alteration in the Fibroblast Growth Factor Receptor 3 (FGFR 3) Gene is Associated with Proportionate Non-syndromic Short Stature	Clair Francomano
9:00	Molecular, Radiologic, and Histopathologic Correlations in Thanatophoric Dysplasia	William Wilcox
9:15	Biochemical Effects of Mutations in FGFR3 which Cause Skeletal Dysplasias	Leslie Thompson
9:30	Molecular Basis of the Most Common Craniosynostosis Syndromes	Max Muenke
10:00	TWIST Mutations Disrupting the b-HLH Domain are Specific to Saethre-Chotzen Syndrome	Arnold Munnich
10:30	COFFEE BREAK	
10:45-12:00 Noon	MODERATOR – JURGEN SPRANGER	
10:45	A Key to Bone Development: The Gene for Cleidocranial Dysplasia - CBFA1 - is Essential for Osteoblast Differentiation and Skeletal Patterning	Stefan Mundlos
11:15	Mutations in the Osteoblast-Specific Transcription Factor OSF2/CBFA1 in Cleidocranial Dysplasia	Brendan Lee
11:30	Mutations In and Around the SOX9 Gene in Campomelic Dysplasia: A General Lack of Genotype/Phenotype Correlations	Gerd Scherer
11:45	Pycnodysostosis: Identification of Novel Disease-Causing Mutations in the Pro and Mature Polypeptide Regions Encoded by the Cathepsin K Gene	Bruce Gelb
12:00 Noon-1:15 p.m.	LUNCH	

(cont'd Friday)

1:15-3:00 p.m.	MODERATOR – CLAIR FRANCOMANO	
1:15	The Molecular Genetic Analysis of Brachydactyly Type C	Matthew Warman
1:45	Abnormal Limb Development in Grebe Syndrome Caused by Mutations in CDMP-1	Petros Tsipouras
2:00	Sulfate Transporter Chondrodysplasias: The Mosaic Pieces Fall Into Place	Andrea Superti-Furga
2:30	Tracing the Biochemical Pathogenesis of *DTDST* Chondrodysplasias: Correlations Between Residual Transporter Activity *IN VITRO*, Degree of Undersulfation in Cartilage and Clinical Phenotype	Antonio Rossi
2:45	Linkage of Multiple Synostoses to Chromosome 17Q21-22	Deborah Krakow
3:00	COFFEE BREAK	
3:15-4:45	MODERATOR – ARNOLD MUNNICH	
3:15	The Type XI Collagenopathies	Jurgen Spranger
3:45	Structurally Abnormal Type II Collagen in a Severe Form of Kniest Dysplasia Caused by an Exon 24 Skipping Mutation	David Eyre
4:00	Mutations in the Pseudoachondroplasia - Multiple Epiphyseal Dysplasia Disease Spectrum	Dan Cohn
4:30	Synthesis of Cartilage Oligomeric Matrix Protein (COMP) by Cultured Cells from Patients with Pseudoachondroplasia and Multiple Epiphyseal Dysplasia	Emmanuele Delot
4:45	ADJOURNMENT	
5:15	Buses leave for Hollywood Bowl - Dinner and Concert TCHAIKOVSKY SPECTACULAR with fireworks Hollywood Bowl Orchestra John Mauceri, conductor San Francisco Ballet USC Trojan Marching Band Swan Lake, Act II Overture-Fantasy, Romeo and Juliet 1812 Overture with fireworks	

SATURDAY, AUGUST 9, 1997
TREATMENT AND COMPLICATIONS

8:00-10:15 a.m.	MODERATOR – JUDITH HALL	
8:00	New Techniques for Limb Lengthening and Realignment for Skeletal Dysplasias	Dror Paley
8:45	Extended Limb Lengthening in the Skeletal Dysplasias - The Barcelona Experience Lumbar Canal Stenosis in Achondroplasia	Albert Gomez Prat
9:15	Limb Lengthening - The Cedars-Sinai Experience	Joseph Isaacson
9:30	Function and Alignment of the Lengthened Limbs in Patients with Achondroplasia and Hypochondroplasia	Natsuo Yasui
9:45	Clinical Use of Human Growth Hormone in Achondroplasia	Deborah Krakow
10:00	Growth Hormone Treatment Trial of Children with Types III and IV Osteogenesis Imperfecta	Joan Marini
10:15	DISCUSSION: Limb Lengthening and Growth Hormone Therapy	
10:30	Coffee Break	
10:45-12:00 Noon	MODERATOR – MARTINE LE MERRER	
10:45	Medical Complications in Achondroplasia	Alasdair Hunter
11:00	Gait Analysis Before and After Tibial Osteotomy in Children with Achondroplasia	Vernon Toio
11:15	Seizures Presenting as Apnea in Nine Infants with Achondroplasia	Orest Hurko
11:30	Comparison of MRI and Myelo-CT in the Evaluation of Spinal Stenosis in Achondroplasia	Ilhan Elmaci
11:45	Upper Airway Obstruction in Achondroplastic Infants and Children	Eugene Flaum
12:00 Noon	Closing Remarks and Adjournment	Ralph Lachman David Rimoin

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Judith Hall, M.D. - Lilly, Genentec

Dror Paley, M.D. - Smith & Nephew Orthopedics

DIAGNOSING SKELETAL DYSPLASIAS

C. Hall
Great Ormond Street Hospital for Children NHS Trust

I would like to present a clinical evaluation of a Knowledge Based (expert) system for diagnosing skeletal dysplasias.

Skeletal dysplasias and malformation syndromes are rare individually. Some 200 skeletal dysplasias and of the order of 2000 malformation syndromes with significant abnormalities are currently recognized. As a group, they occur frequently, affecting about 1% of the population. Early and accurate diagnosis is vital if appropriate management, treatment and counseling are to be offered. It has been shown that interpretation of the radiographic findings is crucial in establishing an accurate diagnosis. Radiological expertise in the diagnosis of these conditions is rare and diagnosis using standard text books and databases is difficult. The economic costs of misdiagnosis are difficult to estimate but they are considerable. The human costs are even more difficult to quantify.

For the purposes of this clinical trial, the material consisted of 32 radiographic skeletal surveys of the sclerosing and cranio-tubular disorders, comprising 19 different conditions. The diagnoses were verified by experts in the field. For the trial protocol, 8 general radiologists assessed two groups, each consisting of 8 cases. One group of cases was assessed using books and the other using the expert system. The results were grouped under the following categories: Correctly identified (CI), correctly suggested (CS), no suggestion (NS), incorrect suggestion (IS) and incorrect concluded (IC).

The measure of correct outcome included all cases where the correct diagnosis was given in the top three diagnostic possibilities. A measure of unfavourable outcomes was inferred from the sum of IS + IC. The summed unfavourable outcome using books was 29. The sum of unfavourable outcomes using the expert system was 9. Statistical analysis showed that the use of the system was significantly more accurate ($P>0.005$). These results compare favourably with previously reported clinical trials.

Some problems and future implementations will be discussed.

THE SAME AND NOT THE SAME

A. Giedion.
Kinderspital Zürich, Switzerland

Analysis of the phalangeal cone shaped epiphyses of the hand (PhCSEH) and their distribution (formula) of 3 dysplasias well defined by cytogenetic or molecular genetic characteristics (65 cases with Cartilage-Hair Hypoplasia (CHH), 70 cases with Tricho-Rhino-Phalangeal-Syndrome I (TRP I), 12 cases of TRP II was performed. This included 30 longitudinal studies over up to 45 years as well as familial comparative studies, 15 families with TRP I with parents and or siblings, 14 families with CHH with siblings affected. The results of this multidimensional approach were: 1. All three dysplasias showed in almost 100% a characteristic pattern of PhCSEH with a "heraldic leader" within a quite typical group of other types, thus forming a "clan" of cones, the ones of TRP I and II however beeing near identical. The number of PhCSEH varied considerably (1-14), but the "leader", always among the midphalanges, and usually on the index finger, invariably was present. 2. PhCSEH "mature" to their diagnostic shape, which is usually reached between 5-7 years but is lost with physeal closure. A strikingly abnormal pattern heralding future cones may be recognized already in the first year of life, sometimes visible only with the magnifying glass, and characteristic types of basal infolding or excavation of the phalangeal metaphysis together with the associated local brachyphalangy allow a retrospective diagnosis of some types of cones in the adult. 3. Some correlation between the extent of "coneing" and clinical severity of the clinical picture was observed among siblings. No significant difference between the formula of the TRP's and that of type 12 peripheral dysostosis (Shore-Brailsford) (12 cases) was found. Various characteristic "clans" of other dysplasias are presented.

OCULO-FACIO-CARDIO-DENTAL (OFCD) SYNDROME, OTODENTAL SYNDROME AND LOBODONTIA - DENTAL DISORDERS OF INTEREST TO THE PEDIATRIC RADIOLOGIST

R. J. Gorlin.
Department of Oral Sciences, University of Minnesota School of Dentistry, Minneapolis, Minnesota, USA

Oculo-facio-cardio-dental syndrome is characterized by congenital cataracts with secondary glaucoma, pointed nose with separation of terminal cartilages, ASD/VSD, floppy mitral valve, submucous cleft palate, syndactyly of toes 2-3, and canine teeth with marked radiculomegaly. Less common findings include septate vagina and sensorineural hearing loss. Since all known examples are female and since there is mother-daughter transmission, X-linked dominant, lethal in the male, inheritance is possible. Several cases will be illustrated. The otodental syndrome combines sensorineural hearing loss and gigantism of tooth crowns, at times producing odontomas. Inheritance is autosomal dominant. Lobodontia is an autosomal dominant disorder of teeth in which crown form is similar to that of a wolf.

REGRESSIVE METAPHYSEAL DYSPLASIAS : FURTHER DELINEATION

Martine Le Merrer , Pierre Maroteaux . U 393 Hopital des Enfants Malades ,149 rue de Sèvres Paris 75015

Metaphyseal chondrodysplasia is an heterogeneous condition with flaring and variable irregularities of metaphyses and normal vertebrae . Several well definied entities have been clearly delineated on radiological criteria or with associated extraskelettal clincal features .Usely a progressive dwarfing due to deceleration of the long bone growth during the second year is the first finding of the disease and on Xrays the metaphyseal changes are evolutive. In the newborn these changes are often absent or very moderate.

In contrast in an other group of metaphyseal dysplasia the metaphyseal changes are very striking at birth and progressivly disappear during the growth which is almost normal.

P Maroteaux et al in 1991 definied a new type of this group and proposed the name of *metaphyseal anadysplasia* . The diagnosis is possible in the first months on the irregularities of the distal metaphyses of the long bones and on the hypoplastic femoral neck . These features disappear after two years . Stature is not affected and the mode of inheritance is probably Xlinked recessive .We described here an other form of these regressive metaphyseal dysplasias on six children ,3 boys and 3girls . At birth or during the first months metaphyseal changes were already present . Clinically there was enlarged costochondral junctions and knobby wrists.

On Xrays the metaphyseal limit was enlarged and irregular like a finetooth comb specially on the knee and the wrist .The upper femoral metaphyse is blurred . The iliac crests are also irregular ,but the hand and the vertebral bodies were normal . Biological data namely calcium, phosphate, alkaline phosphatase levels were normal .The height was normal at birth and further growing remain almost on the mean. During the evolution the irregularities of the metaphyses decreased and they became progressively normal .No familial cases were observed and both sex were affected .

We propose the name of *anadysplasia type 2* for this entity which is distinct from the previous description by the radiological aspect of the femoral neck and the metaphyse at birth .

CONGENITAL OSTEOLYSIS SYNDROMES

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There are a number of osteolysis syndromes which can be differentiated by the location of bone or joint involvement as well as by associated abnormalities. Carpal and tarsal osteolysis is seen in autosomal dominant and recessive forms. It is called Carpal-tarsal osteolysis or Multicentric Osteolysis since other joints such as the knee or elbow may also be involved. Osteolysis which involves primarily the distal phalanges (acroosteolysis) is seen in the Hajdu-Cheney syndrome (AD), mandibuloacral syndrome (AR), juvenile hyaline fibromatosis, pachydermoperiostosis, progeria, pyknodysostosis, Rothmund-Thompson syndrome, Singleton-Merten syndrome and Werner syndrome. It may also be seen a number of congenital conditions which may have acquired acroosteolysis including Lesch-Nyhan syndrome, epidermolysis bullosa and congenital indifference to pain. Carpals, tarsals and interphalangeal joints are involved in the Torg and Winchester syndromes. In the Torg syndrome one of the characteristic findings which helps to distinguish it from other disorders is poor modeling of the metacarpals which results in wide metacarpal diaphyses. Osteolysis syndromes affecting other bones includes the Gorham syndrome, Juvenile hyaline fibromatosis and familial expansile osteolysis. There are also many acquired causes of osteolysis, particularly juvenile rheumatoid arthritis which may be difficult to differentiate from carpal-tarsal osteolysis or Torg syndrome in their early stages. Acquired disorders associated with acroosteolysis may occur in frost bite, burns, ionizing radiation, chemical exposure (as in polyvinyl workers), repetitive trauma (as in guitar players), neurotropic disorders, hyperparathyroidism, vascular causes (as in meningococcemia, Kawasaki disease and scleroderma), leprosy, psoriasis, sarcoid, and plantar wart syndrome. Congenital short distal phalanges which can mimic acroosteolysis may be seen in brachydactyly B, amniotic bands, fetal dilantin syndrome, Adams-Oliver syndrome, Coffin Siris syndrome and Keutel syndrome.

NATURAL HISTORY OF CERVICAL KYPHOSIS IN DIASTROPHIC DYSPLASIA

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Hospital for Children and Adolescents, Helsinki University

Introduction: Diastrophic dysplasia (DD) is an autosomal recessive type of skeletal dysplasia, characterized by disproportionate short stature, foot and spinal deformities and generalized joint deformities. Cervical kyphosis, which can in the most severe cases even lead to quadriplegia and death, is common in DD.
Aim of the study: Was to find out the frequency and natural history of cervical kyphosis.
Material: We studied 110 patients of whom 43 were male and 67 female. Their ages varied from newborns to 63-year-olds. Average follow-up time among those who had kyphosis was 7.9 years and was partly prospective.
Results: A total of 32 patients out of 110 (29 %) had cervical kyphosis. Among those of whom the first radiographs had been taken during the first 18 months of life, 27 patients out of 29 (93%) had cervical kyphosis. In the most severe casekyphosis was eventually 165 degrees. In all, except eight, cases kyphosis resolved spontaneously. Those patients who had unresolved kyphosis, three had died partly due to kyphosis and medullar compression and two patients had actually mild kypholordosis. Apex of kyphosis was C3 or C4. Hypoplasia of C3 to C5 was always related to kyphosis.
Conclusions: Majority of cervical kyphosis resolve spontaneously and need no surgical treatment. Observation of symptomless cervical kyphosis is sufficient. Poor outcome of kyphosis is to be expected, if 1)kyphosis is more than 65 degrees during the first 4-5 years of life 2) kyphosis persist at the age of five and/or 3) kyphosis will progress over 20 degrees during the first 2-3 years of life. Radiographing the cervical spine in patients with DD is very important in early childhood and especially before surgical procedures.

PROGRESSIVE CRANIOCERVICAL DEFORMATION IN OSTEOGENESIS IMPERFECTA

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At the first International Skeletal Dysplasia meeting the results of a study demonstrating that 25% of subjects in an unselected clinic population had radiographic features of Basilar Impression (BI) was presented. While 16% of subjects with OI type I had BI (all symptomatic) 64% of subjects with OI type IVB had demonstrated BI. Since 1990, six patients [OI IVB(4), IVA(1), IB(1)] from our initial clinic study have developed clinical or radiographic evidence of progression of their BI. A 20 year followup of 37 of the 85 patients with OI studied in Victoria 1975-77 also demonstrated that basilar impression is common in subjects with OI type III/IVB. Six subjects with OI type III/IVB who were children in 1975 were reviewed in 1995 and three were found to have developed symptomatic BI. A further group of subjects referred to our clinic since 1991 is presently being studied. In this group three new subjects with BI have been diagnosed [OI type IVA (2), IVB (1)]. Further studies are in progress to define the age specific incidence of BI in subjects with various types of OI.

We have undertaken several treatment studies in which craniocervical parameters have been closely monitored. In a study of 15 children receiving growth hormone, two subjects who completed therapy while in early puberty, one with OI type IVA and one with OI type IVB, have developed BI, although only the subject with OI type IVB is symptomatic. Twelve subjects have entered a study of cyclic intravenous pamidronate. No progress in BI has been demonstrated although only one subject has completed two years of therapy. Since 1991 all new patients with OI including a number with OI type IVB have been managed with reclined posturing until they have sufficient trunk control to sit upright. It is our intentiou to commence treatment with a bisphosphonate in all young OI patients by 4 years of age where consent is obtained. Studies of the natural history of OI in our clinic patients reveal that axial osteopenia is progressive with age and may contribute to the pathogenesis of BI. Two subjects with OI type IB, with multi-exon deletion in COL1A2 have been studied. In both subjects long term ascorbate induced matrix derived from cultured cells demonstrated exclusion of mutant polypeptides from skin and skin fibroblast derived matrix but inclusion in bone and osteoblast derived matrix. Further studies comparing inclusion/exclusion of mutant polypetides in skin vs cranial bone and teeth are needed in OI patients with OI type IB and OI type IVB.

CLINICAL CARE FOR SKELETAL DYSPLASIAS IN THE MANAGED CARE ENVIRONMENT

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Clinical care for individuals with skeletal dysplasia becomes very complex in the managed care environment. The mentality that everything should be cost-effective and evidence-based pervades the health care systems in North America.

Skeletal dysplasias are rare as a group but even rarer as individual entities. Thus to develop guidelines and reasonable approaches to care becomes very difficult. In order to develop clinical guidelines, natural history has to be defined so that proper clinical care can be given. This is a type of health services research and requires the collaboration of many centres.

Clinical guidelines or pathways help to define the frequency with which individuals should be seen, how frequently tests like x-rays should be done, as well as the quality of those studies, what defines an expert, and how often affected individuals should be referred to centres of expertise.

The AAP guidelines for achondroplasia should help to set a model of what can be outlined for other skeletal dysplasias. However, the guidelines for achondroplasia should, of course, not be used for other skeletal dysplasias.

Interdisciplinary clinics are ideal for the management of the complex medical issues presented by skeletal dysplasias. It is essential to build the expertise of many different disciplines to provide the right kind of care for individuals with skeletal dysplasias. However, there are a number of challenges involved in interdisciplinary clinics, not the least of which is billing since usually it is not possible to bill more than one consultant in a day for the same disorder.

Educational resources for families are not easy to come by in rare disorders. Thus organizations like Little People of America, Little People of Canada and the Human Growth Foundation have been important sources of information. Parents, however, strike out on their own and not infrequently now go to the internet and accumulate the world's literature before coming for their first consultation. Health care professionals need to have the same kind of resources at their fingetips!

Many families are willing to take part in research but also sometimes in inappropriate studies. Thus within the managed care environment, some type of clearing house for referral, consultation, and research studies is appropriate and needed.

DIAPHYSEAL MEDULLARY STENOSIS WITH BONE MALIGNANCY

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Diaphyseal medullary stenosis with bone malignancy or "hereditary bone dysplasia with malignant change" (HBD) is a rare autosomal dominant bone dysplasia, cancer syndrome whose etiology is unknown. Radiologically, HBD is characterized by diaphyseal sclerosis, medullary stenosis, endosteal scalloping and splitting, bony infarctions and metaphyseal striations. Clinically, HBD manifests as pathologic fractures secondary to minimal trauma, progressive wasting and bowing of the lower extremities and a marked predisposition to the development of an uncommon sarcoma, malignant fibrous histiocytoma. We have now had the opportunity to study a number of affected patients from different families. The radiographic features are discussed and a proposed screening algorithm is presented.

SPONDYLOEPIMETAPHYSEAL DYSPLASIA WITH FLOCKY EPIPHYSEAL CALCIFICATION, ADVANCED CARPAL OSSIFICATION, AND CONGENITAL HYDROCEPHALUS

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We report three patients, a sporadic patient (a girl) and two sibs (two brothers) born to nonconsanguineous parents, who were identically affected with a previously undescribed spodyloepimetaphyseal dysplasia (SEMD). Fetal ultrasonography revealed marked dilatation of the lateral ventricle, which did not progress postnatally. The clinical features included rhizomelic shortening of the limbs, severe developmental delay, epilepsy, and muscular hypotonia without spinal cord compression at the craniocervical junction. The sporadic case was also associated with thrombocytopenia.The elder brother of the familial case died of status epileptics at age 1 9/12 year and the younger brother suddenly died of unknown etiology at age 14/12 year, whereas the sporadic patient was still alive at age 4 years with frequent upper respiratory infection. The skeletal alterations in the neonatal age comprised platyspondyly with multiple coronal clefts, hypoplastic pelvis, delayed epiphyseal ossification, and mild metaphyseal modifications. Unique skeletal changes developed in early childhood, which included flocky calcification in the epiphyses and vertebral endplates, premature calcification of the costal cartilage, serrated iliac crests, and, most important, advanced carpal ossification. The differential diagnosis included SMED short-limbed calcification type (Borochowitz et al., 1993; Langer et al., 1993), SEMD with puntate calcifications within the vertebral bodies (Borochowitz et al., 1995), and osteochondrodysplasia with rhizomelia, platyspondyly, callosal agenesis, thrombocytopenia, hydrocephalus, and hypertension (Faye-Petersen et al., 1991). However, the clinical and radiologic constellation of our patients did not completely fit that of these entities.

PRESENTATION OF 5 CASES OF STÜVE-WIEDEMANN SYNDROME

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In 1971, Stüve and Wiedemann described a new syndrome with bowing of the lower limbs, camptodactyly respiratory distress and autosomal recessive inheritance. Recently, cytochrome oxidase deficiency has been reported by N. Philip et al in two cases of Stüve-Wiedemann syndrome. We report 5 cases of Stüve-Wiedemann syndrome with a respiratory chain study in 2 cases. Parents were consanguineous in 3 cases. Short stature was constant (-2,-3 SD) and bowed femora were noted during pregnancy in three cases. Dysmorphic features were constant including short neck, micrognatia, abnormal simian creases, camptodactyly, malposition of the feet and bowing of the lower limbs. Hypotonia and swallowing difficulties were always noted in the course of the disease. Three children had respiratory distress with pulmonary hypoplasia. All 5 patients died between 3 days and 18 months of acute episode of unexplained hyperthermia. X-rays showed bowed and broad femora and tibiae with a thickened inner cortical and straight fibulae. Enzymatic study of the respiratory chain was performed in the muscle and fibroblasts of one case and in the fibroblasts of another case and was normal in the two cases suggesting that not all Stüve-Wiedemann cases are related to respiratory chain deficiency.

RADIOGRAPHIC FEATURES OF GENOTYPED ACHONDROPLASIA AND HYPOCHONDROPLASIA PATIENTS

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Recent evidence has shown that achondroplasia (ACH) and hypochondroplasia (HCH) are genotypically distinct disorders, most of which involve distinct point mutations of the fibroblast growth factor receptor 3 (FGFR3) gene. On the other hand, overlapping clinical and radiographic features of ACH and HCH have also been identified by several authors. To determine whether the genotype could be distinguished from the phenotype, we analyzed skeletal radiographs from ACH and HCH patients who had been genotyped with the aid of a common G380R mutation of FGFR3 as a diagnostic marker for ACH, and a common N540K mutation for HCH. Measurement of skeletal radiographs (the lumbar spine, the pelvis, and the lower legs) revealed that both ACH and HCH shared classical pathological radiographic features (a reduced or unchanged interpedicular distances in the lumbar spine, a squared and shortened ilia of the pelvis, and a disproportionally long fibula). The ratio of the interpedicular distances at the first and fourth lumbar vertebrae for sixteen G380R patients was significantly higher than that for seven N540K patients ($p<.01$), indicating that the reduction of the interpedicular distances in the lumbar spine was more severe for ACH than HCH. The ratio of the width of the iliac wing to the interteardrop distance was significantly higher for twenty-two G380R patients than for eight N540K patients ($p<.01$), meaning that the shape of the pelvis is more squared in ACH than in HCH. Finally, the ratio of the length of the fibula to the length of the tibia for twenty-two G380R patients was significantly higher than that for eight N540K patients ($p<.01$), indicating that the fibulae of ACH are disproportionally longer than those of HCH. Although ACH was quantitatively more severe in all respects, considerable overlap was seen between some mildly affected ACH patients and some severely affected HCH patients, reflecting the phenotypic homogeneity of these two conditions. We conclude that, although the genotype statistically reflects the phenotype, it is not completely distinct from the phenotype.

UNKNOWN CASES

Case A	Yoshito Matsui, Natsuo Yasui
Case B	John Campbell
Case C	Virginia Fano, Cristina Barreiro, Claudia Perandones, H. Lejarraga
Case D	B. Say
Case E	Geert Mortier
Case F	Dee Miller, E. Sujansky, Orest Hurko
Case G	Geert Mortier
Case H	C. Scott
Case I	R. Ball
Case J	T. Hsia, K. Reinker
Case K	William Wilcox

SKELETAL PHENOTYPES CAUSED BY FIBROBLAST GROWTH FACTOR RECEPTOR-3 MUTATIONS.

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Clinical and radiographic similarities between achondroplasia, hypochondroplasia and thanatophoric dysplasia first led Jurgen Spranger to propose that there is an "achondroplasia family" of skeletal dysplasias, with a common etiologic pathway. Molecular studies have since born out this prediction. Mutations in the Fibroblast Growth Factor Receptor 3 (FGFR3) gene on human chromosome 4p16 are now known to cause all three of these conditions, in addition to a number of rarer or newly recognized phenotypes. The latter include several craniosynostosis phenotypes (Crouzon syndrome with acanthosis nigricans and non-syndromic Craniosynostosis) as well as a severe skeletal dysplasia characterized by profound short stature, mental retardation and acanthosis nigricans. Several unusual features characterize the FGFR3 associated phenotypes. (1) There is a high degree of genotype-phenotype correlation. More than 95% of cases of achondroplasia, for example, are caused by 2 mutations, both of which cause a G380R amino acid substitution in the transmembrane domain of the FGFR3 molecule. The majority of cases of hypochondroplasia are similarly caused by two mutations, both affecting amino acid 540 in the first tyrosine kinase (TK1) domain of the receptor. Although multiple different mutations in FGFR3 have been found in thanatophoric dysplasia type I, thanatophoric dysplasia type II mutations are limited to a single nucleotide substitution in the second tyrosine kinase (TK2) domain. (2) Certain nucleotides of the FGFR3 gene appear to be highly susceptible to mutation. The pathophysiologic mechanism underlying each of the disorders studied to date is that of constitutive activation of the receptor. It is possible that other types of mutations have not been observed because they result a lethal phenotype, or in a phenotype markedly distinct from those of the achondroplasia family of disorders. Ongoing studies of mutation mechanism, signal transduction by normal and mutant receptors, and animal models should greatly enhance our understanding of the molecular mechanisms underlying these phenotypes.

Experimental approaches to studying achondroplasia.

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Activating mutations of fibroblast growth factor receptor 3 (FGFR3) have been found to cause the achondroplasia class of human chondrodysplasias. We have developed experimental models to examine the mechanisms involved. Targeted expression of the classical achondroplasia mutation to cartilage in transgenic mice results in postnatal growth deficiency associated with a reduction in the number of terminally differentiating cells in the growth plate. Overexpression of FGF ligand that binds to FGFR3 in transgenic mice produces a very similar phenotype. Addition of FGF ligands to cultured cells behaving as growth plate cells induces expression of p21(WAF1/CIP1), a known inhibitor of mitosis. Excessive amounts of this inhibitor have been found in the growth plate of patients with thanatophoric dysplasia type II. These observations suggest that one mechanism by which activating FGFR3 mutations exert there adverse effects on bone growth is by blocking cell cycle progression of growth plate chondrocytes. This would reduce the number of cells that terminally differentiate in the growth plate and thereby reduce the rate at which cartilage template is formed for endochondral ossification. It is likely that there are other mechanisms involved

MOLECULAR, RADIOLOGIC, AND HISTOPATHOLOGIC CORRELATIONS IN THANATOPHORIC DYSPLASIA

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Various mutations in the fibroblast growth factor receptor 3 (FGFR3) gene have recently been reported in thanatophoric dysplasia (TD). We examined the clinical, radiographic, and histologic findings in 91 cases from the International Skeletal Dysplasia Registry and correlated them with the specific FGFR3 mutation. The identified substitutions were: arg248cys, 45 cases; ser249cys, 4 cases; gly370cys, 1 case, tyr373cys, 18 cases; lys650met, 1 case; lys650glu, 17 cases; and mutations in the stop codon, 4 cases. The mutation has not yet been identified in 1 case. Radiographically, all of the cases with the lys650glu substitution demonstrated straight femurs with cloverleaf skull (CS). For all of the other cases, the femurs were curved and CS was infrequently present but was occasionally as severe as TD with the lys650glu substitution. Histopathologically, all of the cases shared similar abnormalities. However, cases with the lys650glu substitution demonstrated relatively more preservation of the physeal chondrocyte columns. The fibrous band was present only adjacent to the perichondrium. In contrast, the fibrous band was more extensive and the column preservation poorer in all of the other cases. Cases with the tyr373cys substitution tended to have more severe manifestations than the arg248cys cases, but there was significant overlap in the phenotypic spectrum between them. One common classification of TD distingnishes affected infants based on the presence or absence of CS. In contrast, and as originally proposed by Langer et al. (Am. J. Med. Genet. 3:167-179, 1987), our data suggest TD can be divided into at least two groups based on the presence of straight or curved femurs. The variable presence of CS and severity of the radiologic and histologic findings in the other substitutions may be due to other genetic, environmental, or stochastic factors.

BIOCHEMICAL EFFECTS OF MUTATIONS IN FGFR3 WHICH CAUSE SKELETAL DYSPLASIAS

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Departments of Biological Chemistry* and Physiology[5], University of California, Irvine, USA

Mutations in the tyrosine kinase fibroblast growth factor receptor 3 (FGFR3) have been shown to cause a number of skeletal dysplasias including achondroplasia (ACH), the most common genetic form of short limbed dwarfism, as well as the milder hypochondroplasia (HCH) and neonatal lethal thanatophoric dysplasia types I and II (TD). Evidence indicates that these syndromes are not due to simple haploinsufficiency, but rather related to an enhancement of FGFR3 function as a negative regulator of endochondral bone growth. To date, very little is known regarding signal transduction mediated by FGFR3 or the effects of the skeletal dysplasia mutations upon activation of downstream cellular targets. To study these effects, chimeric receptors composed of the extracellular domain of hPDGFRβ and the transmembrane/intracellular domains of hFGFR3 were constructed and stably expressed in PC12 cells. PC12 cells are a well characterized monitoring system of signal transduction that contain no endogenous PDGFR, allowing ligand stimulation of chimeric receptors only. A range of mutations were introduced into these chimeric receptors incuding those causing ACH (G380R, G375C), HCH (N540K), TD1 (K650M), TD2 (K650E), and Crouzons with acanthosis nigricans (A391E) and differences in signaling as measured by neurite outgrowth assays (indicative of differentiation) and phosphorylation (activation) of intracellular targets were analyzed. Most of the mutations result in a more rapid neurite outgrowth response to ligand and a reduced degree of activation of cellular targets, including ras/MAPK pathway proteins, compared to wild type, consistent with cellular "preactivation". The TD2 mutation (K650E) produces markedly different results consistent with a different autoactivation mechanism of the receptor. The manner in which these receptor modulations contribute to the disease pathology are under investigation. Supported by CSMC21395, NS25631 and AG09735.

MOLECULAR BASES OF THE MOST COMMON CRANIOSYNOSTOSIS SYNDROMES

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Craniosynostosis is a common birth defect (1 in 2100 - 2500 infants) which affects the premature fusion of one or more of the cranial sutures. Classic craniosynostosis syndromes such as Apert, Pfeiffer, Crouzon, Jackson-Weiss, and Saethre-Chotzen syndromes were previously classified based on their clinical findings and have now been defined at the molecular level (for a recent review see: Wilkie AOM *Hum. Mol. Genet.* **6**, in press).
Here we present clinical and molecular data in patients with coronal synostosis and a unique mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Based on linkage to chromosome 4p, this *FGFR3* mutation (C749G; Pro250Arg) was initially identified in two families who had some findings consistent with Pfeiffer syndrome (Bellus et al. *Nature Genet* **14**:174, 1996). In a study of 26 patients with apparently non-syndromic craniosynostosis 8 were positive for the *FGFR3* C749G mutation. Two of these were familial and 6 sporadic having arisen *de novo* from unaffected parents (Moloney et al. *Lancet* **349**:1059, 1997). The *FGFR3* C749G mutation rate is one of the highest described in the human genome. This unique mutation defines a new craniosynostosis syndrome based on an analysis of 61 individuals from 20 families. The clinical findings consist of bi- or unicoronal synostosis and abnormalities on radiographs of hands and feet including thimble-like middle phalanges, coned epiphyses, and carpal and tarsal fusion in some patients. Sensorineural hearing loss and developmental delay was seen in a minority (Muenke et al. *Am J Hum Genet* **60**:555, 1997). In a study of consecutive patients with apparently sporadic unicoronal synostosis, 4 of 37 were positive for the *FGFR3* C749G mutation. It is of interest that three fathers with subtle findings and without craniosynostosis were identified as mutation carriers (Gripp et al., submitted). Since the phenotype can be extremely variable all parents of mutation-positive patients should be tested regardless of their clinical findings.

TWIST mutations disrupting the b-HLH domain are specific to Saethre-Chotzen syndrome

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Saethre-Chotzen syndrome (acrocephalo-syndactyly type III, ACS III) is an autosomal dominant craniosynostosis syndrome. We have recently shown that this condition is accounted for by mutations in the *TWIST* gene, a basic-helix loop helix (b-HLH) transcription factor regulating head mesenchymal cell proliferation during cranial neural tube formation in mouse (El Ghouzzi et al, 1997 Nature Genet 15:42-46; Howard et al, 1997 Nature Genet 15:36-41).
Studying a large series of 21 ACSIII patients we observed that most *TWIST* mutations disrupt the b-HLH domain of the protein, suggesting that the disease is the result of a gene dosage effect (haploinsufficiency). Indeed, non sense mutations (10/21), insertion mutations (4/21) and deletions (3/21), truncated or disrupted the b-HLH domain of the protein (17/21) as they were located either upstream to or within the corresponding domain of the *TWIST* gene. Missense mutations (in the b-HLH domain) were less frequent (4/21).
In seven additional ACSIII patients, no *TWIST* gene mutations were identified and 3/7 had a recurrent P250R mutation in the FGFR 3 gene. Interestingly, these patients presented a milder phenotype than those harboring *TWIST* mutations. Conversely, no *TWIST* mutations were detected in 80 patients with non syndromic craniosynostosis.
We conclude that *TWIST* mutations truncating the b-HLH domain are specific to Saethre-Chotzen syndrome and that molecular studies would greatly improve the clinical diagnosis of this disorder. Finally, these results further illustrate the close relationship between FGFRs and the *TWIST* genes during craniofacial and limb development.

A Key to Bone Development: The Gene for Cleidocranial Dysplasia - CBFA1 - is Essential for Osteoblast Differentiation and Skeletal Patterning

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Cleidocranial dysplasia (CCD) is an autosomal-dominant condition characterized by hypoplasia/aplasia of clavicles, patent fontanelles, supernumerary teeth, short stature, and other skeletal changes. We have identified *CBFA1* as the CCD-gene. In a previous study we described linkage of the CCD phenotype to chromosome 6p21 and identified one family with a deletion. In this family we were able to identify large deletions which include *CBFA1*. *CBFA1* was cloned and the intron exon boundaries determined. In contrast to the other CBF members *CBFA1* shows a long glutamine/alanine stretch N-terminal. In patients without deletions we identified deletions, insertions, mis-sense and non-sense mutations within the *CBFA1* coding region. The function of *Cbfa1* was further evaluated in two mouse models. Ccd is a radiation induced mutant that has a CCD-like phenotype. Ccd maps to chromosome 17 to a region syntenic to human 6p21. A large deletion that includes *Cbfa1* was identified. In the other model *Cbfa1* was disrupted. In the heterozygous state both mice have identical phenotypes featuring open fontanelles, hypoplastic clavicles and other skeletal changes observed in CCD. Thus, the heterozygous mouse is a paradigm for CCD. The loss of both *Cbfa1* alleles leads to a complete arrest in osteoblast differentiation and, consequently, to an absence of bone. *Cbfa1*$^{-/-}$ mice develop normal cartilage anlagen and chondrocytes proliferate and hypertrophy. However, there is no calcification of cartilage, no bone formation, and no vascular invasion. *Cbfa1* mRNA can be detected as early as day 10.5 in mandibular precursor cells. By day 12.5 it is present in most areas of mesenchymal condensation. With the appearance of ossification centers it is detected in osteoblasts only. In conclusion, our data show that loss of function mutations in *CBFA1* cause CCD. Patterning defects may be due to expression in the early cartilage anlagen, whereas growth defects are caused by insufficient differentiation of osteoblasts. *Cbfa1* is one of the master genes for osteoblast differentiation.

MUTATIONS IN THE OSTEOBLAST-SPECIFIC TRANSCRIPTION FACTOR OSF2/CBFA1 IN CLEIDOCRANIAL DYSPLASIA

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Cleidocranial dysplasia (CCD) is a dominantly inherited skeletal dysplasia characterized by hypoplastic clavicles, delayed ossification of sutures and fontanelle, and delayed eruption of teeth. The clinical phenotype is suggestive of a primary defect of membranous ossification and to a lesser degree endochondral ossification. The condition has previously been mapped to chromosome 6p21. We hypothesized that defects in a runt domain osteoblast-specific transcription factor OSF2/CBFA1 might result in CCD. We have mapped the human OSF2/CBFA1 gene to 6p12 bordering 6p21 and demonstrate two de novo missense mutations, Ser191Asn and Met175Arg, in this gene in two sporadic cases of CCD, respectively. The substitutions occur in highly conserved regions of the runt DNA binding domain. In vitro DNA binding studies with the mutant runt domains show that the mutations abolish DNA binding of the respective polypeptides to their target sequence (OSE) in the osteocalcin promoter. Co-expression of the mutant runt polypeptides with an osteocalcin promoter/reporter construct confirm a predicted abolition of transactivating activity. These data suggest that CCD arises from haploinsufficiency of a molecular determinant of the osteoblast phenotype. Additional mutation and functional studies are in progress with other patients with CCD.

MUTATIONS IN AND AROUND THE SOX9 GENE IN CAMPOMELIC DYSPLASIA: A GENERAL LACK OF GENOTYPE/PHENOTYPE CORRELATIONS

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Campomelic dysplasia (CD) is a usually lethal skeletal malformation syndrome caused by *de novo* heterozygous mutations in the chondrogenic regulatory gene *SOX9* on 17q. A total of 25 *SOX9* mutations in CD have been described by us and others. We have meanwhile identified 14 additional *SOX9* mutations. These confirm the previous conclusion of a general lack of correlation between the type and position of a mutation within the gene with disease severity, survival time, and XY sex reversal. The exception are nonsense mutations at the C terminus that correlate with survival beyond the neonatal period.

An unresolved puzzle is posed by CD translocation cases. Five CD translocation breakpoints have been mapped 50 kb to more than 130 kb from *SOX9*. We have now located the breakpoints in two new cases at around 300 kb and at more than 600 kb from *SOX9*. The mutation mechanism involved could be a long-range effect due to removal of one or more *cis*-regulatory element(s) essential for correct *SOX9* expression. Alternatively, the breakpoints could disrupt a second CD gene. Notably, of the ten CD translocation or inversion cases known, seven patients are still alive aged 2 to 30 years, and only three present with campomelia. In CD cases without chromosomal rearrangements, only 10 % survive 2 years and 90 % show campomelia.

PYCNODYSOSTOSIS: IDENTIFICATION OF NOVEL DISEASE-CAUSING MUTATIONS IN THE PRO AND MATURE POLYPEPTIDE REGIONS ENCODED BY THE CATHEPSIN K GENE

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Pycnodysostosis (Pycno) is a rare sclerosing skeletal dysplasia inherited as an autosomal recessive trait. Features include short stature, osteosclerosis, bone fragility, and numerous abnormalities of the cranial and facial bones. Previously, we mapped the Pycno locus to chromosome 1q21 with a large Israeli Arab Pycno family. Using a positional candidacy approach, we mapped the gene for the lysosomal protease, cathepsin K (Cat K) to the Pycno critical region, demonstrated mutations in three Pycno families, and transiently expressed one mutant that resulted in no immunologically detectable protein (*Science* 1996, **273**:1236). Nine additional Pycno families were analyzed for CatK mutations and computational approaches were used to study the functional consequences of certain missense mutations. Seven Cat K exons containing the entire coding region were amplified from genomic DNA and sequenced. Putative mutations, identified by sequence comparison, were confirmed using PCR-based restriction polymorphisms. Seven Cat K mutations were identified, including a proregion nonsense (K52X), a proregion missense (G79E), and five mature enzyme missense (G146R, Y212C, R241X, A277E, and R312G). Molecular modeling of the G79E proregion mutation revealed that a charge change was introduced at position 6 within the conserved GxNxFxD motif which was predicted to cause significant conformational alteration of this region, probably resulting in improper folding of the mature peptide and/or protein instability. A three-dimensional molecular model of the mature enzyme was constructed based on known structures of other papain family members. The R146 and E277 mutant residues were buried within the active cleft but could be accommodated. The R146 mutation appeared to shift the pK's of the active site Cys-His sufficiently to preclude the proton transfer required for catalysis. The effects of the E277 mutation seemed to be primarily steric due to the bulky side group. Y212 was a surface residue but C212 might interfere with the C170-C210 disulfide bridge, potentially destabilizing the molecule. Future studies of Cat K mutations should facilitate development of inhibitors useful for the treatment of bone diseases with relatively excessive bone degradation such as osteoporosis and certain arthritides.

THE MOLECULAR GENETIC ANALYSIS OF BRACHYDACTYLY TYPE C

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Brachydactylies comprise a clinically and pathogenically heterogeneous group of disorders which share the common feature of having skeletal elements within hands or feet that differ from "normal" with respect to size or shape. Hereditary brachydactylies can provide an opportunity to identify processes which contribute to normal morphogenic differences in analogous skeletal structures. For example, in Brachydactyly type C (Bd-C), the 2nd, 3rd, and 5th middle phalanges are more severely affected than the 4th middle phalanx. We mapped a Bd-C locus to an interval on chromosome 20 that also contains the gene for Cartilage-derived Morphogenetic Protein-1 (CDMP1), a member of the TGF-β superfamily of peptide growth factors. Testing CDMP1 as a candidate for Bd-C, we found heterozygous missense, nonsense, and frameshift mutations in patients from 7 unrelated kindreds. Most of these mutations are predicted to cause functional haploinsufficiency. CDMP1 mutations had previously been identified in two autosomal recessive disorders, Hunter-Thompson acromesomelic dysplasia and murine brachypodism, neither of which had a reported heterozygous phenotype. Consequently, finding that heterozygous mutations in CDMP1 also cause a dominant phenotype is somewhat surprising. The precise mechanism of action by which CDMP1 mutations cause different phenotypes remains to be elucidated. Nevertheless, our results suggest that morphogenic variation between analogous skeletal elements is in part due to site specific, and species specific, differences in responsiveness to peptide growth factors.

ABNORMAL LIMB DEVELOPMENT IN GREBE SYNDROME CAUSED BY MUTATIONS IN CDMP-1

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Grebe Syndrome (GS) is an autosomal recessive acromesomelic dysplasia, characterized by shortening of the upper and lower extremities following a proximal-distal gradient of severity and polydactyly. Four GS families, originating from Bahia state in Brazil, were studied. The lower extremities appeared to be more severely affected. Five of seven affected individuals presented with postaxial polydactyly. The fingers and toes lacked articulation and appeared as skin appendages. The range of motion of the elbows, wrists, hands, knees and ankles was either severely restricted or non-existent. Heterozygotes were of average stature and presented with a variety of skeletal manifestations including postaxial polydactyly, brachydactyly, delayed bone age, metatarsus adductus, valgus deviation of toes and flexion contracture of fingers. Skeletal radiographs showed bone aplasias and hypoplasias. An MRI image of the forearm showed the mesenchymal ghost of tissue destined to become the distal ulna. Using a candidate gene approach we genetically mapped GS to chromosome 20q11.2, a region containing the human cartilage-derived morphogenetic protein-1 (CDMP-1) gene. CDMP-1 is one of two recently identified members of the TGF-β superfamily, closely related to BMP-5 and BMP-6, expressed predominantly at sites of skeletal morphogenesis. Six of seven individuals with GS are homozygous for a G to A transition at nucleotide 1461 of CDMP-1, predicting a C400Y substitution in the mature region of the protein. The seventh individual was found to be heterozygous for the G1461A mutation and deletion of a G at nucleotide 1406 that predicts a premature termination signal. Use of specific anti CDMP-1 antibodies supports the notion of a dominant-negative effect through homo and hetero dimerization. The GS phenotype provides insight into the mechanism by which CDMP-1 acts and supports a pivotal role for this molecule in human skeletal development.

Sulfate transporter chondrodysplasias: the mosaic pieces fall into place

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In late 1994, the discovery of a sulfation defect in achondrogenesis type 1B and the identification of the diastrophic dysplasia gene as a sulfate transporter converged to establish a new family of chondrodysplasias. Current knowledge about this chondrodysplasia family is as follows:

Molecular basis: Over 20 recessive mutations in the sulfate transporter gene DTDST have been identified. More than one half-induce frame shifts and/or premature truncation of the protein, the rest being amino acid substitutions, deletions, or splice-site mutations.

Phenotypes and nosology: The phenotypes of patients with identified mutations form a continuous spectrum which ranges from achondrogenesis type 1B (ACG1B) to diastrophic dysplasia (DTD) and includes atelnsteogenesis type 2/McAlister dysplasia (AO2) as well as intermediate forms. The original family with "de la Chapelle dysplasia", characterized by marked ulnar and fibular hypoplasia, may fall outside of this spectrum.

Biochemical pathogenesis: (1) In a panel of fibroblast strains with defined DTDST mutations there was good correlation between clinical severity and the degree of impairment in sulfate uptake and proteoglycan sulfation. There is also good correlation between clinical phenotype and the amount of non-sulfated proteoglycan disaccharides prepared from patients' cartilage samples. These observations indicate that the DTDST mutations are the most important factor in determining the phenotype, with little or no epigenetic factors. (2) Patients' cells in vitro use increased amounts of sulfate derived from sulfur containing amino acids for the synthesis of proteoglycans. To which extent this rescue mechanism occurs in vitro and whether this helps explaining the fact that the clinical phenotype is restricted to cartilage remains to be studied.

Diagnosis: AO2 and DTD patients are usually correctly diagnosed on radiographs while distinction between different achondrogenesis types can be difficult. Cartilage histology and sulfation studies in cell culture allow a specific diagnosis. Identification of DTDST mutations is rapid and efficient and allows for diagnostic confirmation of index cases and for prenatal diagnosis. Four pregnancies at risk for DTD and AO2 have been monitored by CVS DNA analysis and the prediction of two affected and two unaffected fetuses confirmed by pathological or clinical examination.

Contributions of biological samples, x-rays, and laboratory results by colleagues (J. Hästbacka, A. Rossi, I. Kaitila, D. Cohn, W. Wilcox, D. Rimoin, J. Bonaventure, M. LeMerrer, H.Plauchu, P.Freisinger, P. Meinecke, C. Schrander-Stumpel, P. Sastrowijoto, H. van der Harten, W. Kleijer, F. Beemer, A. Verloes, R. Winter, R. Sutphen, K. Wcislo, D. Witt, B. Steinmann, G. Eich, A. Giedion) is gratefully acknowledged. - Supported by the Swiss National Foundation (32-45401.95, 32-42198.94).

TRACING THE BIOCHEMICAL PATHOGENESIS OF *DTDST* CHONDRODYSPLASIAS: CORRELATIONS BETWEEN RESIDUAL TRANSPORTER ACTIVITY *IN VITRO*, DEGREE OF UNDERSULFATION IN CARTILAGE AND CLINICAL PHENOTYPE

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Mutations in the diastrophic dysplasia sulfate transporter (*DTDST*) gene, encoding for a sulfate-chloride antiporter of the cell membrane, define a family of chondrodysplasias that comprises, in order of increasing severity, diastrophic dysplasia (DTD), atelosteogenesis type 2 (AO-2) and achondrogenesis type 1B (ACG-1B). In spite of the correlations found between the nature of the mutations and the clinical phenotype, the biochemical aspects of these disorders are poorly documented. We have studied chondroitin sulfate proteoglycan (PG) sulfation in cartilage samples obtained from patients affected by *DTDST* chondrodysplasias (DTD, n=7; AO-2, n= 2; ACG-1B, n= 5) by disaccharide HPLC analysis after digestion with chondroitinase ABC. In the patients' cartilage samples the amount of non-sulfated disaccharide was higher compared to age matched controls (patients, 15% - 75%; controls, 2-7%, n=8); the highest amount being present in the ACG-1B patients (n=5) in accordance with the most severe clinical phenotype. The function of the sulfate transporter was tested in fibroblasts from 9 patients (DTD, n=3; AO-2, n=3; ACG-1B, n=3) by $^{35}SO_4$/[^{3}H]glucosamine incorporation and $^{35}SO_4$ uptake assay. Compared to controls, uptake and incorporation were more markedly reduced in ACG-1B than in AO-2 and DTD. Thus, DTD patients have the highest residual sulfation and ACG-1B the lowest both in cartilage and in fibroblast culture, confirming a direct relationship between impairment of sulfate uptake, degree of PG undersulfation in cartilage and clinical severity.

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LINKAGE OF MULTIPLE SYNOSTOSES TO CHROMOSOME 17Q21-22.

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Multiple synostoses syndrome is an autosomal dominantly inherited disorder characterized by premature onset of joint fusions, predominantly affecting the interphalangeal joints. We have identified a large Hawaiian family who manifests the following findings; distinct facies, early onset otosclerotic deafness, fusions of the interphalangeal joints and cervical vertebral ankylosis. The interphalangeal joint fusions commence in the fifth PIP joint and proceed in an ulnar to radial and proximal to distal direction. Proximal symphalangism, a dominantly inherited synostoses syndrome primarily affecting the interaphalangeal joints, has been mapped to loci at chromosome 17q21-22. Utilizing polymorphic loci from the proximal symphalangism interval, we determined that the multiple synostoses phenotype is linked to the same chromosomal region. A maximum lod score of 3.13 was achieved for the marker at locus D17S787. Further genetic analysis identified individuals with recombinant genotypes, allowing the genetic interval for the disease gene to be localized within the interval D17S797-D17S792, a 14 cM region. Presently, there are no identifiable candidate genes. These data provide evidence that multiple synostoses and proximal symphalangism are either allelic disorders, or result from defects in closely linked genes that function in the maintenance of joint integrity.

The Type XI Collagenopathies

J. Spranger, Mainz

Type XI collagen is a heterotrimer composed of ∂1 (XI) and ∂1 (XI) and ∂1 (II) chains, products of the COL11A1, COL11A2, and COL2A1 genes, respectively. It copolymerizes with type II collagen and appears to regulate fibril thickness.

Mutations of the COL11A1 gene lead to a Stickler phenotype with characteristic vitreo-retinal changes differing from those in classical Stickler arthroophthalmopathy.

Mutations of the COL11A2 gene lead to OSMED, a phenotype resembling Stickler disease but without eye involvement and with large epiphyses. It manifests in heterozygotes [1,2] Weissenbacher and Zweymuller's original patient has this disorder (caused by a glycine to glutamate substitution at position ∂2-955)[2]. Homozygocity of COL11A2 mutations has also been claimed to cause the OSMED phenotype.

Mutations of the COL2A1 gene that truncate ∂1(II) procollagen chains preventing their incorporation into type XI collagen fibrils cause classical Stickler arthroophthalmopathy.

Disorders published under a vast array of names such as Stickler-Wagner-Marshall-Weissenbacher-Zeymuller-, Insley-Astley- Syndromes, micrognathic dwarfism, dominant and recessive oto-spondylo-megaphyseal dysplasia appear to be -or may turn out to be-type XI collagenopathies. They share a phenotypic patter -i.e. constitute a "family because of the common morphogenetic consequences of abnormal type XI collagen. Phenotypic differences among the members reflect non-allelic, and possibly allelic, genetic heterogeneity.

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STRUCTURALLY ABNORMAL TYPE II COLLAGEN IN A SEVERE FORM OF KNIEST DYSPLASIA CAUSED BY AN EXON 24 SKIPPING MUTATION

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Type II collagen mutations have been identified in a phenotypic continuum of chondrodysplasias that range widely in clinical severity. They include achondrogenesis type II, hypochondrogenesis, spondyloepiphyseal dysplasia congenita (SEDC), spondyloepimetaphyseal dysplasia (SEMD), Kniest dysplasia, and Stickler syndrome. We report here results that define the underlying genetic defect and consequent altered structure of assembled type II collagen in a neonatal lethal form of Kniest dysplasia. Electrophoresis of a cyanogen bromide (CNBr) digest of sternal cartilage revealed an α1(II)CB11 peptide doublet and a slightly retarded mobility for all major CB peptides, which implied post-translational overmodification. Further peptide mapping and sequence analysis of CB11 revealed equal amounts of a normal α1(II) sequence and a chain lacking the eighteen residues (361-378 of the triple helical domain) corresponding to exon 24. Sequence analysis of an amplified genomic DNA fragment identified a G to A transition in the +5 position of the splice donor consensus sequence of intron 24 in one allele. Cartilage matrix analysis showed that the short α1(II) chain was present in collagen molecules that had become cross-linked into fibrils. Trypsin digestion of the pepsin-extracted native type II collagen selectively cleaved the normal length α1(II) chains within the exon 24 domain. These findings support a hypothesis that normal and short α-chains had combined to form heterotrimeric molecules in which the chains were in register in both directions from the deletion site accommodated effectively by a loop out of the normal chain exon 24 domain. Such an accommodation, with potential overall shortening of the helical domain and hence misalignment of intermolecular relationships within fibrils, offers a common molecular mechanism by which a group of different mutations might act to produce the Kniest phenotype.

MUTATIONS IN THE PSEUDOACHONDROPLASIA - MULTIPLE EPIPHYSEAL DYSPLASIA DISEASE SPECTRUM.

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Mutations in the cartilage oligomeric matrix protein (COMP) gene have been identified in patients with pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED), two autosomal dominant chondrodysplasias. To determine the nature and frequency of COMP mutations in these conditions, we carried out sequence analysis of each of the 19 COMP exons in a panel of patients. For pseudoachondroplasia, mutations were identified in 7/7 patients analyzed. All of the mutations resulted in small deletions or single amino acid substitutions in the calmodulin-like (CaM-like) domain of the protein. The mutations primarily altered conserved residues among the CaM-like repeats of the protein, identifying residues essential to the structure and/or function of the molecule. Together with data from previous studies, we can conclude that, with rare exceptions, PSACH results from mutations within a restricted domain of COMP. These findings also support linkage data indicating absence of locus beterogeneity in PSACH. In contrast, mutations were identified in only 3/11 MED patients, suggesting significant locus heterogeneity. The mutations identified were within the CaM-like domain of COMP, providing further evidence that COMP mutations in MED patients primarily reside within the same domain as mutations that produce PSACH. Among all of the COMP mutations characterized in MED patients, those that predict substitution for aspartate residues within the CaM-like domain have suggested an underlying pathology related to a primary effect on calcium binding. However, other MED mutations imply single amino acid substutions for conserved residues within the CaM-like repeats of COMP. For these mutations, neither the nature nor the location of the defects suggest why they result in MED while structurally similar mutations produce PSACH. Mutations in patients with PSACH and MED were not identified within the amino-terminal chain-association domain or the EGF-like repeat region, and have only rarely been characterized in the carboxyl-terminal globular domain. Thus, if mutations in these regions have phenotypic consequences, the clinical spectrum resulting from defects in COMP could include additional chondrodysplasias not currently recognized to be related to PSACH and MED.

SYNTHESIS OF CARTILAGE OLIGOMERIC MATRIX PROTEIN (COMP) BY CULTURED CELLS FROM PATIENTS WITH PSEUDOACHONDROPLASIA AND MULTIPLE EPIPHYSEAL DYSPLASIA.

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Pseudoachondroplasia (PSACH) and Multiple Epiphyseal Dysplasia (MED) are autosomal dominant chondrodysplasias for which mutations have been found in the Cartilage Oligomeric Matrix Protein (COMP) gene. COMP is a homopentameric extracellular matrix protein of unknown function, expressed predominantly in the territorial matrix of cartilage. To understand the pathophysiology of these diseases at the molecular level, we have undertaken a study of the synthesis and secretion of COMP in cultured cells from both controls and patients.

Control ligament cells, tendon cells and chondrocytes, grown in monolayer, synthesized COMP. Pentameric COMP was detected in both the secreted protein pool and in the cells, indicating that pentamerization is an intracellular process. Cultured chondrocytes from a patient with a mild form of PSACH and cultured tendon cells from a patient with MED, both of whom have COMP mutations, synthesized and secreted COMP in a manner quantitatively and qualitatively indistiguishable from the controls. Although transmission electron microscopy of PSACH and MED patients cartilage reveals inclusions in the rough endoplasmic reticulum (RER) of chondrocytes, accumulation of protein in the RER could not be detected in cultured cells, at least in short-term cultures. These data suggest that abnormal COMP monomers can be incorporated into pentamers and secreted by cultured cells. If replicated *in vivo*, this implies that phenotypic expression is due to the combination of a quantitative defect - due to retention of structurally abnormal proteins in the RER - and of impaired cartilage function - resulting from the presence of abnormal COMP in cartilage extracellular matrix.

New Techniques for Limb Lengthening and Realignment for Skeletal Dysplasias

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Short stature and lower limb malalignment are two major sequellae of many of the skeletal dysplasias. New treatment options exist because of advances in the field of limb lengthening and deformity correction. Lengthening for stature involves one or more lengthenings and depends on the etiology, age, sex, and goal of the patient (which is usually to reach the low normal range of stature for the patient's sex).

In achondroplasia, for example, treatment usually requires 25-35cm of lengthening and involves two age strategies depending upon age of presentation: initial lengthening at age 6-8 years and subsequent lengthenings at 10-13 years. The first lengthening at age 6-8 is 5cm in both femurs and tibias bilaterally (total 10cm each side), and is combined with varus deformity correction of both tibias. The rest of the lengthening strategy is as for age 10-13 presentation. The first lengthening at age 10-13 is 10-15cm (double level) of both tibias; the second lengthening is 10-12cm of both humeri; and the third lengthening is 10-12cm of both femurs. The total lower limb lengthening possible in the 10-13 age group ranges from 20-27cm while that in the 6-8 onset age group ranges from 30-37cm. At age 10-13, femoral lengthening is frequently combined with a valgus extension osteotomy of the hip to treat hyperlordosis and waddling gait. During tibial lengthening at this age, lateral collateral ligament laxity is tightened, Botox injections are used to reduce tendo-achilles tension, and the foot is positioned in neutral by the external fixator to prevent equinus deformity. Stature lengthening in hypochondroplasia is less extensive (15-20cm) since the height at skeletal maturity is greater.

In conditions such as pseudoachondroplasia and epiphyseal dysplasia, in which joint surfaces are fragile and can be damaged by the muscle forces created during lengthening, the priority in management should be joint preservation by realignment and coverage of the hip, knee, and ankle. Valgus extension osteotomy of the hip, correction of frontal and sagittal plane deformities of the knee as well as ligament tightening of the collaterals, and realignment of the ankles are performed as the first priority. Modest lengthening (10-15cm) can be combined with these corrections.

An increase in stature improves body image, interpersonal relationships, and facilitates activities of daily living at home, school, and work. The main concern with lengthening for stature is worsening of the patient's functional abilities. Although complications such as nerve injury, secondary deformities, joint stiffness, contracture, and arthrosis do occur, almost all are completely reversible or preventable if treated aggressively. Pivotal to the success of treatment, is having lengthening for stature performed by an experienced surgeon in a center that specializes in limb lengthening and the management of patients with skeletal dysplasias. Despite excellent results achieved in our center, lengthening for stature is not an option for all patients and should be embarked upon judiciously. The process is expensive and physically and psychologically demanding for the patient and their family.

Lumbar Canal Stenosis in Achondroplasia

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Lumbar canal stenosis is the most serious complication in achondroplasic adults. Two anatomical factors cause the stenosis: short pedicles and decreased interpedicular distance. Lumbar hyperlodosis is the constant and essential additional factor in the cause of neurological symptomatology. We have reviewed 27 achondroplastic patients with total leg lengthening and have measured the lumbosacral, sacral angle and lumbar hyperlordosis. Following correction of the hyperlordosis, none have developed neurological symtomatology due to lumbar canal stenosis. We performed a retrospective study and evaluation. The results were compared among three age groups: <9y.o., 9-15y.o.> and 15y.o. and in this same group the following parameters were evaluated. Amount of lengthening (cm.), the kind of osteotomy and type of callus obtained, pin osteolysis, and end results. The best results were observed in 9-15 year olds who had their first elongation at eight years (first tibias and then femur or humerus elongation). The results had no relation to the resulting callus or kind of osteotomy, etc.

FUNCTION AND ALIGNMENT OF THE LENGTHENED LIMBS IN PATIENTS WITH ACHONDROPLASIA AND HYPOCHONDROPLASIA

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Since 1986, thirty-five patients with achondroplasia and seven patients with hypochondroplasia underwent bilateral lower limb lengthening using an Orthofix monolateral external fixation device. In the initial 28 patients, one femur and one tibia in the same limb were lengthened simultaneously. The opposite limb was then lengthened in the same manner, with an interval (about 3 months) between the 2 stages. A built up shoe was used to compensate for the temporary limb length discrepancy. In the next 5 cases, the femur and tibia on opposite sides were lengthened simultaneously. In the most recent 9 patients, bilateral and bifocal tibial lengthening was followed by parallel lengthening of both femurs. The mean age of the patients at the time of first operation was 14.5 years, and at followup 18.8 years. The mean lengthening achieved in the femur was 7.2 cm (range, 4.5-12 cm) and in the tibia 7.1 (range, 4.5-13 cm). More lengthening was achieved in the more recent cases. Range of motion of the knee and ankle joints was reduced during the treatment period while the external fixation device was in place, but had recovered fully at the time of followup. The function of lengthened limbs, evaluated by physical strength tests, was better at followup than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.

CLINICAL USE OF HUMAN GROWTH HORMONE IN ACHONDROPLASIA

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We previously published the results of a one year trial of human growth hormone therapy (hGH) to increase the growth velocity in a group of patients with achondroplasia. We now report the results of a two year trial of hGH therapy in a group of patients with a variety of skeletal dysplasias. There were 34 patients enrolled and 33 completed the clinical trial. Nine different skeletal dyplasias were represented, but the largest majority of patients had achondroplasia (16/34, 47%). The age of the patients ranged from 18 months to ten years. The protocol for the trial included enrollment six months prior to treatment and evaluation Q 6 months of the following parameters: measurements, bone age, MRI/Foramen Magnum dimensions, tracheal volume, HgA1C, alkaline phosphatase, and growth hormone antibody. Growth hormone was administered at .04mg/kg/day over a two year period. The growth data was normalized and analyzed in the achondroplasia patients. In year 1 of treatment there was an increase in growth velocity of 2.5 cm over predicted growth (* $p<.0002$). And in year 2 of treatment there was also a 1.5 cm increase in growth velocity over predicted (* $p< .0002$). Interestingly this increase in growth velocity was primarily observed in the lower segment and arm span, and not in the upper segment and head circumference. There was no change in bone age/chronological age ratios and there was no difference in the foramen magnum dimensions pre- and post- treatment. No patient had a complication associated with therapy. These initial data suggest that the use of human growth hormone did continue to increase growth velocity during the second year of therapy, but it appeared to be less than that attained in the first year of therapy. It is unclear to whether the prolonged use of human growth hormone therapy will continue to sustain increased growth velocity. Longer clinical trials will be needed to assess its long term potential for increasing final adult height in these patients.

GROWTH HORMONE TREATMENT TRIAL OF CHILDREN WITH TYPES III AND IV OSTEOGENESIS IMPERFECTA

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We are engaged in a treatment trial of recombinant growth hormone (Nutropin, donated by Genentech, Inc.) in children with types III and IV Osteogenesis Imperfecta. The purpose of the study has been to assess the effect of growth hormone on linear growth velocity, biochemical markers of bone metabolism, and bone histomorphometrics. We have treated 26 children, 9 males and 17 females, ages 5-12 years and including 9 type III OI and 17 type IV OI children. All children have been treated for at least one year.

During the treatment trial, children were treated with 0.1 U/kg/d of Nutropin, 6 days per week for 6 months and then the dose was doubled. A tetracycline tagged iliac crest biopsy was performed at baseline and after a year of treatment, for bone histomorphometric. Bone mineral density measurements were obtained at baseline and every 6 months. Also at baseline and every subsequent 6 months, we obtained measurements of IGF-I, Growth Hormone Binding Protein, IGFBP-2, IGFBP-3, Alkaline Phosphatase, Bone Specific Alkaline Phosphatase, Type I Collagen Peptide, and Osteocalcin.

Fourteen of the 26 children demonstrated a positive response to treatment, defined as a sustained increase in linear growth rate by at least 50% over the baseline rate. The responder group was composed predominantly of children with type IV OI: 10 of the responders have type IV OI and 70% of the treated type IV children were growth responders.

The only bone metabolic marker which differentiated responders vs. non-responders was type I collagen peptide ($p=.04$). The total patient group showed significant increases over baseline in IGF-I ($p=2.24E-8$), IGFBP-3 ($p=.00012$), Col I peptide ($p=.0028$), and osteocalcin ($p=.0029$) by 6 months of treatment. Bone specific alkaline phosphatase was significantly increased over baseline ($p=.024$) by one year.

Bone histomorphometrics of responders show a significant increase in bone volume/total volume, mineralized bone volume/total volume and bone formation rate/total volume. We see no evidence for a positive effect of growth hormone on OI bone which occurs in the absence of linear growth stimulation.

Our interpretation of our results is that there is a significant population of OI children , especially with type IV OI, who respond to growth hormone treatment with increased growth rates and positive changes in bone formation. We plan to treat up to 20 OI children who are responsive to short term growth hormone until final adult stature is attained. This will enable us to determine the long term effects on final stature, trunk length and pulmonary function, bone density and histology.

MEDICAL COMPLICATIONS IN ACHONDROPLASIA

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Achondroplasia is the most prevalent chondrodysplasia and numerous authors have documented the varied social and medical complications that may compromise a full and productive life. Complications include cervicomedullary compression, spinal stenosis, restrictive and obstructive lung disease, otitis media and tibial bowing, among others. These known complications have lead to recommendations for the anticipatory management of such patients. However, there are relatively few data on the actual frequency and timing of these problems. This paper reports data on the rates and age of occurrence of several of these complications based on a review of recorded chart information, supplemented in some cases by interview, of 193 patients ascertained from several established genetic centers with a known interest in chondrodysplasias. The length of followup varied and the rates of occurrence at specific age intervals were used to estimate the cumulative percentage affected for each complication. The report includes information on otitis media, ventilation tubes, hearing loss, tonsillectomy, speech problems, tibial bowing and osteotomies, ventricular shunting, apnea, cervicomedullary decompression and neurologic signs attributable to spinal stenosis.

GAIT ANALYSIS BEFORE AND AFTER TIBIAL OSTEOTOMY IN CHILDREN WITH ACHONDROPLASIA

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Two children with achondroplasia were studied in our Motion Analysis Laboratory before and after corrective surgery for marked varus deformity of the lower extremities. Pre-operative gait analysis demonstrated abnormalities in walking that included excessive knee flexion, foot dorsiflexion, and hip abduction and flexion during stance phase. A "lateral thrust" of the knee began early in stance phase and remained for the entire stance phase. Following tibial and fibular osteotomies bilaterally, both patients were re-studied 17 months after surgery. On the follow-up gait analysis, both patients had essentially all parameters of gait within a normal range. The "lateral thrust" of the knee was eliminated, and the position of the hip, knee, and ankle throughout both stance and swing phases of gait were within a normal range. Walking speed improved significantly, as did stride length. On computerized gait analysis evaluation, the use of simple tibial and fibular osteotomies in achondroplastic children with marked bowlegs has been demonstrated to be very effective in returning these children to normal parameters of walking, making their ambulation more energy efficient.

SEIZURES PRESENTING AS APNEA IN NINE INFANTS WITH ACHONDROPLASIA

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Central apnea, resulting from stenosis at the level of the foramen magnum, and obstructive apnea, resulting from midface hypoplasia, are cardinal features used by many clinicians to identify those children with achondroplasia at risk of sudden death. We have identified a third, independent cause of apnea in 9 infants with achondroplasia in whom apneas resulted from seizures, in a characteristic syndrome not previously recognized in this disorder. Three of these infants were recognized as part of an ongoing longitudinal study of 140 unselected children with achondroplasia, using a standardized clinical, neuroradiological and sleep study protocol Formal EEG was only undertaken when seizures were suspected clinically. In these 9 infants, apneic episodes began before 5 months of age, occurring in clusters of 2 to 15 episodes of unresponsiveness of less than a minute followed by arousal and then 15 minutes of sleep, at hourly intervals. Clusters occurred regularly every 7 to 14 days. In 3 infants, simultaneous EEG and pulse oximetry were undertaken, demonstrating concordance of temporal lobe seizures with oxygen desaturations, the electrical abnormality anteceding desaturation. These apneas did not recur on therapeutic levels of phenobarbital, with up to four and half years follow up. Several infants required foramen magnum decompression or respiratory intervention for other indications. We conclude that seizures are an infrequent but significant cause of apnea in infants with achondroplasia, whose small thoracic volume predisposes to significant desaturation during brief respiratory arrests. Failure to recognize these seizures may lead to inappropriate management, including neurosurgical intervention. We wonder if these seizures may be the direct result of the FGFR3 mutation on the developing brain.

COMPARISON OF MRI AND MYELO- CT IN THE EVALUATION OF SPINAL STENOSIS IN ACHONDROPLASIA

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Introduction: CT myelography and MRI have been used in the work-up of spinal stenosis in achondroplastic patients. This study tries to compare their respective usefulness.
Methods: We present data from 10 achondroplastic patients (5 non-operated previously and 5 previously operated). The data obtained by the review of both imaging modalities were correlated to the surgical findings.
Results: CT myelography provides a more precise delineation of the bony canal, than MRI. This information is of great usefulness in planning a surgical procedure in a previously operated spine. However CT myelography is invasive and does not clearly delineate any structure (except for the bone) below the level of a block. On MRI areas of block corresponded to areas where the CSF signal is absent. Below the block, MRI was superior to the CT scan in outlining the different anatomical structures. MRI was particularly useful in delineating below the block anterior bulging due to either disc or spur.
Conclusions: To this date, we feel that the two test are complementary and it would be unwise to rely exclusively on either one.

UPPER AIRWAY OBSTRUCTION IN ACHONDROPLASTIC INFANTS AND CHILDREN

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Upper airway obstructive signs and symptoms with or without obstructive sleep apnea is common in the younger Achondroplastic population. Tonsillectomy and adenoidectomy has been the hallmark of the treatment for this problem. Uvulopalatoplasty has been used more recently, with the use of nasal endoscopy. Ten children were examined and noted to have enlarged inferior turbinates as well as adenoid tissue protrusion through the posterior chroanae into the nasal cavity. A surgical approach was developed, with the use of a co2 laser and operating microscope, to reduce the turbinate tissue to remove the adenoid mass (following a routine transoral adenoidectomy). All the children in this group had a marked improvement in their upper airway function. None of these Achondroplasts underwent tonsillectomy.

OSTEOGENESIS IMPERFECTA, COLE CARPENTER TYPE: ANOTHER CASE OF THIS UNUSUAL SYNDROME.

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The association of craniosynostosis, ocular proptosis, hydrocephalus and bone fragility with recurrent diaphyseal fractures was reported by Cole and Carpenter in 1987, suggesting that it could represent a new variant type of osteogenesis imperfecta (OI).

Stopfer et al described a probable additional case of this syndrome in 1992, but the patient of this report presented multiple clinical findings that could not be easily associated with the malformation pattern recognized by Cole in two unrelated infants.

We present a new case of this rare syndrome in a 4 year old infant, thus providing further confirmation of this variant OI phenotype.

The proband was the product of a preterm pregnancy of a healthy, non-consanguineous couple. At the time of birth the mother was 26 and the father was 20 years of age. There was no relevant family history. Vaginal delivery was at 36 weeks with a weight of 1950g. During the neonatal period he had feeding difficulties, respiratory distress and severe hypotonio. Physical examination at age of 4 showed craniosynostosis, shallow orbits, remarkable ocular proptosis, midfacial deficiency, faintly blue tinted sclerae, and low set and posteriorly rotated ears. The teeth were small and the enamel has become hypoplastic.

Skeletal survey revealed multiple diaphyseal fractures, deformities and bowing of the long bones. His skull showed wormian bones with an abnormal configuration. The osteopenia of the skeleton was remarkable.

The purpose of this report is to contribute to the phenotypic delineation of this syndrome and to strengthen the assumption that the association of bone fragility and this striking facial dysmorphism is not fortuitous but that it reflects a rare new variant of OI.

SYRINGOMYELIA, A RARE COMPLICATION IN PATIENTS WITH OSTEOGENESIS IMPERFECTA (OI).

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Syringomyelia can be the consequence of different etiological factors. Disturbed liquor circulation or liquor pulsation is thought to be the pathomechanism. In patients with OI basilar impression is a well known phenomenon. Other neurological complications are rare. We report on three patients who presented with neurological problems, where syringomyelia was diagnosed.

Our patients aged 23 (m), 30 (m) and 49 (f) years were classified into type IV according to Sillence. They developped a broad spectrum of neurological symptoms like motoric or sensory deficits. MR-Imaging revealed basilar impression in all patients and variably developped syringomyelia. Patients 1 and 3 underwent surgical cranio-cervical decompression. This intervention could not be done in patient 2 because of his short neck. He got syringo-subarachnoidal shunting. All patients improved from their neurological symptoms. Patient 2 died six weeks after surgery probably from sleep apnoe.

Syringomyelia seems to be a typical complication in OI patients with basilar impression. Although rare it should be considered in all patients with basilar impression and spinal MR Imaging should be done to allow early and adequate therapy.

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BRUCK SYNDROME : NEONATAL PRESENTATION AND NATURAL COURSE

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A.D.(°1995) and M.D.R.(°1983) two unrelated boys born to healthy non-consanguineous parents following uncomplicated pregnancies and normal at term deliveries, had a normal birthweight. OFC was not recorded and length at birth difficult to determine because of flexion contractures at elbows and knees and bilateral clubfeet. In the following weeks, several rib and long bone fractures with well developed calluses were detected radiographically in addition to general osteopenia and innumerable wormian bones in the cranial vault. In either child the clinical diagnoses of arthrogryposis multiplex congenita and osteogenesis imperfecta Sillence type unknown were proposed. Evaluation at 6 mo (MDR) and 16 mo (AD) showed anthropometric data within normal limits, sclerae of normal color and no hearing loss. MDR could sit alone at l yr and walk unaided at 3 yrs. Teeth were of normal quality in both patients. In MDR the further clinical course was complicated by occasional long bone fractures, mildly disproportionate increase of OFC, steadily worsening gait and kyphoscoliosis. Follow-up radiographs demonstrated persisting wormian bones, basilar impression of the skull, some diaphyseal bending of the slender long bones, grotesque deformation of the pelvis, severe kyphoscoliosis, worsening osteopenia and cystic changes at old fracture sites.
The neonatal features, natural course, radiographic characteristics prompt the diagnosis of Bruck syndrome in both patients. In either biochemical analysis of the collagen type I polypeptides and molecular study (heteroduplex and SSCP analysis) of the COL1A1 and COL1A2 genes has not revealed any abnormality.

SCHIMKE IMMUNOOSSEOUS DYSPLASIA: CEREBRAL MOYAMOYA AND AUTOSOMAL RECESSIVE INHERITANCE

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Schimke immunoosseous dysplasia (SID) is an autosomal recessive skeletal dysplasia that was first described by Schimke in 1971. To date eleven patients have been reported with this disorder. SID is further characterized by (1) spondyloepiphyseal dysplasia; (2) progressive nephropathy leading to renal failure; (3) a characteristic habitus and facies (short neck and trunk, exaggerated lumbar lordosis, protruding abdomen, broad depressed nasal bridge, bulbous nasal tip); (4) episodic lymphopenia; (5) defective cellular immunity; and (6) pigmentary skin changes.

We report two girls with SID who have cerebral moyamoya leading to cerebral infarction (CVA). Although premature arteriosclerosis and CVA have been previously reported by Sanger *et al.*, this is the first characterization of the cerebral vascular abnormality found in SID. In addition, on magnetic resonance angiography, one patient has diffuse arterial narrowing consistent with the arteriosclerotic changes described by Sanger *et al* on autopsy. Both of our patients have had cerebral vascular infarctions, although only one had a clinically significant CVA. The vascular pathology may be another primary effect of the underlying genetic defect. Meticulous control of the renal hypertension and hypercholesterolemia may help reduce the morbidity of these arteriosclerotic changes, and screening for the development of cerebral moyamoya could be considered in the appropriate clinical setting.

We also report that our two patients are the children of different consanguineous unions. This provides further evidence for the autosomal recessive nature of this disorder. Prior to this report the evidence for autosomal recessive inheritance was based on the occurrence of an affected boy and girl in the same family.

To further characterize the genetic basis and the clinical course of SID, we have initiated a study to map the SID disease gene, define the immunodeficiency, and catalog the clinical manifestations and course of this disorder.

SCHIMKE IMMUNO-OSSEOUS DYSPLASIA: CASE REPORT OF SIBLINGS AND REVIEW

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Schimke immuno-osseous dysplasia is a multisystem disorder consisting of nephrotic syndrome and renal failure, spondyloepiphyseal dysplasia, immune dysfunction with episodic lymphopenia and abnormal cellular immunity, skin pigmentation changes and a characteristic facies. A total of 19 cases are previously described in the literature, including two sibships with multiple cases.

We present two further cases occurring in a family, show the progression of skeletal changes and expand the phenotype to include bicuspid aortic valve and single umbilical artery. The first child was delivered by cesarean section at 34 weeks for poor fetal movement, fetal distress and IUGR. Oligohydramnios was evident in the third trimester. Chest x-rays and a cranial ultrasound were normal with a renal ultrasound showing bilateral pyelectasis. Subsequently developed nephrotic syndrome with focal segmental glomerulosclerosis, hypertension, skeletal features of spondyloepiphyseal dysplasia, lylmphopenia and cerebral infarcts. He passed away at age 3 years and 10 months.

Our patient was the third child of this family born at 31 weeks by cesarean section for fetal distress after a pregnancy complicated by oligohydramnios and IUGR. A neonatal renal ultrasound was normal and skeletal survey showed minor changes. A two-vessel cord, PDA and bicuspid aortic valve were found. Subsequently, renal failure, lymphopenia, skeletal changes and further growth failure ensued.

SPONDYLOEPIPHYSEAL DYSPLASIA WITH NEPHROTIC SYNDROME (SCHIMKE IMMUNOOSSEOUS DYSPLASIA). A CLINICAL CASE

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We report a 6 year old boy with dwarfism, T-cell deficiency and nephrotic syndrome. He has sparse hair, high pitched voice, short barrel trunk, multiple lentigines. Radiographs were compatible with spondyloepiphyseal dysplasia.
The manifestations are very similar to those reported by Spranger et al (1991) as Schimke Immunoosseous dysplasia. As far as we know few cases have been reported in the literature.
The differential diagnosis of immunoosseous dysplasia in the framework of spondiloepiphyseal dysplasia is discussed.

ASSOCIATION OF SYRINGOMYELIA AND ACHONDROPLASIA

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OBJECTIVE AND IMPORTANCE: This study evaluates the role of achondroplastic spinal stenosis in the pathogenesis of syringomyelia.
CLINICAL PRESENTATIONS: We present data from 3 achondroplastic patients (2 males, 1 female; ages, 29,35,50 years-old). These patients presented with neurologic symptoms of upper cervical compression. Imaging studies demonstrated syrinx cavities at the cervical level, in addition to other stenotic complications of achondroplasia.
INTERVENTION: One patient required C3-4 anterior diskektomy and fusion with posterior occiput to C7 laminectomies; one, suboccipital craniectomy, C1 laminectomy, resection of cerebellar tonsils and duroplasty; one, presently considering surgery. At present 2 patients have recovered from surgery.
CONCLUSION: The presence of congenital spinal stenosis, due to achondroplasia, seems to be an important predisposing factor in the development of syringomyelia when concurrent risk factors, such as Chiari malformation and/or cervical disc and/or trauma are present.

REOPERATION FOR SPINAL RESTENOSIS IN ACHONDROPLASIA

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Introduction: This study evaluates characteristics of spinal restenosis in achondroplasia and the problems associated with redecompression. The results were correlated with radiological and surgical findings to establish the causes of achondroplastic spinal restenosis and the benefits of its therapy.
Methods: We present data from 8 achondroplastic patients (5 males, 3 females; age range , 33-52 years) who required repeat spinal decompressions.
Results: The most common neurological signs of recurrent stenosis was impaired motor function. Four patients had been previously operated on once, one patient twice, one patient three times, one patient four times and one patient five times. One patient required revision of cervical laminectomy; one, revision of thoracic laminectomy; two, revision of thoracolumbar laminectomies; four, revision of lumbar laminectomies. Fusion was utilized in four cases. Mean interval between of last two surgeries in the same location was 9.5 years. The most common causes of recurrent stenosis were facet hypertrophy and disc pathology.
Conclusions:The restenosis can occur many years after original decompression in the achondroplastic spine and reoperation was successful in lessening pain and neurologic symptoms in the majority of the patients

PERIOPERATIVE INTRACRANIAL HEMORRHAGE IN ACHONDROPLASIA

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OBJECTIVE AND IMPORTANCE: We present an unusual complication of spinal surgery in achondroplasia.
CLINICAL PRESENTATION: A 35 year-old man with achondroplasia and a previous history of spinal surgery developed recurrence of spinal claudication, progressive weakness of the right lower extremity and urinary urgency. Imaging studies demonstrated cord compression at the thoracolumbar junction.
INTERVENTION: At surgery, patient underwent a repeat thoracolumbar decompression, removal of a thoracic disc and spinal fusion with instrumentation. Postoperatively he developed confusion. Computerized tomography (CT) revealed hemorrhages in both cerebellar hemispheres with surrounding edema and mild mass effect. These were interpreted to be venous hemorrhages. Conservative therapy was successfull.
CONCLUSION:This is the first case report of perioperative venous intracranial hemorrhage in achondroplasia. It is important to draw attention to this potential complication because of the increasing number of surgical procedures performed in achondroplasia.

ATLANTOAXIAL DISLOCATION IN ACHONDROPLASIA

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OBJECTIVE AND IMPORTANCE: We present an unusual combination of atlantoaxial dislocation and achondroplasia.
CLINICAL PRESENTATION: A 53 year-old achondroplastic female presented with paresthesia and weakness both in the upper and lower extremities. She had urinary urgency , some neck stiffness and vertigo. The neurological examination suggested compression of the upper cervical cord. Imaging studies demonstrated dislocation at the atlantoaxial junction.
INTERVENTION: At surgery, patient underwent a C1 laminectomy, occipital-C2 arthrodesis with instrumentation. She was discharged on post-surgical sixth day. At 8 month follow up her strength and functional capacity were improved compared to her preoperative status and fusion appeared to be solid.
CONCLUSION: This is the first case report of atlantoaxial dislocation in adult achondroplasia. It is important to draw attention to the possibility of this association as a less common cause of cervical myelopathy.

BONE DYSPLASIAS : APROACH TO PRENATAL DIAGNOSIS.

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Genetic diseases are frequent causes of morbidity and mortality in neonatal period. Among them,bone dysplasias have a low frequency of occurrence. It has been estimated in 1/4000 in stillbirth and liveborn. The diagnosis of these entities is very important for a correct genetic counselling.
Prenatal ultrasound has become common in routine obstetric care. However, the osteodysplasias often cause diagnostic problems.
Differentiation among bone dysplasias is difficult particularly in cases where no family history is present.
It is absolutely essential to use a systematic approach when observing the fetal bones, to reach a correct presumptive diagnosis, which will allow us a correct management of pregnancy and delivery.
In the present study we propose a simplified protocol for the prenatal diagnosis of bone dysplasias, discriminating the findings according to segments (had: cranium, face; thorax: ribs; abdomen: kidneys; limbs: long bones, hands and feet), type, and associations (movements; umbilical cord; amniotic fluid). The protocol is illustrated with the authors' casuistic, particularly: osteogenesis imperfecta, achondrogenesis, thanatophoric dysplasia and Kniest dysplasia

CUMMINGS SYNDROME: REPORT OF TWO ADDITIONAL CASES

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We report two unrelated cases with a similar pattern of multiple congenital anomalies to a syndrome first described in a single offspring of consanguineous parents by Cummings et al. (AJMG 25:783-790, 1986) and later in two siblings by Urioste et al. (AJMG 41:475-477, 1991). Features common to all of these patients include: marked lymphedema with nuchal cystic hygroma, micromelia with campomelia, and a small, tapered thorax. Our first case had the additional skeletal findings of midface hypoplasia, hypoplastic scapuli, bowlder spur-like abnormality of the ulna (and perhaps the tibia), hypoplastic vertebral bodies, and elongated handle-bar clavicles. No mutations in the SOX9 gene could be identified (A. Schafer, Ph.D., personal communication). Our second case also had midface hypoplasia with micrognathia, a cleft palate, and congenital heart disease (double outlet right ventricle, hypoplastic left ventricle large VSD, coarctation of the aorta). Renal cystic dysplasia, present in the three previously reported cases, was identified in our first case, but not the second. None of the previously described patients, however, had a cardiac malformation, as was seen in our second patient. Absent in both of our cases were additional visceral anomalies including hepatic and pancreatic cystic dysplasia, polysplenia, arrhinencephaly, cecal atresia, short gut, or accessory thyroid tissue. Our two cases help to expand and better characterize the clinical and radiologic spectrum of Cummings syndrome.

AN UNUSUAL LETHAL SKELETAL DYSPLASIA IN SOMALI FAMILY

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We report a patient detected prenatally with a severe and unusual skeletal dysplasia.

The patient was born to a 26-year-old G2P1 mother and a 35-year-old father. The couple was healthy, of Somalian origin and non-consanguineous. The pregnancy was uncomplicated and the first fetal ultrasound done at 25.5 weeks gestation revealed teramicromelia, small thorax, nuchal thickening with cystic changes and generalized skin edema. A female child was delivered at term, spontaneously and by Cesarean section. Her birth weight was 2.93 kg (25-50th percentile) and length 31 cm (-8 SD). Her head was disproportionately large with OFC of 40 cm (+5SD). There were craniofacial abnormalities including a flat occiput, redundant nuchal skin, low posterior hairline and a short neck. The forehead was high with frontal bossing and nevus flammeus on the mid forehead. There were bilateral epicanthic folds, the nasal septum was hypoplastic with ridges over the alae nasi. There was a U shaped cleft palate and micrognathia. The auricles were thick, simple, cupped, and symmetric (right smaller than the left). The chest was narrow with a circumference of 29 cm (-1SD). The abdomen was prominent. All four extremities were short. There were bilateral simian creases. Skeletal survey showed shortening of the long bone with normal bone density. The vertebrae were small, hypoplastic and flattened. They were narrow laterally with antero posteriorly. C1 and C2 were poorly ossified. The skull was normocephalic with midface hypoplasia and hypotelorism. The pelvis was abnormal. The iliac bones were arched and decreased in height and width. The greater sciatic notch was absent. The hips were dislocated. The chest was short and the ribs were abnormal. They were cupped and flared anteriorly. The scapulae were hypoplastic. The long bones were shortened with widened metaphysis. Both feet showed no ossification of the talus and calcaneous. Permission for autopsy was not granted and thus no bone was submitted for histopathological studies. The skeletal dysplasia has some features in common with achondrogenesis, type 1B, but is not entirely consistent with that diagnosis.

ATYPICAL THANATOPHORIC DYSPLASIA IN A 19 WEEK FETUS

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We describe an African American male fetus, stillborn at 19 weeks gestation following induced vaginal delivery. A skeletal dysplasia was diagnosed prenataly by sonogram. Prenatal findings included severe micromelia of all long bones, short ribs, curved femurs and a small chest. The skeleton appeared appropriately mineralized. No fractures were identified. The family history was negative for consanguinity, skeletal dysplasias and birth defects. The stillborn fetus had a length of 18 cm (<5%ile) and an arm span of 14.5 cm. The upper to lower segment ratio was 13.5cm:4.5 cm. The face was non-dysmorphic.The chest was narrow with a bell-shaped appearance. The abdomen was protuberant. Both upper and lower extremities had mesomelic and rhizomelic shortening with abnormal curvature. The genitalia were normal male. Radiographs showed normal bone density with shortening and campomelia of all long bones; flattened, hypoplastic thoracic and lumbar vertebrae; a hypoplastic pelvis; and moderately shortened ribs. A post mortem examination revealed a malformed foramen magnum, flattened vertebrae, and pulmonary hypoplasia. Bone histology showed normal resting cartilage with a severe disturbance in endochondral ossification, lack of columnar alignment, minimal proliferation of chondrocytes and ingrowth of vascular mesenchymal tissue interrupting the growth plate. The radiographic findings were thought to be most consistent with an atypical form of thanatophoric dysplasia; platyspondylic lethal neonatal dwarfism (SanDiego type). The histologic findings were less clear, though not inconsistent with this diagnosis. This case illustrates the difficulty that can be encountered when trying to distinguish the variants of thanatophoric dysplasia in fetuses of this age. Although specific genetic mutations would be helpful in making the distinction, recent evidence suggests that the same "common" mutations at the FGFR-3 locus may be responsible for both common and variant forms of thanatophoric dysplasia.

RADIOGRAPHIC AND MORPHOLOGIC FINDINGS IN A PREVIOUSLY UNDESCRIBED TYPE OF MESOMELIC DYSPLASIA

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The mesomelic chondrodysplasias are a heterogeneous group of dwarfing disorders characterized by hypoplasia of the middle segments of long bones. Here, we report a previously undescribed mesomelic dysplasia in a 25 week fetus with disproportionate shortening of the extremities. Radiographic findings at necropsy included ulnar deviation of the hands, talipes equinovarus, distal tapering of the humerus, and hypoplastic fibulae, radii, and ulnae. The radiographic appearance of the long bones are distinct from previously described mesomelic dysplasias. Chondro-osseous morphological studies were performed on samples from the humerus, radius, ulna, femur, tibia, fibula, vertebra, and rib. There was mild shortening of the physeal columns, bony overgrowth, and peripheral mesenchymal ingrowth. Most notably, there were numerous areas of fibrillar degeneration and rings of collagen surrounding the chondrocytes. The histologic abnormalities were present in all the sites studied, but were more severe in the forearm and lower leg. Ultrastructural findings included a degenerated territorial matrix, pericellular halos of collagen, and dilated loops of rough endoplasmic reticulum in chondrocytes. The morphologic findings are similar to diastrophic dysplasia and the distal tapering of the humerus is reminiscent of ateolosteogenesis type II, but the pattern of matrix degeneration and the presence of inclusion bodies in the chondrocytes distinguish it from disorders of sulfate transport. We hypothesize that this disorder may be due to an abnormality in a substrate for the sulfation pathway, perhaps an extracellular matrix proteoglycan.

A FAMILIAL ACROMESOMELIC SHORT STATURE WITH DISTAL METAPHYSEAL INFARCTIONS, WORMIAN BONES, IVORY EPIPHYSES AND OSTEOPENIA. A NEW FAMILAIL AUTOSOMAL RECESSIVE BONE DYSPLASIA.

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We have identified a family with 3 sibs affected with identical physical and radiological findings consisting of short stature, short forearms, hands and lower limbs, wormian bones, severe metaphyseal changes of long bones and osteopenia. Bone fractures were never occurred.

The propositus, a male, was the older son to his unrelated healthy Arabic-Moslem parents, born after an uneventful pregnancy and delivery. Birth weight: 2800 gr. He was known to be short since the age of 2 years. No delay in walking was mentioned. On exam at the age of 3 5/12 years: all growth parameters were on the -3 to -4 SD for age. Other features including wide open anterior fontanel, short fingers, mild skin syndactily, wide wrists, pectus carinatum, short and bowed tibiae, and normal mentation. Blood chemistry was within normal limits including Ca, P, Vit. D, PTH, Alk-Phosphatase, copper and amino acids. Radiological examination showed ostopenia, wormian bones, severe mtaphyseal changes in distal radii, ulnae, tibiae and fibulae, ivory epiphyses in distal phalanx of 2nd and 3rd fingers with short and cone-shaped epiphyses of several phalanxes. The spine had normal configuration. Recent follow up examination at 11 5/12 years showed same growth parameters, anterior fontanel was still open, bowed tibiae and same bony changes.
His younger brother had the same physical and radiological findings, however, his sister's examination revealed such severe metaphyseal changes in her left arm only. Family history was negative for individuals with short stature or bowed legs. In consideration with the family pedigree, an autosomal recessive pattern of inheritance was the most likely possibility, however, mitochondrial inheritance can not be completely ruled out.

A review of the literature had failed to identify a similar disorder. Type I and II collagen analysis was normal.

More cases are needed for further delineation of the etiological causes of this peculiar bone dysplasia.

PARASTREMMATIC DYSPLASIA. REPORT OF A NEW CASE.

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Parastremmatic Dysplasia is a very unfrequent bone dysplasia. A new case with the major traits previously described by Langer, Horan and other authors is reported. A five year old native Bolivian boy attended our growth clinic, complaining of severe kyphoscoliosis. He was the first son born after an uneventful pregnancy from young, non consanguineous parents. Birth weight was 2.900 Kg. The boy had one younger and healthy brother. The patient suffered from several episodes of pneumonia before his visit to the growth clinic. Physical examination showed a well nourished, smart boy, with short sature (-3.8 DS) , short trunk, normal head circumference, severe dorsal and lumbar kyphoscoliosis, pectum carinatum, short neck, prominent joints, deformed limbs, and multiple joint contractures. Hypotonia of upper and lower limbs lead to the performing of an electromiogram, with normal results. X-Rays showed generalised osteopoenia, with markedly irregular ossification, twisted long bones, metaphyseal widening and severe platyspondyly.
The case confirms the quite constant phenotype reported in the previous eight published cases.

SPONDYLO METAPHYSEAL MEGAEPHYSEAL DYSPLASIA. REPORT OF ONE CASE

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Spondylo Metaphyseal Megaephyseal Dysplasia (SMMD), seems to be a heterogenic entity. Since there are not very many cases available in the literature and its radiological expression is not identical in all cases, we report a new case with severe coxa vara and kyphoscoliosis.
First daughter, born after a full term pregnancy from non - consanguineous parents, uneventful labour, head presentation. Both healthy parents are 30 years old. Parents have two other younger, non affected daughters. Birth weight 2950 g. From the first year of life, growth delay and kypohoskoliosis was apparent. The psychomotor development was always normal. We see the patient at the age of 11 years; height was 112.6 cm, (- 3.8 SD from local standards), sitting height 52.1 cm (short trunk for trunk/leg length standards); Head circumference 50.2 cm. Physical examination showed a normal face, short neck, short trunk, dorso-lumbar kyphoscoliosis, prominent abdomen, normal sized hands and feet, discreet limitation of hip movements. Neurological examination was normal. There were no signs of puberal development. Kyphoscoliosis progressed steadily.
Bone X-Rays show: cervical spine platyspondyly and slight odontoid hypoplasia. In the toracolumbar spine there was a marked kyphoscoliosis. Long bones showed generalized metaphyseal irregularity and large epiphyses; femoral megaepiphysis were evident, as well as coxa vara. Peudoepihysis in all metacarpals of the right hand and in the second metacarpal of the left hand were observed. There are also methaphyseal widening and irregularities.
It is important to emphasize the severity of the scoliosis previous to puberal growth spurt. At 12 years, a dorsal spine arthrodesis produced a clinical improvement.
The present case contributes to the clinical description of the syndrome at an age older than the previously published cases.

DUPLICATION OF THE DISTAL PHALANX OF THE TOES IN TWO CHILDREN WITH THE SYNDROME OF RUBINSTEIN-TAYBI

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Two children with this rare disorder are described. Family history, prenatal and perinatal period in both children is uneventful. Mental retardation, short stature and occurrence of broad thumbs, as typical features of the Rubinstein-Taybi syndrome were present in both cases. The first one, aged 13 months displayed psychomotor retardation (still only seating, with no words yet uttered), while the second one, aged 8 years, displayed a clear mental retardation (IQ 54). Both children had a stature below the third percentile for sex and age. The height velocity in the case of the 8 year old was also under the third percentile. Broad thumbs were present in both of the cases. In addition, a "bird" face with thin and prominent nose distinguishing itself from oblique and malformative forehead was seen in both of them.

Interestingly, the infant was found to have a persistent ductus arteriosus and a foramen ovale, while the other child did not have any cardial malformations. Both of them were screened for possible urinary malformations, and the results were negative. No chromosomal anomalies were found, and the 16th chromosome seemed to be normal.

The infant showed broad terminal phalanx on the thumbs. The toes showed double and fused terminal phalanxes. The 8-year old boy had broad terminal phalanxes of the thumbs, and also doubles terminal toe phalanxes. Cone shaped epiphises were found on the distal phalanxes of the I-III hand digits. Both children displayed no spine or pelvic anomalies.

Two children with classical features of the syndrome Rubinstein-Taybi are described. The hallmark of the syndrome-broad thumbs and toes are present in both of them. Although a duplication of the first metatarsal phalanx was described, an association of the syndrome with double terminal phalanxes has not described so far.

A SYNDROME OF OSTEOPETROSIS, RENAL TUBULAR ACIDOSIS, CEREBRAL CALCIFICATIONS AND DIABETES MELLITUS TYPE I

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The syndrome of osteopetrosis, renal tubular acidosis and intracranial calcifications is a well described entity. However, its association with diabetes mellitus type I has not been published so far. A 18 months old child is a third child in a family without consanguinity or significant diseases. The mother had 5 spontaneous abortions in the first months of pregnancy. His two siblings (brother and sister) are healthy. The child complained of weakness and hypothonia. At this age (18 months) he gave impression of slight motor inpairment (followed until 12-years of age he also displayed learning difficulties and mild mental retardation). His face is round, eyes slightly bulging. The X-rays of the bones showed high density and had a chalklike appearance (age 18 months). The basis of the scull and the metaphisis were dense with "bone within bone" appearance. There was little difference between the densities of the cortex and the medullar channel. Mild hypocromic anaemia was also noticed.

The tubular acidosis was proximal (blood pH 7.2-7.28, initial bicarbonates 11-16.6 mmol/l, initial urine pH 6.5-6.8, bicarbonate 11-15, acidification power was normal; creatinin clearance was normal, no glucose, proteins or amino-acids excretion in urine was found). Addition of bicarbonates was started, but the compliance was unsatisfactory. During the follow-up X-ray showed a decrease in the bone density, so far that at the age of 11 bones were hyperdense but at density levels much lower than the initial X-rays. The X ray of the scull and the CT of the brain revealed multiple calcifications scattered throughout the brain.

At the age of 12 he was admitted in hospital because of acidosis, dehydratation and sopor. The glucose in blood was 37 mmol/l, serum potassium 1.8 and 2.7 mmol/l, blood pH 7.18, serum bicarbonate levels 8 mmol/l, base excess - 45. The urine showed a massive glucosuria, urine pH was 6.5. The ECG showed low T waves, progressive bradycardia and eventually asystolia. In spite of the intensive reanimation procedures the child dyed after 2 hours. The autopsy was denied on religious grounds.

2 CASES OF A LETHAL CHONDRODYSPLASIA WITH IRREGULAR OSSIFICATION-POSSIBLE HYPOPHOSPHATASIA ?

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We report on 2 unrelated cases with a lethal skeletal dysplasia with a peculiar distribution of ossification defects: in the first case, a female foetus, pregnancy was interrupted after 18 weeks for micromelic dwarfism. A babygramm revealed severe shortening of all long bones with bowing of the femora and to a milder degree of tibiae and humeri. There were no fractures. Bone density of the long bones and the cranial vault were markedly reduced. All vertebrae with exception of the first lumbar vertebra were not ossified, surprisingly the latter had a normal radiographic appearence. There were no abnormalities of the inner organs. CNS showed severe cortical differentiation disorder with premature gyration.
The second case, a female foetus of 20 weeks of gestation, presented very similar radiographic features. Additionally there were fractures of the ribs and the femora. Radii and ulnae were not mineralized at all. The vertebrae were not ossified apart from the last thoracic and the first two lumbar vertebrae.
Hypomineralisation is a characteristic feature of lethal Osteogenesis imperfecta and the severe form of Hypophosphatasia. The radiographic appearance of both disorders is clearly different from our cases. Typ I Collagen analysis in skin fibroblasts was normal, however the activity of alcaline phosphatase (AP) was severely reduced in the amniotic cells suggesting a major role of this enzyme in the pathogenesis of the here described disorder. Molecular studies of the tissue-non-specific AP (TSNAP) gene are in progress, the results will be presented.

BRACHYDACTYLY TYPE A-4, MICROCEPHALY, SHORT STATURE, LEARNING DISABILITIES AND DUODENAL ATRESIA

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We report on 5 families with brachydactyly type A-4 (short mesophalanges II and V with toe amesophalangy), microcephaly and variably present learning disabilities, short stature, duodenal atresia, PDA, hallux valgus, restricted elbow and finger movements, and syndactyly of toes. Three previously reported families manifested the full spectrum of the syndrome and in another 4 reports the phenotype was incomplete.Penetrance of digital and toe anomalies was almost complete and microcephaly was present in 85% of known cases. Short stature was present in 60% of our cases. Esophageal and duodenal atresias were present in 22% of known cases. Correction for ascertainment bias gave a lower estimate of 14.2%. Learning disabilities were present in at least 33% of all patients.Longitudinal follow up suggested that hypoplasia or absence of the diaphyseal ossification centers is the primary cause of the phalangeal changes. Observations in a 9-year-old girl, followed since age 3.3, suggest that the eventual absence of the middle phalanges of the toes may be caused by fusion.

MESOMELIC SHORTENING OF THE UPPER EXTREMITIES WITH SPUR FORMATION AND CUTANEOUS DIMPLING

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We report a case of mesomelic dysplasia with predominant involvement of the forearms. Skin dimples over both forearms, congenital cataracts, bypotonia, mild dysmorphic features and sensorineural hearing loss were also present on physical exam. In addition humerus and hands were normal. The tibias were mildly bowed and the feet revealed metatarsus adductus. The facial features were significant for flat orbital ridges and protruding eyes, broad nasal bridge and short nose with anteverted nostrils, as well as high arched palate and retrognathia. The ears were low set on the left, but normally placed on the right and both posterior helices were underdeveloped. Prominent Radiologic findings included bony spurs of the diaphyses of the radiae bilaterally with angulated significantly shortened radii and ulnae and elbow dislocations. Mesomelic changes in the lower extremities were confined to bowing of both tibia an fibula bilaterally. To our knowledge this case represents an unusual and unique combination of findings not previously reported in association with mesomelic dysplasia. Some resemblance was found to a recently reported case by Kozlowski et. al. 1993.

CRANIOFACIAL DYSMORPHOLOGY IN DIASTROPHIC DYSPLASIA

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Diastrophic dysplasia (DTD) is an autosomal recessive osteochondrodysplasia. Mutations in the DTDST gene, which codes for a sulphate transporter membrane protein, are responsible for the disease. The clinical features include disproportionate short stature, generalized joint dysplasia, and spinal deformities. Also, palatal deformities, either cleft palate or submucous cleft palate, are frequent.
We studied 50 DTD patients both clinically and radiographically for the craniofacial characteristics. From the lateral cephalograms we observed short anterior cranial base length, short and posteriorly positioned upper and lower jaws, and increased anterior facial height. The transverse facial dimensions were studied from the postero-anterior (PA) cephalograms, and were found to be close to normal. Our results indicate that the craniofacial dysmorphic features in DTD most likely result from deficient development and growth of the cartilaginous structures, whereas the intramembranously developing bones and the appositional growth pattern do not seem to be primarily affected.

HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH GENETIC SKELETAL DYSPLASIAS

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While medical knowledge on genetic skeletal dysplasias has expanded, very little is known about the patients' health-related quality of life (HRQOL). The aim of our study was to examine the perceived HRQOL of all the 172 patients with achondroplasia (ACH), cartilage-hair hypoplasia (CHH) and diastrophic dysplasia (DTD) from the Department of Clinical Genetics, Helsinki University Central Hospital, who were currently aged 12-54 years. A previously validated, age-appropriate, multidimensional questionnaire (15D or 16D for patients aged 16-54 years, and 12-15 years, respectively) was mailed to the patients with written instructions. The response rate after one reminder was 150/172 (87%). In addition, 10 incompletely filled questionnaires were excluded. Of the respondents, 121 were age 16-54, and 19 age 12-15. 661 controls of the same age from the National Population Register (adults) and five elementary schools (adolescents) had completed the 15D and 16D measures and their valuation questionnaires previously. The age and sex standardized overall HRQOL score of the adult patients (mean 0.885, SD=0.083) was significantly lower than that of normal controls (mean 0.928, SD=0.071) ($p<0.001$). The patients reported significantly lower status than the controls on the dimensions of mobility, usual activities, sexual activity, and discomfort and symptoms ($p<0.001$). In addition, there was a significant inverse correlation between HRQOL and age, most marked in patients with DTD. Adolescent patients demonstrated HRQOL profiles similar to those of adults. However, age-specific problems occurred on the dimensions of school and hobbies, friends, and physical appearance ($p<0.05$). In detailed examination of the patient groups some clinically unexpected findings were observed, suggesting that denial is at least in part involved. We conclude that subjective assessment of HRQOL of patients with chondrodysplasias is valuable for provision of optimal care. In treatment and management, special attention should be paid to the dimensions on which the patients' perceived status is currently suboptimal, especially during adolescence which probably is the most critical period in the lives of these individuals.

PHENOTYPIC AND RADIOLOGICAL ANALYSIS IN SEVEN CASES OF 3-M SYNDROME IN TWO FAMILIES

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The 3-M syndrome is a rare autosomal recessive syndrome of prenatal and postnatal growth deficiency. It was initially reported by Miller et al in 1975 and a total of approximately 22 cases have been published. Features include proportionate short stature, relatively large cranium, prominent forehead, triangular face, malar/maxillary flatness, upturned nose, infancy flat nasal bridge, infancy micrognathia, prominent mandible with age, pectus excavatum/carinaturm, short incurved 5th fingers, joint hyperextensibility with increased incidence of dislocated hips, and reduced elbow extension or dislocation. Radiologically, the long bones are slender, the ribs thin, and the vertebrae show reduced anteroposterior diameter.

We present 4 siblings (ages 18, 15, 8, newborn) from non-consanguineous eastern Kentucky parents and 3 siblings (ages 12, 9, 6) from non-consanguineous Phillipino parents. All 7 cases were short at term birth (range 37cm-41cm) and reduced in birth weight (range 2kg-2.5kg) but with relatively large head circumferences (range 33cm-36.5cm). All grew well-below 3rd centile in length and weight postnatally, but maintained normal head circumferences imparting relative macrocephaly. All demonstrated the above noted facial, chest, and limb findings. Radiologically, thin/slender long bones/ribs were noted and some showed foreshortened vertebral bodies.

The 3-M syndrome is distinct craniofacially and radiologically. It has been confused with non-lethal disproportionate dwarfing conditions and Russell-Silver syndrome. Its major impact is the moderate to severe proportional short stature.

THE ASSOCIATION OF IPSILATERAL PHOCOMELIA AND ASYMMETRIC CRYING FACIES. A MERE ASSOCIATION OR A NEW SYNDROME

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A male patient age 10 months presented by Right upper limb phocomelia, the left upper limb and both lower limbs were normal, he was born at term after a normal pregnancy and delivery, he is the second child to healthy first cousin parents with no family history of any similar condition, his mental and motor development were normal, attacks of convulsions occurred and were diagnosed as due to Vitamin D deficiency ricket. He also had iron deficiency anemia (Hb 7gm%). Examination revealed asymmetric crying facies, normal tone and reflexes in both upper & lower limbs, he had no ophthalmoplegia nor deafness, the chest & heart and abdomen were free except for umbilical hernia, there was no dysmorphic features, growth parameters were within the normal range for his age, cytogenetic study was 46Xy by G banding and high resolution revealed no abnormality, induction of breakage was relative by Desoxyn butane, CT brain was normal, EMG & nerve conduction for facial nerve were normal, renal function as well as abdominal and pelvic sonography were normal, Echocardiography, auditory brain stem, EEG revealed no abnormalities, Metabolic screen including serum uric acid level were normal. Radiologic examination of the Right upper limb revealed a shortened humerus, its lower end was bifurcated and fused with hypoplastic radius & ulna forming an inverted Y with unequal limbs, the radial limb was longer than the ulna.

Review of the literature revealed no similar association, is it a coincidental association or a new syndrome.

PLATYSPONDYLIC LETHAL SKELETAL DYSPLASIA WITH SECONDARY PELVIC OSSIFICATION CENTERS: A SUBTYPE OF THE SAN DIEGO VARIANT OR A DISTINCT ENTITY?

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The platyspondylic lethal skeletal dysplasias (PSLSD), or thanatophoric variants, are a heterogeneous group of disorders characterized radiographically by decreased ossification of the cranial base, short ribs, platyspondyly, micromelia, and metaphyseal cupping. We report 13 cases of PSLSD that radiographically resemble the San Diego variant but are distinguished by the presence of extra ossifications centers close to, but separate from, the acetabular roof and/or ishium. These novel secondary ossification centers have not been observed previously in the skeletal dysplasias. The chondro-osseous morphology of these cases at the light and electron microscopic level are remarkable for irregular physeal columns, prominent overgrowth of perichondral bone, peripheral ingrowth of mesenchymal tissue across the physis, and rough endoplasmic reticulum inclusion bodies containing a granular material. The morphology of these cases is indistinguishable from typical cases of PSLSD, San Diego type. Whether these 13 cases represent a subtype of the San Diego variant or should be classified as a distinct entity will await the elucidation of the basic defects in the PSLSD's.

BRACHYDACTYLY TYPE C - CLINICAL AND MOLECULAR CHARACTERIZATION CAUSED BY MUTATIONS IN THE MORPHOGEN CDMP-1

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Autosomal dominant Brachydactyly Type C (BdC) is characterized by reduction in size of the middle phalanges of the 2nd, 3rd and 5th digits together with the 1st metacarpal. We evaluated skeletal features in a five generation kindred with 12 affected individuals. Although 2nd, 5th middle phalanges and 1st metacarpal were the principal skeletal elements involved, metacarpal phalangeal profiles revealed affectation of other skeletal elements. Interestingly one affected individual also had a bilateral Madelung's deformity. Linkage mapping of BdC in this family placed the locus on chromosome 20 near D20S470. The prior localization of Cartilage - derived morphogenic protein - 1(CDMP-1) mutations also to chromosome 20 suggested it as a candidate for BdC. Sequencing of CDMP-1 revealed a premature termination mutation in the coding sequence as the likely cause of the phenotype. Previous mutations CDMP-1 have been shown to cause two autosomal recessive disorders - Hunter-Thompson acromesomelic dysplasia in humans and brachypodism in mice. Additional CDMP-1 mutations have now been found in other BdC kindreds. Our results show that CDMP-1 mutations can cause autosomal dominant as well as autosomal recessive phenotypes.

SKELETAL REMAINS FROM AN OSTEOCHONDRODYSPLASTIC DWARF FROM ANCIENT EGYPT

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Wall paintings and descriptions clearly indicate the presence of dwarfs in ancient Egypt. Particularly from the first periods of Egyptian high culture, the Early Dynastic Period and the Old Kingdom (1st-8th dynasty, ca. 2920-2160 BC) several archeological findings including drawings, wall reliefs and stelae describe dwarfic individuals. In contrast to the usual ancient Egyptian convention of drawings with strict body proportions, the dwarfs present with a variable shortening of limbs and trunk indicating dysproportional dwarfism. The nature of dwarfism, however, remains unclear. Some dwarfs have been burried in distinct tombs. Due to insufficient conservation or loss of skeletal findings from those tombs, no osseous material has been available for further investigation of the type of dwarfism of those dwarfs who lived approx. 5000 years before today.

During a recent excavation campaign executed by the German Institute of Archeology Cairo, we identified in the tomb complexes of the Kings DEN and QUA'A (early dynastic period, ca. 2920-2770 BC) a left distal humerus and several metatarsal bones which could clearly be identified to be those of dwarfs.

Particularly interesting are several metatarsal bones from King DEN's tomb presenting with an extreme shortenting and significant metaphyseal widening. The growth plates were closed indicating an individual's age of more than 20 years. On plain radiographs the osseous structure confirms the macroscopic observations with normal bone mineralization.

Although we cannot provide a distinct diagnosis in this unusual case our findings clearly provide evidence for the presence of osteochondrodysplastic dwarfism in ancient Egypt. Furthermore, this observations indicates that ancient drawings of dwarfs seem to correspond to real pathologic cases. Possibly, a molecular genetic analysis will provide a distinct diagnosis in this particular dwarf provided that the genomic DNA present is still preserved.

AN UNUSUAL FORM OF CHONDRODYSPLASIA PUNCTATA

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We report a male neonate born at 31 weeks after an uncomplicated pregnancy. There was no evidence of alcohol abuse by the mother. Birth weight was 2020 g (P75-90), length 43 cm (P50) and head circumference 32.7 cm (P90=32cm). Because of respiratory distress the baby was intubated soon after birth. Physical examination revealed craniofacial dysmorphism characterized by hypertelorism, cloudy corneae, high nasal bridge, bilateral cleft lip and palate and microtia. Skin defects were found at the edges of an extremely large anterior fontanelle. The genitalia were small with cryptorchidism. Hands and feet showed brachydactyly with short and broad distal phalanges and hypoplastic nails. Radiographs of the skeleton revealed stippling in the shoulder, hand, ankle and sacral regions without rhizomelia or mesomelia. At least two thoracic vertebral bodies showed coronal clefting. The thorax was short with eleven pair of ribs. Some ribs had a wavy and slender appearance. Hypoplasia of the distal phalanges, severe shortening of the proximal phalanx of the second finger and absent ossification of the first metacarpal and fifth middle phalanx were present. Cytogenetic analysis at the high resolution level did not reveal any abnormalities. Levels of very long-chain fatty acids and phytanic acid in plasma and plasmalogens in red blood cells were normal. Immunohistochemical and morphologic studies confirmed the presence of peroxisomes in the liver. MRI of the brain revealed a Dandy-Walker anomaly and hypoplasia of the corpus callosum. The baby died 24 hours after birth. Autopsy revealed in addition a ventricular septal defect and multiple rib anomalies. The clinical and radiographic features of this patient do not fit well with any known form of chondrodysplasia punctata. Because of the resemblance of the hand radiographs with the brachytelephalangic type and the presence of associated dysmorphic features, molecular investigations are currently performed to rule out the possibility of a contiguous gene deletion syndrome on the short arm of the X chromosome where the gene for arylsulfatase E has been mapped.

A SYNDROME OF MENTAL RETARDATION, SHORT DISTAL PHALANGES. NAIL DYSPLASIA AND SMALL PENIS.

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A patient with unknown diagnosis is reported. N.D. is a 12 years old male. He was referred, to the Pediatric Clinic of Catania University, for mental retardation and anomalous features. The main anomalies were localized in the face and in the extremities. He showed narrow forehead, bitemporal hollowing, thick eyebrows with synophrys, upslanting palpebral fissures, thick lips, large and protruding ears. At the extremities the anomalies were bilaterally present. They consisted of large thumb, brachydactyly, clynodactytly of the 5th finger. The halluces were large, there was nail hypoplasia of II and IV right toes and of IV and V left toes; the 4th right toes was overlapped on the 3rd. The other features were small penis, bilateral inguinal hernia, moderate mental retardation. The X-rays of the hands showed partial hypoplasia of the II, III and V distal phalanges and slightly short 4th metacarpal bilaterally. X-ray examination of the feet showed bilaterally hypoplasia of the distal phalanges of the hallux with pointed apex, hypoplasia of the distal phalanges of II and IV toes on the right and of the IV and V on the left. Valgus metatarsus. Rudimentary, supernumerary rib was also present. Searching on LDDB Database and on POSSUM/OSSUM software, combining different criteria (brachydactyly, nail hypoplasia, small penis), we found 38 syndromes for a possible diagnosis, but only two of them share some features with our patient: that one described in the article of Tonoki and coll. entitled "A new syndrome of dwarfism, brachydactyly, nail dysplasia and mental retardation in sibs" (Am J Med Genet 1990, 36:89-93) in which a brachydactyly type B is present, and the syndrome reported in the article of Tsukahara and coll. entitled "New syndrome. Type A1 brachydactyly, dwarfism, ptosis, mixed partial hearing loss, microcephaly and mental retardation" (Am J Med Genet 1989, 33:7-9). In our patient, however, the brachydactyly seems of a different type and hearing loss is absent.

NAGER ACROFACIAL DYSOSTOSIS WITH ATYPICAL ANOMALIES

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Nager acrofacial dysostosis includes the facial anomalies of mandibulofacial dysostosis and the predominantly preaxial limb defects. The spectrum of the condition has variable additional features. We report a case of this very rare congenital anomaly. The boy was born at 37 gestational weeks (1442g, 37.0cm) to healthy and non-consanguineous parents. No congenital anomalies were detected in this family. The facial anomalies of this infant included severe mandibular and frontal hypoplasia, hypoplastic malar and maxillary bones, absent lower lateral eye lashes, low set ears, and a soft-palate cleft. Upper limb anomalies consisted of the right missing thumb, the left floating thumb, the bilateral brachydactylies of the second and fifth rays, and ankylosis of the elbows. Lower limb anomalies consisted of the bilateral brachydactylies of the first ray and congenital club feet. Radiographical examination of both arms showed right humeroradial synostosis and the apposed surfaces of the left distal humerus and the proximal radius were irregular and sclerotic. Humeroradial synostosis and frontal hypoplasia have not been reported in other cases of Nager acrofacial dysostosis described in the literature.

A NOVEL CHONDRODYSPLASIA IN A CHILD WITH WAARDENBURG SYNDROME

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We present a child with Waardenburg syndrome type I and a novel chondrodysplasia punctata. B.H. was born to a mother with Waardenburg syndrome and a father with nonsyndromic sensorineural deafness. Pregnancy was complicated by polyhydraminos. Femoral shortening was noted on prenatal ultrasounds. Birth weight was 3210 gms (50th percentile), length 42.75 cms (<<3rd percentile), and OFC 37.5 cms (95th percentile). Neonatal films were significant for platyspondyly and amorphous calcifications in the shoulders, knees, and hips. Small punctate calcifications were noted in the 2nd, 3rd, and 4th metatarsals with marked shortening of the 2nd and 3rd toes. Head ultrasound was normal. BAERs revealed profound sensorineural hearing loss.

Physical examination at 3.75 months revealed a weight and length less than third percentile. A white forelock and telecanthus was present. There was rhizomelic shortening of the upper and lower extremities with decreased range of motion at the shoulders and elbows. The infant cried when these joints were manipulated. There were single transverse palmar creases bilaterally. The second and third toes were markedly shortened. Investigation included normal very long chain fatty acids, plasmalogens, karyotype, ophthalmologic examination, head CT, and sleep study. B.H. has required supplemental nocturnal oxygen and feeds via percutaneous gastrostomy tube.

B. H.'s cutaneous albinism, telecanthus, sensorineural hearing loss, and maternal family history suggest that he has Waardenburg syndrome. He also has a novel chondrodysplasia characterized by stippling, metaphyseal cupping, and platyspondyly. The radiographic findings are similar but more severe than SMED, Short Limb-Abnormal Calcification type (*Am J Med Genet* 45:488, 1993). This constellation of findings may represent a severe form of Waardenburg syndrome, a digenic interaction between the Waardenburg (PAX3) gene and the nonsyndromic deafness gene, or the presence of two different diseases.

FAMILIAL BRACHYDACTYLY, MYOPIA AND RENAL ANOMALIES. A NEW ENTITY?

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We report on a family in which a constellation of acral, renal and eye anomalies, inherited as autosomal dominant trait with variable expressivity is present. The affected individuals are the mother and her children. They showed IUGR, short stature, early-onset myopia, brachydactyly with cutaneous syndactyly and/or interdigital webbing. In one of them a bifid hallux and double right urether were present. Two of the patients showed chorioretinic dystrophy and relative macrocrania; in one of them a supernumerary VII cervical rib and an absent eleventh left rib were detected. No other notable anomalies as joint stiffness, Duane anomaly, deafness etc. were present. The mental development was normal. Weill-Marchesani syndrome can be excluded because of the absence of spherophakia, maxillary hypoplasia, characteristic facial features and joint stiffness. In the acro-renal-ocular syndrome brachydactyly and cutaneous syndactyly are present as observed in our patients, but this syndrome is also characterized by hypoplastic or absent thumb and by coloboma of the optic nerve and of the retina, all features absent in our family. The syndromes listed, searching by different features, on the LDDB Database and on the POSSUM/OSSUM software did not fit with the clinical findings showed by our patients.
In conclusion this family could be an example of a new autosomal dominant condition.

TWO CASES OF HEREDITARY ACHONDROGENESIS TYPE I B (FRACCARO) IN A NONCONSANGUINOUS MACEDONIAN FAMILY

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A 32 years old woman delivered four times. While the second and the third pregnancies were terminated with uneventful deliveries and the new-borns were healthy, the first and the fourth pregnancies were spontaneously interrupted. The first delivery was terminated in the 24-th weak of gestation by spontaneous delivery of a dead female fetus. The fetal head was large and was sitting on the shoulders without a neck. The face was swollen, the facial features broad. The limbs were short and "flipper-like".

Radiological diagnoses determined poorly ossified calvaria with a bone plaques in the frontal region. In addition, absence of ossification of the cervical and thoracic vertebrae and partial ossification of the lumbar and sacral vertebrae, thin ribs which were poorly mineralised, deformed iliac wings and absence of ossification of pubis and iscia were noted. A pronounced shortening of long bones and concave metaphyseal ends associated with lateral spurs were also observed. Those features were likely to classify the disorder as achondrogenesis type IB (Fraccaro).

The fourth pregnancy was followed by ultrasound. Polyhidramnion and retardation in development was noted. The poor mineralisation of the fetus, retarded development and trunk-limbs disproportion allowed a prenatal diagnosis of achondrogenesis type IA. The parents did not chose to terminate the pregnancy. However, a spontaneous delivery occurred in the 27th week of gestation. The child was female and stillborn. Its appearance ant roentgenografical features were essentially the same as in the previous child.

Since the disorder appeared only in the sibship of the proband, and not in parents or other relatives an autosomal recessive inheritance seems likely.

A CASE OF PRENATALLY DIAGNOSED THANATOPHRIC DYSPLASIA TYPE I

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A second pregnancy in a 34-year woman was routinely followed by regular ultrasound examinations. During the check-up in the 20th week of gestation a retardation of development, trunk-limb disproportion, narrow chest and grossly undermineralised skeleton was noticed. A severe form of lethal skeletal dysplasia therefore demonstrated. The parents have chosen an inducted induction of premature delivery at 22nd week of gestation. A female with large head sitting on shoulders without neck, with flat and broad face, slanted eyes and narrow chest cage was stillborn. The limbs were short and broad, the subcutaneous tissue was abundant.

Radiographs showed large head with frontal bossing and small face. The nasal bridge was depressed. The chest cage was narrow, the ribs short with spikes on their anterior ends. Small and deformed scapulae were also found, while the clavicles were not malformed. The vertebral bodies were severely flat, the intervertebral spaces were wide, while the interpedicular distances were narrowed. Iliac wings were short and small with medial and lateral spurs. The tubular bones are extremely short and bowed. Their metaphyses were flared.

Histologically the epyphyseal growth zone was retarded and disorganised. Enchondral ossification was severely disturbed. The cartilage columns in the juxtaphyseal primary spongiosa of the methaphyses were reduced in number and were distorted. Bands consisting of fibrous tissue penetrated the growth plate.

A DISTINCT FORM OF SPONDYLOEPIMETAPHYSEAL DYSPLASIA IN AN INBRED PAKISTANI KINDRED

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A large inbred kindred from a remote area of Pakistan, comprised of 8 generations, with a distinct form of spondyloepimetaphyseal dysplasia is described. We evaluated 19 affected individuals, 12 males and 7 females. Analysis of the pedigree is strongly suggestive of autosomal recessive inheritance and consanguineous loops could account for all the affected individuals being homozygous for the abnormal allele. The clinical findings included: short stature (121 -140 cm), short bowed limbs, kyphosis, an abnormal gait, enlarged joints, precious osteoarthropathy, and normal intelligence. Radiographs revealed epiphyseal delay at the hips and knees, platyspondyly with irregular end plates and narrowed joint spaces, diffuse, early osteoarthritic changes and mild brachydactly. There were mild metaphyseal abnormalities seen predominantly at the hips and the knees. This distinctive phenotype can be distinguished from other autosomal recessive forms of SEMD because of the mild degree of metaphyseal involvement, the normal chest circumference and the absence of loose joints or other anomalies.

RADIOGRAPHICAL EVALUATION OF THE LOWER LIMB DEFORMITIES IN PATIENTS WITH DIASTROPHIC DYSPLASIA (DD)

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Diastrophic dysplasia (DD), from the group of osteochondrodysplasias transferred recessively in autosomes, is exceptionally common in Finland where it has been ascertained in 183 patients thus far.The gene responsible of DD, i.e. the DTDST gene with a number of its mutations has been defined (Hästbacka et al. CELL 78, 1994.). Together with the short-limbed dwarfism, kyphoscoliosis (37%), generalized dysplasia and contractures of the joints (~100%), symphalangia of the finger joints, hitchhiker´s thumbs, deformities of the feet (~100%), cleft palate (30-40%) and deformation of the ear lobes, are recognizable already in a newborn.

Deformities of the lower limbs are described with the findings in plain radiographs and ultrasonographic examination.

Progressive deformation of the hips may be observed in all the patients and the deformity varies from a moderate to a severe form. The moderate form includes flattened, near-spherical femoral head; moderately shortened femoral neck; visible proximal femoral bony epiphyses; shallow acetabulum and satisfactory joint congruity. The severe form leads to markedly flattened and inferomedially bulked femoral head; shortened and widened femoral neck, nonforming or grossly deformed and fragmented proximal femoral epiphyses; prominent overgrowth of the greater trochanter, shallow flat-rooflike acetabulum and development of the joint configuration into a double hump deformation with marked loss of joint space.

In the knee joint, the femoral sulcus is narrow and deep, the lateral femoral condyle is hypoplastic compared to the prominent medial condyle, the position of the patella is inferior to the tibiofemoral joint and the ossification center of the patella appears delayed or not at all. Ostearthrotic changes; degeneration of the articular surfaces with loss of articular space and formation of the ostephytes, can be observed at the end of growth. Natural development of the hip and knee joints leads to severe secondary osteoarthrosis before early middle age.

Foot deformities in DD have been classified by Ryöppy : 1. "normal", 2. metatarsal adduction, 3. tarsal valgus and metatarsal adduction, 4. equinus and 5. equinovarus with adduction (Ryöppy et al. JBJS 74-B,1992).

Radiographic Anthropometry In Patients with Multiple Epiphyseal Dysplasia.

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This study was performed to investigate the diagnostic value of radiographic anthropometry in patients with multiple epiphyseal dysplasia (MED).
In 15 individuals of one family with MED (12 affected, three not affected), all of whom were younger than 16 years, measurements were made of the distal femoral metaphysis and epiphysis on standard anteroposterior radiographs of the knee joint. In each individual, the height of the epiphysis was plotted against the width of both the epiphysis and the metaphysis (1). Sensitivity, specificity, and positive and negative predictive values were calculated.
In 11 of 12 individuals with MED, the plotted values were more than two standard deviations below the mean. Sensitivity was 92%, specificity was 100%, and positive predictive value was 100%.
Conclusion. Anthropometry is useful to detect involvement of a patient in a family with MED. In this particular family, anthropometry achieved a high positive predictive value.

1. Schlesinger AE, Poznanski AK, Pudlowski RM, Millar EA. Distal femoral epiphysis: normal standards for thickness and application to bone dysplasias. Radiology 1986; 159:515-519.

SCLEROSTEOSIS IN A VENEZUELAN KINDRED

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Sclerosteosis is an autosomal recessive disorder characterized by generalized osteosclerosis with syndactyly and other abnormalities of the digits. Most patients have been South African of Dutch ancestry. The condition is considered to be, clinically and radiologically, almost indistinguishable from Van Buchem disease. We report a 16 years old female patient, the youngest of four sibs, from a consanguineous marriage (first cousins) in which there was also a spontaneous abortion. At 15 years of age, the index case has had an episode of increasing intracranial pressure with headache, vomits and diplopia. A ventricle-peritoneal derivation was then performed. At 16 years of age she reports some hearing loss. Physical findings at this age include: Ht: 1.65 m. OFD: 57.4 cm (>98% tile). ICD: 34 mm. OCD: 100 mm. The face is somewhat distorted with frontal prominence, mild proptosis, hypertelorism and the mandible is prognathic, broadened and squared. Hands and nails looked normal. Radiographic studies showed: hyperostosis and osteosclerosis of neurocranium, mandible, ribs, clavicles, pelvis, vertebrae, and tubular bones. The phenotypic and radiographic features are consistent with the diagnosis of Sclerosteosis in the index patient, whose parents shared and unusual family name and were born in the Northwestern part of VENEZUELA, in an area in close geographical proximity with the Neetherland Antilles (Curacao, Aruba, Bonaire), which have been occupied by Hollanders since the 17th century. These findings would be consistent with the speculative concept of being Sclerosteosis a marker of Dutch ancestry.

CORONAL AND SAGITTAL CLEFTS IN SKELETAL DYSPLASIAS

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Objective: To assess the role of coronal and sagittal clefts in diagnosing skeletal dysplasias.
Methods: A search was done in the database at the International Skeletal Dysplasia Registry to find all reported cases with coronal or sagittal clefts. 100 cases, representing 40 different diagnoses, were found. The major groups from the search were: Chondrodysplasia punctata, Atelosteogenesis, Kniest dysplasia, Short-Rib-Polydactyli syndrome and Dyssegmental dysplasia. So far ¼th of the about 8000 cases in the Registry are computerized according to specific findings. We therefore reviewed all cases in the major groups, including also those not computerized. Only cases with both AP and lateral films of the spine were included in the study and we registered all cases with coronal and sagittal clefts.
Results: Findings are summarized in this table and the numbers represent a sum of all firm types in each group:

Groups	Total numbers	Coronal and/or sagittal clefts	Overall percentage
Atelosteogenesis (ATO)	16	15	94%
Chondrodysplasia punctata (CP)	33	24	73%
Dyssegmental dysplasia	11	8	73%
Kniest dysplasia	52	32	63%
Short-Rib-Polydactyli S.(SRP)	31	18	58%
Total	201		

Sagittal clefts were noticed in ATO - III, CP (many types), Dyssegmental d. (S-H and R-D) and SRP-II (Majewski). Coronal clefts were found in all groups, most frequent in ATO. The location of coronal clefts was predominantly thoracic in CP and SRP, lumbar in ATO and Kniest.
Conclusion: Coronal and sagittal clefts are of major diagnostic value in the groups mentioned in the table. The search did not come up with new groups where clefts in the vertebral bodies are of major diagnostic value.

NAUMOFF SHORT RIB POLYDACTYLY SYNDROME POSSIBLY COMPOUNDED WITH MOHR SYNDROME.

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This stillborn baby boy had findings of severe constitutional dwarfism - short limbs, very short ribs, polydactyly, and multisystem congenital anomalies. The skeletal radiographic findings are consistent with Naumoff (type III) short rib polydactyly syndrome. Among the additional anomalies in this stillborn baby were cleft palate, notching of the upper lip, small tongue with accessory tissue at its base, and oral frenula. These additional anomalies together with the digital findings are suggestive of Mohr (type II) orofaciodigital syndrome. The combination of findings supports the possibility of a Naumoff-Mohr compound presumably via an autosomal recessive mode of inheritance.

GRACILE BONE DYSPLASIA

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Gracile bones are a frequent abnormality associated with fetal hypokinesia of any etiology. With the exception of thin, undermineralized bones, the chondro-osseous morphology is usually normal in these cases. We present a lethal skeletal dysplasia characterized by dysmorphic features, central nervous system abnormalities, gracile long bones, and abnormal chondro-osseous morphology. In addition to a short, disordered growth plate, the chondrocytes contained dilated loops of rough endoplasmic reticulum, suggesting an abnormality in an extracellular matrix protein. This protein appears to have effects on chondro-osseous as well as facial and central nervous system development. We suggest the term "gracile bone dysplasia" to describe this disorder.

UNKNOWN CASES FOR **POSTER** PRESENTATION

Case #45	Craniosynostosis - RU Synostosis J. Campbell, M.D.
Case #46	AO, Type J. Campbell, M.D.
Case #47	M.M. D. Miller, O. Hurko
Case #48	Lethal Micromelic Dysplasia P. Freisinger, M.D.

A SPLICE SITE ALTERATION IN THE FIBROBLAST GROWTH FACTOR RECEPTOR 3 (FGFR3) GENE IS ASSOCIATED WITH PROPORTIONATE NON-SYNDROMIC SHORT STATURE.

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Analysis of the FGFR3 gene was performed on a population of individuals with proportionate, non-syndromic short stature in an attempt to identify differences in this gene which may correlate with this trait. Probands were all less then 2.5 standard deviations below the mean for height. We report the identification of a splice site base change in intron 9 of the fibroblast growth factor receptor 3 gene. This base change, a G to T transversion, occurs at the +5 position of intron 9, deviating from the consensus splice donor sequence at this base. We have identified this difference in 5 of 100 individuals with generalized short stature. This base change results in the creation of an AlwNI restriction site. Amplified genomic DNA was analyzed from 195 control individuals by restriction digestion, with only 1 having the change at this position ($p<.05$). The height of this individual, an adult female, was 5'4". Studies are currently underway to determine if this base substitution has an effect on splicing of the FGFR3 mRNA. A base change in the intron 9 splice donor sequence may result in exon-skipping of exon 9 in the mRNA. The identification of this FGFR3 sequence alteration in 5 of 100 persons with non-syndromic proportionate short stature suggests that FGFR3 variation may contribute to the multifactorial determination of height.

CRANIOSYNOSTOSIS SYNDROMES AND FGFR3 MUTATIONS WITHOUT PROBLEMS IN LONG BONE DEVELOPMENT

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As knowledge unfolds concerning the role of specific mutations in fibroblast growth factor receptors (FGFR) in causing various craniofacial dysostosis syndromes, investigators will have the opportunity to study the molecular mechanisms of altered morphogenesis that result in such syndromes. Recently, a unique point mutation in FGFR3 (Pro250Arg) was reported in 61 individuals with coronal craniosynostosis from 20 unrelated families (Am. J. Hum. Genet. 60:555-564, 1997). Previous reports of individuals with this syndrome termed this disorder Jackson-Weiss syndrome, then subsequently termed it Adelaide-type craniosynostosis, and emphasized associated coned epiphyses, brachydactyly, capitate-hamate fusions, calcaneo-navicular fusions, and hearing loss in some of the affected individuals (Am. J. Med Genet 51:121-130, 1994). Others emphasized the association of this disorder with brachydactyly and/or carpal-tarsal fusions (Clin. Dysmorphology 3:215-223, 1994; Proceed. Greenwood Genet Center 12:106-107, 1993). We compare the clinical characteristics of previously reported cases of this mutation with our own case material and suggest that this entity be designated FGFR3-associated Coronal Craniosynostosis with Brachydactyly and Carpal/Tarsal Fusions to emphasize these features.

A second type of craniosynostosis has been linked to Crouzon Syndrome with Acanthosis Nigricans and a specific FGFR3 mutation (A1a391Glu). Individuals with this disorder have early onset of acanthosis nigricans during childhood, often with associated choanal atresia and hydrocephalus. There is a striking female predominance for this disorder, and the association of choanal atresia with hydrocephalus in an individual with Crouzon facial features should suggest molecular analysis for this mutation. We compare the clinical characteristics of previously reported cases of this disorder with our own case material and suggest that this disorder be termed FGFR3-associated Crouzon syndrome with Acanthoasis Nigricans, Hydrocephalus and Choanal Atresia to help guide the search for specific molecular mutations.

BIOCHEMICAL ANALYSIS OF FIBROBLAST GROWTH FACTOR RECEPTOR 3 (FGFR3) IN THE CELLS FROM SKELETAL, SKIN, AND BRAIN (SSB) DYSPLASIA PATIENTS

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Since 1994, mutations in fibroblast growth factor receptor 3 (FGFR3) have been found in a number of skeletal dysplasias, including achondroplasia, hypochondroplasia and thanatophoric dysplasia (TD) type I and II. A novel mutation in FGFR3, A1949T: K650M, has been reported in three unrelated patients with Skeletal, Skin, and Brain (SSB) Dysplasia, a previously undescribed skeletal dysplasia characterized by extreme short stature, severe tibial bowing, profound developmental delay and acanthosis nigricans (Francomano, et al., Am. J. Hum. Genet. 59, A25, 1996). Previous reports have shown that a mutation at the adjacent nucleotide, A1948G: K650E, causes TD type II, a lethal form of skeletal dysplasia. Both of these mutations result in substitutions of the same amino acid residue, K650, which is located in the activation loop of the tyrosine-kinase domain of FGFR3. Nonetheless, the phenotypes resulting from the two mutations at K650 are clearly distinct from each other. *In vitro* expression studies of FGFR3 with the K650E mutation have shown that this mutation leads to a constitutive activation of the tyrosine kinase activity of the protein, which, in turn, activates and induces nuclear translocation of the transcription factor, Stat1 (Su, et al. Nature, 386, 288-292.1997). The substitution to Asp, Gln, and Leu, stimulates the receptor in varying degrees as measured in vitro autophosphorylation assays (Webster, et al. Mol. Cell. Biol. 16, 4081-4087. 1996). Biochemical analysis of the properties of FGFR3 in the patient cells is essential for bridging an understanding between the genotype and phenotype of these K650 mutations. We have established bone marrow osteogenic stem cell lines and skin fibroblast cell cultures from patients with SSB dysplasia. To analyze FGFR3 tyrosine kinase activity, cells were metabolically labeled with ^{35}S-Met/Cys, and the FGFR3 proteins were immunoprecipitated. The kinase reactions were analyzed by SDS-polyacrylamide gel electrophoresis and autoradiography. The autophosphorylation observed in bone marrow osteogenic stem cells from SSB dysplasia proband was approximately 2 times higher than seen in cells from the control individual. Further analysis of signal transduction pathway and comparison with similar cell lines from patients with other FGFR3 mutations may help to elucidate the pathophysiological bases of genotype-phenotype correlation in these skeletal dysplasias.

NON-FGFR3 HYPOCHONDROPLASIA TREATED WITH GROWTH HORMONE

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A significant percentage of children diagnosed with hypochondroplasia do not demonstrate a FGFR3 mutation and multiplex families have not shown linkage to chromosome 4p. The cause of this form of short stature remains unknown. A six year old female was diagnosed with hypochondroplasia at 7 months of age based on macrocephaly (head circumference 48 cm), with mid-facial hypoplasia, rhizomelia , increased US/LS (1.54 with height of 61 cm and arm span of 60 cm) and minimal radiographic changes. Subsequently, her growth has plotted along the +1 to +2 S.D. on an achondroplasia chart. She was the only child of her average-sized, unrelated parents.

Following the lack of finding a FGFR3 mutation, further evaluation showed an IGF-1 of 22 ng/mL (17-248), IGFBP-3 1.0 mg/L (0.9-4.1), growth hormone 2.2 ng/mL and a bone age of 2 and 6/12 years at a chronological age of 5 1/12 years. Her height of 91 cm was 50th centile for a 2 and 1/2 year old female. A growth hormone stimulation test consisting of 1.5 mg/day of rhGH for four days resulted in an increase in IGF-1 from < 34 to 140 ng/mL and IGFBP-3 from 1.7 to 3.1 mg/L. With this response she was begun on rhGH (Neutropin) at a dose of 0.375 mg/kg per week in divided daily injections. After 10 months of treatment she has shown a modest increase in her growth rate.

There are conflicting data on the response of children with hypochondroplasia to growth hormone therapy. Reported studies have not distinquished between those with a FGFR3 mutation and those without such a mutation. Mullis et el. presented data suggesting possible linkage to the IGF-1 locus in those families not linked to 4p. This abstract is submitted in hopes of generating interest in a multi-center study of IGF-1 versus rhGH therapy in hypochondroplastic children who do not demonstrate a FGFR3 mutation.

FGFR 3 MUTATIONS IN TD I FETUSES IMPAIR CHONDROCYTE DIFFERENTIATION.

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Recurrent mutations in the fibroblast growth factor receptor 3 (FGFR 3) were shown to account for a family of chondrodysplasias including achondroplasia, hypochondroplasia and thanatophoric dysplasia type I and II (TD I and TD II). Taking advantage of a series of 18 TD I fetuses, cartilage samples were used for chondrocyte cultures and analysis by immunochemistry and *in situ* hybridization of cartilage sections. In TD I fetuses, disorganized cartilage growth plate was associated to FGFR 3 overexpression at the protein level with no correlative increase of mRNA amount. Consistent with this finding was the observation of increased FGFR 3 immunoreactivity in the perinuclear region of primary cultured TD I chondrocytes. Proliferation of cultured TD I chondrocytes upon stimulation by FGF ligands (FGF 2 or FGF 9) proved to be similar to age-matched control cells. By contrast, *in situ* hybridization with a COL10A1 riboprobe disclosed a dramatically low number of collagen type X expressing cells in the hypertrophic zone of TD cartilage. Taken together these results suggest that constitutive activation of the FGFR 3 receptor through disulfide bond formation could stabilize the dimeric protein and promote its translocation into the nucleus in hypertrophic TD cells, where it probably interferes with terminal chondrocyte differentiation.

SGAP: THE SKELETAL GENOME ANATOMY PROJECT

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The Skeletal Genome Anatomy Project (SGAP) is under development by the Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health. It is intended to be a resource for scientists interested in both normal and abnormal skeletal development and growth, and is being developed in parallel to CGAP, the Cancer Genome Anatomy Project, directed by the National Cancer Institute. SGAP will include a catalogue of genes expressed in bone and cartilage, as well as a tissue bank of normal and abnormal bone and cartilage, tendon, ligament and synovium, to be located at the NIH.

Genes included in SGAP are those which are necessary for general bone development and growth and those which result in the skeletal dysplasias and related monogenic and complex disorders of skeletal growth and development. The initial stage of this project will be to characterize expression patterns of catalogued expressed sequence tags (EST's) in cartilage and bone. This will be done using 15,000 sequenced human ESTs from the dbEST database that have been PCR amplified and robotically arrayed on glass (Derisi et al., Nature Genet. 14:457, 1996). A similar microarray of mouse EST's is also under development. Hybridization of fluorescent probes, derived from mRNA of various cell types of bone and cartilage, to the microarray will determine the EST expression pattern in these cells. EST's representing previously uncharacterized genes, shown to be expressed in skeletal tissue, will be further studied. In the second stage of the project, cDNA libraries from a variety of skeletal tissues will be assembled. Clones from these cDNA libraries will be sequenced by the I.M.A.G.E. consortium, and will be made available through the ATCC. All sequence data will be immediately available to the public on the internet. These clones, which are likely to include novel expressed sequences, will be used to create a skeletal-enhanced microarray, which will then be used to analyze gene expression using probes from specific skeletal tissues in normal and disease states. It is anticipated that SGAP will greatly accelerate the process of gene discovery related to skeletal growth and development, as well as our understanding of the pathophysiology of skeletal disorders.

SCHNECKENBECKEN DYSPLASIA: REPORT OF 8 NEW CASES AND FURTHER DEFINITION OF THE PHENOTYPE.

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Schneckenbecken dysplasia is a recently described from of lethal short-limbed dwarfism characterized by autosomal recessive inheritance, platyspondyly, hypoplastic scapulae, handle bar-like clavicles, short and cupped ribs, micromelia, metaphyseal cupping and flaring, and a snail-like pelvis. We report the radiographic features and chondro-osseous morphology in 8 previously unreported cases of Schneckenbecken dysplasia and compare these findings with the 8 previously reported cases (including 5 from our group). All cases showed the typical radiologic findings but the morphology of the pelvis varied somewhat between the cases. Chondro-osseous morphology demonstrated hypercellularity of the resting cartilage with clusters of chondrocytes. The physeal columns were short and irregular, the primary spongiosa was short, and the trabeculae were thickened and hypercellular. There was prominent overgrowth of perichondral bone and peripheral ingrowth of mesenchymal tissue across the physis. Electron microscopic examination of resting cartilage consistently demonstrated rough endoplasmic reticulum inclusion bodies containing a granular material. This study further defines the radiologic and morphologic phenotype of Schneckenbecken dysplasia.

SHORT-RIB SYNDROME WITH CEREBRAL MALFORMATIONS AND UNIQUE HISTOLOGICAL CARTILAGE ABNORMALITIES IN TWO SIBLINGS - A NEW SUBGROUP OF SHORT-RIB SYNDROMES ?

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We observed in two siblings a unique combination of skeletal dysplasia and cerebral malformations and propose that this may represent a new distinct disease entity. Both gestations had been terminated prematurely due to sonographic evidence for severe malformations, in the first fetus at the 30th week of gestation, in the second at the 19th week. Both showed very similar findings, although to variable extent. They showed mild to moderate shortening of the long bones, a narrow chest with shortened ribs and hypoplastic lungs. Histologically, the cartilage appeared abnormal with increased cellularity of the resting zone and interspearsed areas of cell necrosis and mucoid matrix degeneration. The vascular canals were fibrotic. Immunohistochemically, the collagen types I,II,III,IV,VI and IX revealed a normal distribution of most collagens, however, with a significantly enhanced staining for collagen type III in the cartilage matrix. In addition to the skeletal malformations, severe cerebral abnormalities had to be noted. These comprised a disproportionate hypoplasia of all cortical lobes, aplasia of the cerebellar vermis and dysrhaphic cleft formation of the skull base with medial occipital clefting. In addition, the first fetus showed unilateral renal cysts. A biochemical in-vitro analysis of chondrocytes obtained at autopsy from the second fetus did not reveal major structural abnormalities of cartilage collagens.
Due to the radiological features the skeletal abnormalities were most suggestive for a short-rib syndrome, particularly of asphyxiating thoracic dysplasia (Jeune Sy.) or chondroectodermal dysplasia (Ellis-van-Creveld Sy.). There were, however, no signs of ectodermal malformation and the histomorphological analysis of joint cartilage was significantly different from both entities and from all other known types of short-rib syndromes. There exist, however, two case reports on infants with Ellis-van-Creveld syndrome presenting with „hydrocephalic" cerebral malformations which may be similar to our cases. In conclusion, we suggest that our cases may represent a unique subgroup of skeletal dysplasia of the short-rib group with distinct histological abnormalities, yet with particular additional (cerebral) malformations.

HISTOLOGY OF PULMONARY MATURATION IN LETHAL SKELETAL DYSPLASIAS

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Respiratory insufficiency is the leading clinical problem in most of the severe skeletal dysplasias. It is generally accepted that respiratory failure is the cause of death in lethal skeletal dysplasias. In order to find out whether respiratory failure is due to reduced/retarded lung maturation or just due to the reduced lung volume without structural abnormalities, we conducted a histomorphological analysis on lungs from 40 fetuses/newborns with different lethal skeletal dysplasias. Therefore, autoptical pulmonary tissue was morphometrically investigated for the radial alveolar count (RAC), i.e. the amount of terminal (post-bronchiolar) pulmonary alveoli. We investigated 10 fetuses/newborns (between 15 weeks of gestation and birth) with lethal osteogenesis imperfecta (OI type II), 14 cases of thanatophoric dysplasia (type I), 7 cases with various subtypes of short-rib-syndromes (SRP-type III and IV, Ellis-van-Crefeld-syndrome, Jeune-syndrome), 2 cases with achondrogenesis type Ib and 4 cases with achondrogenesis type II/ hypochondrogenesis. Furthermore 3 cases with campomelic dysplasia were analyzed.

In the age-matched control group the RAC increased almost linearly with rising fetal age (from 15 weeks on) indicating a continous process of alveolar maturation during fetal development. In the skeletal dysplasia group in contrast we observed significantly lower RAC-values in fetuses of more than 21 weeks of gestation, regardless of the cause of skeletal dysplasia. In the diseased fetuses between 15 and 21 weeks the RAC values were within normal limits. Lung weights in the dysplasia group were also significantly lower when compared to the controls, although to a more variable extent indicating that the lung weight is more easily influenced by fluid or cellular infiltration.

Our observations indicate that the lungs in severe lethal skeletal dysplasia undergo reduced/ retarded structural maturation most obviously due to the reduced skeletal development of the osseous thorax. These observations indicate that a „widening" of the chest cage e.g. by surgical intervention may be of only minor value for the respiratory situation.

QUANTITATIVE ASSESSMENT OF THE SKELETAL DYSPLASIAS

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Objective: Many of the skeletal dysplasias exhibit modelling deformities of the tubular long bones that have been described with qualitative expressions such as bowing or splaying. We sought to quantitatively assess the amount of bowing in femurs and tibias for achondroplasia, diastrophic dysplasia, thanatophoric dysplasia campomelic dysplasia, spondyloepiphyseal dysplasia, and metaphyseal dysplasia.
Materials and Methods: Femur and tibia AP radiographs of the six dysplasias were obtained from UCSD and Children's Hospital teaching files. Lateral femur, medial femur, and tibial curves were traced and scanned into a computer. The computer program generated a best fit line, an equation, and a bowing coefficient for each bone curve. Each dysplastic bone curve was compared to a normal bone curve of the same age and sex. 47 cases of dysplastic lateral femur curves, 43 dysplastic medial femur curves, and 59 dysplastic tibial curves were created.
Results: All dysplastic bone curves tested had greater bowing coefficients that corresponding normals. For lateral femur curves, the mean bowing coefficient was greatest in thanatophoric and diastrophic dysplasia (>3.0) and at least in spondyloepiphyseal dysplasia (1.0). The corresponding normals had a mean bowing coefficient range of .24-.71. For medial femur curves, the normal range of mean bowing coefficients was 2.8-3.6. Both metaphyseal and diastrophic dysplasia had the greatest mean bowing coefficients that were >12. For the tibial curves, the normal mean bowing coefficient range was 2.25-4.03. Metaphyseal dysplasia had the largest mean bowing coefficient that was 14.73. In addition, each dysplastic curve equation was evaluated at each variable to a corresponding normal variable. Certain dysplasias contained extraordinarily high coefficients that could potentially distinguish them.
Conclusion: Bowing coefficients may potentially be used to classify individual skeletal dysplasias and distinguish them from normal. Finally, the coefficients generated from the equations of dysplastic bone curves may be able to further classify the individual dysplasias.

PYCNODYSOSTOSIS: RADIOLOGIC AND MOLECULAR FINDINGS IN AN 86-YEAR-OLD PATIENT

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Pycnodysostosis (Pycno) is a rare, autosomal recessive skeletal dysplasia, originally described by Maroteaux and Lamy, and independently by Andrén, in 1962. The features of the disease, characterized in children and young adults, included short stature, osteosclerosis, bone fragility, hypoplasia of the distal phalanges (misnamed acro-osteolysis), and deformities of many bones. Recently, the gene causing Pycno was identified by a positional cloning strategy. Linkage analysis of two Pycno pedigrees localize the gene to chromosome 1q21, and physical mapping identified the lysosomal cysteine proteinase, cathepsin K, as a candidate gene. Subsequently, mutations in the cathepsin K gene were revealed to cause Pycno (Gelb et al., *Science* **273**:1236, 1996).

We report an interesting consanguineous family from Madeira island involving two affected sisters. aged 86 and 84 years, the oldest patients described with Pycno. In addition to the classic finding associated with Pycno, the radiographic features of the well-studied older sister included an unusual osteolytic progression of the skeletal disease. Molecular analyses revealed both sisters to be homoallelic for a C-to-A transversion at bp 935 of the cDNA, predicting an A277E alteration in the mature cathepsin K enzyme. This mutation has also been identified in a young Indian patient who was also homoallelic. Analysis of these patients with polymorphic markers that were tightly linked to the cathepsin K locus revealed that the haplotype of the two sisters from Madeira differed from that of the Indian child, suggesting that their mutations arose independently. This finding is supported further by the fact that this mutation occurred at a CpG dinucleotide. Since the novel phenotype discovered in our aged patient was not found in younger patients with the A277E mutation or other mutations which were predicted to eliminate cathepsin K activity, osteolysis involving the long bones may be a developmental alteration resulting from infarctions in osteosclerotic cortical bone.

GENETIC LINKAGE OF HEREDITARY BONE DYSPLASIA WITH MALIGNANT CHANGE TO CHROMOSOME 9p21-p22

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Hereditary bone dysplasia with malignant change (OMIM #112250HBD) is an autosomal dominant disorder of unknown etiology characterized by diaphyseal cortical thickening, metaphyseal striations, bone infarctions, pathologic fractures, and a predisposition for the development of an uncommon bone sarcoma, malignant fibrous histiocytoma. Several patients have also developed cataracts in early adulthood. In addition to the three families described previously, we recently identified and reported a new four-generation kindred.

As a first step towards identifying the HBD gene, a genetic linkage study was undertaken. Blood samples were obtained with informed consent from 15 individuals from two HBD kindreds and genomic DNA was extracted. A genome scan was performed using polymorphic simple tandem repeat (STR) markers at 10 cM density from the Human Screening Set, Version 4. Genotypic data were entered into the Labman database and analyzed with the Linkage software package. Initial suggestive evidence for linkage was obtained with marker D9S156. Subsequently, additional STRs in the region from the 1996 Généthon Human Genetic Linkage Map were analyzed, and genetic linkage was established. By two-point linkage analysis, a maximal lod score of 4.98 was obtained with marker D9S171 at $\Theta = 0.01$. Using haplotype analysis, the HBD locus was defined by observed recombinant events to the interval between D9S157 and D9S171, a 10 cM region. This locus could be assigned to chromosomal bands 9p21-22 because it included an interferon cluster that had been mapped by fluorescence *in situ* hybridization. Since HBD is a familial sarcoma syndrome, it was noteworthy that a variety of cancers have loss-of-heterozygosity within this interval, and that several cell-cycle regulating genes have been assigned to this region. Current efforts for identifying the HBD gene are directed at refining the critical region by analyzing additional families and evaluating the known candidate genes.

EXCLUSION OF LINKAGE TO COL2A1 IN TYPE I STICKLER SYNDROME.

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In an effort to clarify the relationship between the Stickler syndrome phenotype and underlying gene mutations, we have studied 26 Stickler syndrome families by clinical and molecular means. Recently it has been proposed that two subtypes of Stickler syndrome can be defined based on the severity of ocular findings. According to this hypothesis, families with type I Stickler syndrome manifest the classic Stickler phenotype, characterized by early onset high myopia with vitreous liquefaction and retinal detachment, and Type II Stickler syndrome has milder ophthalmologic abnormalities. Moreover, published molecular analyses have suggested that patients with mutations in COL2A1 typically manifest the more severe type I Stickler phenotype, and it has been proposed that only those families with COL2A1 mutations fall into the type I Stickler syndrome group. Further, the hypothesis suggests that type II Stickler syndrome includes all families with mutations at other loci, including COL11A1 and COL11A2.

In seven of the families we studied, the Stickler phenotype was not linked to COL2A1. In three of these families, linkage to COL11A1 and COL11A2 was also excluded, providing genetic evidence for a fourth Stickler locus. Eye findings in these families were variable. In two of the three families not linked to any of the known Stickler loci , affected individuals had mild eye manifestations, consistent with type II Stickler syndrome. Affected individuals in a third family, not linked to COL2A1, exhibited myopia, as well as retinal holes and detachment, lattice degeneration, cataracts, and glaucoma, consistent with a clinical diagnosis of type I Stickler syndrome. Eye findings in the remaining families in which the Stickler phenotype is not linked to COL2A1 showed varying degrees of myopia and other eye manifestations, suggesting that there is no simple relationship between clinical phenotype and locus. These data demonstrate that not all families with type I Stickler syndrome have mutations in the COL2A1 gene. We suggest that until sufficient families with identified molecular defects are studied, Stickler syndrome subtypes be based on clinical phenotype alone and not defined by the locus carrying the mutation.

PHYSICAL AND LINKAGE MAPPING OF THE GENE FOR THE α3 CHAIN OF TYPE IX COLLAGEN, COL9A3, TO HUMAN CHROMOSOME 20q13.3.

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Type IX collagen is a minor cartilage component which associates with mixed fibrils of types II and XI collagen. Mutations in the gene for the α2 chain, COL9A2, are responsible for multiple epiphyseal dysplasia (MED) in some families. To further investigate the possible role of type IX collagen genes in human chondrodysplasias, we have determined the precise physical and genetic locations for the gene encoding the α3 chain of type IX collagen, COL9A3. Fluorescence in situ hybridization (FISH) on metaphase chromosomes using a phage clone of COL9A3 localized the gene to human chromosome 20q13.3. Radiation hybrid mapping with the Stanford G3 panel placed COL9A3 approximately 700kb telomeric to D20S173. Utilizing an SSCP polymorphism in the COL1 domain, we determined by multipoint linkage analysis that the most likely locus order is cen-D20S173-(*3cM*)-D20S93-(*10cM*)-**COL9A3**-(*5cM*)-D20S19-(*5cM*)-D20S24-tel. We are currently utilizing these data to assess COL9A3 as a candidate gene in genetically heterogeneous human chondrodysplasias such as MED.

RESIDUAL SULFATION OF PROTEOGLYCANS IN CARTILAGE OF A PATIENT WITH McALISTER DYSPLASIA/ATELOSTEOGENESIS TYPE 2: CAN SULFUR-CONTAINING AMINO ACIDS PARTIALLY COMPENSATE FOR THE SULFATE UPTAKE DEFECT?

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We have studied a fetus affected by McAlister dysplasia/AO-2 who was compound heterozygote for the c862t transition (R279W) and the a1300g transition (N425D) in the diastrophic dysplasia sulfate transporter (*DTDST*) gene. Proteoglycan (PG) sulfation was studied in epiphyseal cartilage and in chondrocyte cultures of the patient by disaccharide HPLC analysis of chondoitinase digested PGs. Increased amount of non-sulfated disaccharide was observed; however, residual amounts of sulfated disaccharides were detectable both in cultured cells and tissue. Functional impairment of the sulfate transporter was demonstrated *in vitro* by reduced incorporation of [^{35}S]sulfate relative to [^{3}H]glucosamine in PGs synthesized by chondrocytes and by sulfate uptake assays in fibroblasts. The capacity of fibroblasts to use cysteine as an alternative source of sulfate was evaluated after double labeling with [^{35}S]cysteine and [^{3}H]glucosamine. Relative incorporation of [^{35}S]cysteine-derived sulfate in the glycosaminoglycan chains was increased in the patient's cells (0.728 in the patient *versus* 0.069 in the control), indicating that, *in vitro*, sulfate derived from sulfur-containing amino acids can partially compensate for intracellular sulfate deficiency. Since the *DTDST* gene is widely expressed but defects are mainly restricted to cartilage, it is possible that this alternative recruitment of sulfate can rescue PG sulfation in most other tissues but not, or only insufficiently, in cartilage.

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EXTENSION OF PHENOTYPE ASSOCIATED WITH STRUCTURAL MUTATIONS IN TYPE I COLLAGEN: SIBLINGS WITH JUVENILE OSTEOPOROSIS HAVE AN α2(I)GLY436->ARG SUBSTITUTION.

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We report here the biochemical and molecular characteristics of type I collagen from two siblings referred for assessment of juvenile osteoporosis. Patient 1 (an 11-year-old male) and Patient 2 (a 7-year-old female) were diagnosed with juvenile osteoporosis, based on clinical and radiological examination. Radiographs showed decreased lumbar bone density and multiple compression fractures throughout the thoracic and lumbar spines of both children. The children have some findings overlapping with osteogenesis imperfecta (OI), however, neither child has incurred the long bone fractures characteristic of OI.

Skin fibroblast cultures from both patients produced electrophoretically ahnormal type I collagen which appeared as slightly broadened bands with delayed migration of the baseline. A mismatch was detected in the COL1A2 RNA by RNase A cleavage of RNA/RNA hybrids in the region encoding amino acids 249-525. Mutant and normal alleles were separated by RNase A digestion of DNA/RNA hybrids using cloned PCR fragments from this region. DNA sequence analysis of clones harboring the mutant allele identified a missense mutation (G1715—>A) which predicts the substitution of arginine for glycine at position 436 in the helical domain of the type I collagen alpha 2 chain (G436R). Analysis of genomic DNA identified the mutation in the asymptomatic father, who is presumably a mosaic carrier. The presence of the same heterozygous mutation in two siblings strongly suggests that the patients display the full phenotype. Taken together, the clinical, hiochemical and molecular findings in these patients extend the phenotype associated with mutations in type I collagen.

LACK OF CARTILAGE INTERTERRITORIAL MATRIX EXPLAINS THE ABNORMAL OSSIFICATION IN ACHONDROGENESIS TYPE IB

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Achondrogenesis type IB (Ach-IB), a genetically transmitted and invariably lethal short-limb osteochondrodysplasia, is allelic with diastrophic dysplasia and atelosteogenesis type II being caused by a sulfate uptake defect due to mutations in the gene encoding a cell membrane sulfate transporter. However, it is unknown how mutations of this gene cause shortness and deformation of endochondrally formed bones. We investigated the morphopathogenesis of the skeletal abnormalities in an 18 week female fetus with Ach-IB. A detailed histological study of plastic-embedded samples suggested that interterritorial matrix in epiphyseal cartilage was selectively missing. As a result, the epiphyseal cartilage was organized into discrete 'chondrons' separated by cleft spaces; cartilage seriation, and formation of longitudinal septa which derive from interterritorial matrix were absent; mineralized cartilaginous septa were not formed as a result of the absence of longitudinal septa. The absence of interterritorial matrix as the key histological change determining the lack of proper endochondral ossification has been confirmed by localizing two small proteoglycans, biglycan (BGN) and decorin (DCN), as markers of territorial and interterritorial matrices in epiphyseal cartilage. We found that a BGN-rich, collagen type II-positive territorial matrix was preserved, whereas no DCN-rich interterritorial areas were observed. However, chondrocytes displayed intracellular labeling for DCN core protein. We concluded that a complex derangement in cartilage matrix assembly lies downstream of the deficient activity of sulfate transporter in Ach-IB; that DCN deposition is severely impaired, possibly as a result of undersulfation of the glycosaminoglycan chain, and participates in a severe change in matrix organization with lack of development of a normal interterritorial matrix; that this changes determine the lack of the necessary structural substrate for subsequent phases of growth plate maturation and endochondral ossification, thus explaining the skeletal phenotype.

PROGRESS IN POSITIONAL CLONING OF THE ELLIS VAN CREVELD SYNDROME GENE

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Ellis van Creveld syndrome is an autosomal recessive disorder characterized by disproportionate dwarfism, polydactyly, congenital heart defects and oral manifestations. This disorder is rare worldwide but is prevalent among the Old Order Amish of Lancaster County, Eastern Pennsylvania. Using linkage analysis with highly polymorphic DNA markers on nine inter-related Amish families and three non-Amish ones, the localization of the EVC gene has been refined to 4p16.1 (Zmax=6.91 @ theta=0.02 for marker Hox 7) (Polymeropoulos et al, Genomics 35, 1-5, 1996). We have constructed a partial BAC contig to span the critical interval of 1 Mb. In order to clone the gene responsible for Ellis van Creveld syndrome, we are using the complementary approaches of internal and 3′ terminal exon-trapping via the expression vectors pSPL3 and pTAG4 respectively. We have identified several putative exons that yield novel sequences. We are currently hybridizing these sequences back to the original genomic DNA clones and the proven exons will then be hybridized against Northern blots to determine in which tissue the exon is expressed. Exons expressed in fetal heart and cartilage will be used to probe appropriate cDNA libraries for cDNA clone expansion. The eventual identification of the EVC gene will facilitate prenatal diagnosis in addition to shedding light into the underlying pathophysiology of the disorder and the normal processes of skeletal and cardiac development.

NORMAL FUNCTION OF THE DIASTROPHIC DYSPLASIA SULFATE TRANSPORTER IN A PATIENT WITH PSEUDODIASTROPHIC DYSPLASIA.

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Pseudodiastrophic dysplasia is a rare, autosomal recessive, skeletal dysplasia with some clinical features common to diastrophic dysplasia. However, on the basis of clinical, radiological and chondro-osseous histology it has been considered a distinct disorder. Due to similarities to diastrophic dwarfism we considered the hypothesis of a defect in the diastrophic dysplasia sulfate transporter (*DTDST*) gene in a patient affected by pseudodiastrophic dysplasia. The patient (patient n. 2 in D.J. Eteson et al., J. Pediat. 109, 635-641, 1986), now 16-years old, is affected by dwarfism (he is 1-meter tall) characterized by a very severe scoliosis. He has a lively disposition and normal intelligence. A sulfate uptake assay performed in cultured skin fibroblasts from the patient was within normal values indicating that the function of the sulfate transporter was normal. Proteoglycan (PG) sulfation was analyzed by ion exchange chromatography after metabolic labeling of fibroblast cultures with [^{3}H]glucosamine and [^{35}S]sulfate. PGs were normally charged as evidenced by chromatography profiles and by their $^{35}S/^{3}H$ ratio (1.240 in the patient versus 1.374 in two different controls). These results indicated that the contribution of inorganic sulfate to PGs sulfation was normal confirming that the sulfate transport function was not impaired and that the sulfate activation pathway, at least in fibroblasts, was normal. These data demonstrate that pseudodiastrophic dysplasia is not caused by defects in the DTDST and can not be included in the diastrophic dysplasia "family" of disorders confirming previous observations based on clinical and radiological evidences.

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GENETIC AND MOLECULAR HETEROGENEITY IN MULTIPLE EPIPHYSEAL DYSPLASIA

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Multiple epiphyseal dysplasia (MED) is clinically and radiographically heterogeneous; the mild 'Ribbing' and severe 'Fairbank' forms define a phenotypic spectrum, which also includes a number of unclassified forms. Previously the genetic and molecular bases of some MED phenotypes have been determined. Mutations in the gene encoding cartilage oligomeric matrix protein (COMP) have been shown to result in Ribbing, Fairbank and unclassified forms of MED. Furthermore, mutations have also been identified in the gene encoding the α2 chain of type IX collagen (*COL9A2*) in two families with MED Fairbank. Type IX collagen is a heterotrimer [α1(IX)α2(IX)α3(IX)] of three distinct gene products (*COL9A1, COL9A2* and *COL9A3)*, suggesting the hypothesis that mutations in *COL9A1* and *COL9A3* can also result in MED. To investigate further the genetic and molecular heterogeneity of this disorder we have collected DNA on an additional 18 families with MED.

Five of the families are suitable for genetic linkage analysis and we are using fluorescently labeled primer pairs to amplify micro-satellite markers specific to the *COMP, COL9A1* and *COL9A2* genes. In one large family we have established linkage to *COL9A2* and excluded linkage to *COMP* and *COL9A1*. In a second family we have excluded *COMP* and *COL9A2* while an inheritance pattern consistent with linkage to *COL9A1* was found, however the family was too small to conclude that the mutation is likely to be in this gene. These preliminary results confirm that MED is genetically heterogeneous and may provide the first preliminary evidence that mutations in *COL9A1* can result in this disorder. This hypothesis is currently being tested by direct mutational analysis of the COMP and type IX collagen genes in this and other MED families. To date we have identified 2 novel mutations in the exon3/intron3 slice donor site of *COL9A2* which are predicted to result in the skipping of exon 3. Both of these families have MED Fairbank and these data correlate with previous observations. Furthermore, we have also identified a novel *COMP* gene mutation in a third family with Fairbank's confirming that this form of MED shows considerable genetic and molecular heterogeneity.

FIBROUS DYSPLASIA OF BONE IN McCUNE-ALBRIGHT SYNDROME: AN *IN SITU* CELLULAR ANALYSIS OF ABNORMAL BONE TURNOVER

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Activating missense mutations of the Gsα gene leading to overactivity of adenylyl cyclase and increased levels of cAMP have been etiologically linked to fibrous dysplasia of McCune-Albright Syndrome. We characterized the phenotypic nature of cells in fibrous dysplastic lesions and developed molecular histological techniques to correlate the expression of mutated protein with their morphological and functional features. Lesional fibrous cells were identified as osteogenic precursors by virtue of their expression of alkaline phosphatase, versican, osteonectin, decorin and biglycan. Using RT-PCR *in situ* hybridization with primer sets specific for the normal and mutated alleles, Gsα expression was found to be highly upregulated as these fibroblastic cells matured into osteoblasts, indicating a major effect of Gsα mutation on mature osteogenic cell function. In lesional bone, an abnormal retracted osteoblast morphology was found (a phenomenon mimicked *in vitro* by addition of cAMP analogs to osteoblastic cells) which resulted in formation of abnormal multi-cellular pseudo-osteocytic lacunae and aberrant orientation of newly deposited collagen on forming bone surfaces. Furthermore, expression of anti-adhesive proteins (versican and osteonectin) was dominant over production of pro-adhesive proteins (osteopontin and bone sialoprotein). Retracted cells, some of which were closely associated with mature osteoclasts and mononuclear precursors commonly found in active lesions, were found to produce high levels of IL-6, a cytokine upregulated by cAMP and associated with increased bone resorption. As indicated by the TUNEL assay, lesional osteoblasts were also apoptotic, another phenomenon associated with high levels of intracellular cAMP. We conclude that the critical upregulation of Gsα levels during the transition of osteogenic precursors to osteoblasts in the presence of an activating mutation of Gsα, results in osteoblast misfunction mediated by the high levels of intracellular cAMP and reflected in cell retraction, deposition of abnormal matrix, increased bone resorption and ultimately in cell death. The disruption of the balance between bone formation and resorption may result in the continued recruitment and accumulation of fibroblast-like, pre-osteogenic cells noted in disease.

ABSENCE OF FGFR3 GENE MUTATIONS IN A PATIENT REFERRED FOR ACHONDROPLASIA

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A 5 year and 8 month old white boy was referred for counseling of achondroplasia. He was born to a 20-year-old gravida 3, para 2, abortion 1 mother following cesarean section for breech presentation. Apgar scores were 7 and 9 at 1 and 5 minutes respectively. The birth weight was 2500 gm and the birth length 45.8 cm. Subsequently achondroplasia was diagnosed on the baby. At 14 month, the height was 64 cm. Family history revealed that the father was adopted and is also short (150 cm).

Physical examination at the time of counseling revealed short stature, a large head with prominent forehead, depressed nasal bridge, slightly crowded teeth, rhizomelic shortening of arms and legs, mild trident fingers, bow legs, and lumbar lordosis. Radiographs shortly after birth showed lack of normal increase in interpedicular distance caudally, squared-off iliac wings, short narrow sciatic notch, and ball-in-a-socket epiphyseal-metaphyseal junction of the proximal femurs. Radiographs at 2 years of age showed flared metaphyses of the long bones and relatively long fibulae. The phenotype of the father suggests hypochondroplasia rather than achondroplasia.

Genomic DNA was extracted from leukocytes of the patient and his father. The absence of a mutation in aminoacid residue 380 (Gly380Arg; Gly380Cys) or aminoacid residue 375 (Gly375Cys) of FGFR3 from the patient and his father was revealed by restriction analyses (MspI and SfcI) of PCR amplified genomic DNA using primers flanking the transmembrane domain (Shiang et al, 1994) and by DNA sequencing. This suggests the original diagnosis of achondroplasia is in doubt and the possibility of hypochondroplasia. Mutation analysis for hypochondroplasia is in progress to search for mutation specific for hypochondroplasia.

ACHONDROPLASIA WITH I(21Q) DOWN SYNDROME

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A Mendelian disease has been reported in patients with a chromosomal abnormality in the literature. We have observed such a case in a boy with achondroplasia and Down syndrome. It has been of interest to observe signs of these two entities manifested in the same patient. To our knowledge, this is the second case of achondroplasia associated with Down syndrome but the first case associated with i(21q).

SKS, a white male infant, was born to a 33-year-old mother and a 53-year-old father. The baby was the product of a full-term pregnancy and uncomplicated vaginal delivery. The birth weight was 3,400 gm, birth length 48 cm, head circumference 35 cm, and chest circumference 33.5 cm. Apgar scores were 6 and 8 at 1 and 5 minutes respectively. The physical features suggested Down syndrome, namely hypotonia, cutis marmorata, upslanting palpebral fissures, epicanthal folds, Brushfield spots, depressed nasal bridge, small ears with overfolded helix, flat occiput, short neck with excessive skin folds on the back of the neck, heart murmur, left simian crease and increased space between the great toe and second toe bilaterally. Chromosome analysis revealed 46,XY,+i(21)(q10). Both parents have normal chromosomes. The family history is non-contributory. The infant was followed at 2, 3, and 8 months. In addition to the findings observed at birth, he also presented with short stature, frontal bossing, depressed nasal bridge, narrow chest, rhizomelic shortening of the limbs, trident fingers, and hypotonia with mild gibbus. These signs suggested the concomitant presence of achondroplasia. Skeletal survey revealed frontal bossing, depressed nasal bridge, a narrow chest, short pedicle with caudal narrowing of the interpedicular distance, square ilium with short sciatic notch, rhizomelic shortening of limbs with semilunar lucent proximal femurs, and a minor gibbus formation.

Both signs for Achondroplasia and Down syndrome are present in this patient. Craniofacial features are more typical for Down syndrome than achondroplasia, except for the frontal bossing and the markedly depressed nasal bridge. Otherwise, skeletal findings of achondroplasia dominate the clinical picture. This patient probably represents a new mutation and the paternal age appears to play a role in this case. Achondroplasia has also been reported to be associated with other chromosome anomalies. In cases of achondroplasia associated with Klinefelter syndrome, signs of achondroplasia dominate the clinical pictures and only few signs were attributable to Klinefelter syndrome.

OSTEOCRANIOSTENOSIS: CLINICAL, MORPHOLOGICAL AND BIOCHEMICAL FINDINGS IN A FURTHER CASE

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A term born boy presented at birth with short stature, narrow chest, bowed forearms, acromicria, hypoplastic midface, blue sclerae and dysplastic ears. A babygramm showed very thin, gracile bones with flared metaphyses, fractured forearms and a hypomineralized skull. The patient died after 2 weeks from septicemia and respiratory failure. Radiological features and clinical signs lead to the diagnosis of Osteocraniostenosis. This rare lethal skeletal dysplasia (8 reported cases in the literature) is characterized by distinct skeletal abnormalities. The long bones have a typical „drumstick-shape" appearance with gracile, overtubulated and sclerotic diaphyses, which fracture easily, and flared metaphyses. There is mild micromelic dwarfism and platyspondyly. The skull is poorly ossified with premature synostosis, increased bitemporal diameter and widely open fontanels. There is midface hypoplasia and microstomia. Ocular anomalies like microphtalmia are reported. Spleen hypo/aplasia is the only known associated abnormality of the inner organs.
There is few data on bone and cartilage morphology in the literature. In our patient resting and proliferating zone of the epiphyseal cartilage were normal, at the metaphyseal/ diaphyseal transition there was a marked increase of osteoclasts and loss of medullary spongiosa, confirming the results in one reported case. Cartilage and bone matrix were normal on histologic, immunohistochemical and ultrastructural examination as well as biochemical studies on collagen from cultured skin fibroblasts. Thus it seems unlikely that an abnormality of a matrix component is the cause of this disorder.

MOLECULAR CHARACTERIZATION OF FGFR3 IN ARGENTINE ACHONDROPLASTIC POPULATION

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Achondroplasia is the most common form of human skeletal dysplasia and more than 80% of the cases result from sporadic mutations. Recently, a missense mutation (G380R) located in the transmembrane domain of the FGFR3 was found to account for more than 95% of patients studied.
In order to estimate its prevalence in an Argentine achondroplastic population, 15 sporadic cases and 2 unrelated familial forms were randomly selected from 80 achondroplastic patients followed up in our Hospital.
The G→A transition (responsible for 98% of the G380R substitutions) was analyzed by PCR of exon 10 and allele specific oligonucleotide hybridization using the following primers: Norm: 5'-AGCCCACCCCGTAGCTGAG-3' Mut: 5'-CTCAGCTACAGGGTGGGCTT-3'
This mutation was present in all but two achondroplastic chromosomes (88%).
The frequency found in our population was in agreement with previous reports regarding other populations.

All the patients at follow up showed the typical physical and radiological features of this dysplasia. In addition, epidemiological aspects (paternal age, maternal age, birth order) did not differ from other achondroplastic populations either.

ACHONDROPLASIA AND "SPELLS" : COMPRESSION MYELOPATHY v. OBSTRUCTIVE SLEEP APNEA v. SEIZURES

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Considerable controversy continues about the etiology and management of infants with achondroplasia who experience episodes of apnea. A two week old infant with achondroplasia was placed on an apnea monitor and followed regularly. Apart from slightly more hypotonia than usual, his first eight months of life were uncomplicated. At eight months of age, he began having spells with apnea and cyanosis. These were brief, never occurred during the night and often occurred after a feeding or while in care seat as he was dozing off.

He was admitted to the PICU on 3 occasions after a flurry of these spells, but none were observed to occur in the hospital. The spells recurred at roughly two weeks intervals. MRI showed modest increase in ventricular size and an omega-shaped foramen magnum. His neurological exam was normal apart from hypotonia. A sleep study showed periods of low oxygen saturation consistent with air way obstruction. Bronchoscopy revealed a normal trachea but "floppy aretynoids" which were trimmed but with no apparent benefit. Evoked potential studies were not consistent with motor pathway changes of a myelopathy. He was twice monitored on video-EEG for 72 continuous hours with no spells observed.

After a three week spell-free period on no treatment and at 12 months of age, he had two spells and was quickly hospitalized and placed on an EEG monitor. Over the ensuing 12 hours he had three additional spells captured on video and EEG. The EEG confirmed that each of these spells was a seizure. He was then placed on phenobarbital and experienced no further spells. A video with these spells and superimposed EEG recording has been edited for demonstration.

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