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SPONSORS

The 10th Biennial Meeting of the International Skeletal Dysplasia Society committee would like to thank the following sponsors:

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CONFERENCE CONVENOR & ORGANISING COMMITTEE

Local Organising Committee

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(Conference Chair)
Murdoch Childrens Research Institute
Department of Paediatrics, University of Melbourne

Robin Forbes
Genetic Health Services
Royal Children's Hospital
Melbourne

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John Bateman
Melbourne

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Sheila Unger
Lausanne

Matthew Warman
Boston

Maroteaux Award Judging Panel

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Shiro Ikegawa
Japan

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Conference Secretariat
ASN Events Pty Ltd
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WEB ADDRESS

www.isds2011.org

PLENARY SPEAKERS

Prof John Bateman
Director Musculoskeletal Disorders,
Murdoch Children's Research Institute, Victoria

Professor John Bateman is the Director of the Cell Biology, Development and Disease Theme at the Murdoch Children's Research Institute, and Head of the Skeletal Biology Research Group and is a Professorial Fellow of the University of Melbourne. His research interests include the molecular mechanisms of extracellular matrix protein assembly in health and disease and molecular genetics of musculoskeletal disease. A major focus of current research involves using mouse models of bone and cartilage disease to explore the fundamental disease mechanisms. Recently his laboratory has developed proteomic and RNA expression profiling approaches to study cartilage development and disease including osteoarthritis. He has served on the Editorial Boards of several journals including The Journal of Biological Chemistry; the Biochemical Journal, Matrix Biology. He is a Past-President of International Society of Matrix Biology and Matrix Biology of Australia and New Zealand. He is a member of the NHMRC Academy (Cell Biology and Biochemistry).

Dr Jim McGill
Director, Department of Metabolic Medicine,
Royal Children's Hospital, Queensland

Dr Jim McGill is a paediatrician, metabolic physician, clinical geneticist and biochemical genetics pathologist who is the Director of the Department of Metabolic Medicine, Royal Children's Hospital, Brisbane and Clinical Liaison, Metabolic and Newborn Screening Sections, Division of Chemical Pathology, Pathology Queensland. He has been involved in the care of individuals and families with lysosomal disorders for 25 years. He is currently the Chair of the MPS Advisory Committee and was a foundation member of the Gaucher Disease Advisory Committee of the Life Saving Drugs Program in Australia and is a member of the International MPSI Registry Board.

A.Prof Sally Dunwoodie
Head, Embryology Laboratory,
Victor Chang Cardiac Research Institute, Darlinghirst, NSW

Sally Dunwoodie is head of the Embryology Laboratory in the Division of Developmental Biology, at Victor Chang Cardiac Research Institute. She is an Associate Professor in the Faculty of Medicine at the University of New South Wales. Her research goals are to define molecular and cellular interactions that orchestrate mammalian development, through a mechanistic understanding of how genetic and environmental factors impact upon embryo development. In particular her research has identified that Notch signalling is central to somite and vertebral column formation in mouse and humans. Other research interests include the molecular and cellular mechanisms governing cardiovascular and placenta development.

DELEGATE INFORMATION

VENUE
The ISDS 2011 conference will be held at the picturesque Sea Temple Resort in Palm Cove Cairns, Queensland, Australia.

Sea Temple Spa and Resort
5 Triton Street
Palm Cove
Queensland 4879
http://www.mirvachotels.com/sea-temple-resort-palm-cove
Phone: + 61 7 4059 9600

Alternate Accommodation

Grand Mercure
Cnr Vievers Rd Williams Esp
Palm Cove
Queensland 4879
www.mirvachotels.com/PalmCove
Phone: + 61 7 4055 3999

VENUE LAYOUT

THE REGISTRATION DESK
The Registration desk is located in the Temple 1 & 2 Courtyard. Any enquiries can be directed to ASN staff there other than those about accommodation which should be dealt directly with your hotel.
The conference office hours are:

Friday:	7:00 am – 1:00 pm, 3:00pm – 6:00pm
Saturday:	8:00 am – 1:00 pm, 3:00pm – 6:00pm
Sunday:	8:00 am – 1:00 pm

REGISTRATION
The Full Delegate Registration includes:

- all delegate materials (name tag, & , abstract book),
- breakfasts, lunches, tea breaks (when applicable)
- a ticket to the Welcome Function (Sea Temple)
- a ticket to the Conference Dinner (Cairns Night Zoo)

The Partner Registration includes:

- all breakfasts, lunches and a ticket to the Welcome Function & Conference Dinner

NAME TAGS
Delegates are required to wear their name tags to all scientific and catered sessions.

SESSION LOCATIONS
The scientific sessions take place in the Temple Rooms 1 & 2 and the trade display and break catering in the Temple 1 & 2 Courtyard.

CATERING
All meals are Included with your registration for ISDS. Breakfasts and lunches will be held daily in the Sea Temple Restaurant. Afternoon tea will be served outside Temple room 1 on the Friday afternoon only. Tea & Coffee will be available outside Temple Room 2 through all days of the conference. *Nametags are required during all scientific and catered sessions.

SPEAKER PRESENTATIONS
ASN staff will be able to assist presenters with loading their presentation. Speakers can ask for assistance at the registration desk during any breaks. Speakers are encouraged to load their presentations as soon as possible to avoid any last minute rushes. The standard AV set up for all presentations will be data projection using MS PowerPoint. All presentations will be run from a PC.

DISPLAYING YOUR POSTER
Poster presentations run across all three days of ISDS. If your abstract has been allocated into a poster session please review you presentation number, time and day in the program. Posters can be hung up at 8:00AM each morning and must be removed by no later the 3:00PM the same day. Velcro is available from the registration desk.

MOBILE PHONES
Please ensure your mobile phone is turned off during sessions.

INTERNET ACCESS
ASN has an Ericsson high speed 3G wireless connection available for complimentary use by delegates. The network name is ASN Internet, and the password is 1nternet. If it is slow please retry later when traffic is not as heavy.

HOTEL CHECK OUTS
You are required to check out of your room before 10am. The resort reception has facilities to store your luggage. If you apply early enough to reception, you may be able to organise a late check out

SOCIAL FUNCTIONS

The Welcome Function – Friday 24th June

On Friday night there is a welcome function from 6:00pm – 7:30 pm at the Lagoon Bar. The Welcome Function consists of local beers and wines accompanied by finger food and are included with your registration. Registered partners are welcome.

The Conference Dinner – Cairns Night Zoo - Saturday 25th June

On Saturday night there is a conference dinner at the Cairns Night Zoo. The Bus picks delegates up at 6:45 pm and departs the Zoo at 10:00 pm. This thoroughly "Aussie" night begins with a hearty barbecue dinner of steak, chicken, fish, prawns and salads, plus complimentary beers, wines and soft drinks. After feasting on dinner, you'll join your intrepid guide to see what some Australians get up to after dark! Supplied with your own flashlight, you'll be led into the darkness to meet Australia's creatures of the night. You'll see crocodile eyes glow in the torchlight, learn how owls hunt, touch a possum and pat a koala. On clear nights the guides will take you star gazing to see the Southern Cross, Big Dipper and other well-known constellations. Tickets are included in your registration; however you will need to provide the organisers with your ticket when boarding the bus. If you and your partner haven't indicated that you would like a ticket, please visit the registration desk for availability. Partner registrations include The Conference dinner as part of the package. ***Please note delegates must wear closed in shoes**.

OPTIONAL SOCIAL ACTIVITES

Mii Spa:

Located at the Sea Temple resort The Mii Spa Offers three beautifully appointed treatment rooms, two with private outside verandas leading onto a man-made rainforest, where you can relax and unwind after your treatment. Ergonomically designed massage tables will ensure the neck, spine and leg muscles are cradled in complete comfort while taking the strain off any pressure points as well as heated to ensure the body's temperature remains constant throughout the entire treatment.

Contact Details
Web: www.mirvachotels.com/sea-temple-resort-palm-cove/mii-spa
Email: miispa@strspc.mirvac.com.au
Phone: + 61 7 4059 9613.

Sky Rail:

Skyrail Rainforest Cableway located just a few minutes' drive from Palm Cove is truly one of the most magnificent experiences for any holiday in far north Queensland The Skyrail experience, spanning 7.5kms over pristine rainforest, allows you to explore the wonders of an ancient tropical rainforests and learn about one of the most botanically fascinating and diverse areas on earth. Gliding just metres above the rainforest canopy in comfortable 6-person gondola cabins the Skyrail journey immerses you in an intimate rainforest experience where you'll see, hear, smell and become part of the tropical rainforest environment.

Contact Details:
Web: www.skyrail.com.au
Email: mail@skyrail.com.au
Phone: 61 7 4038 1555

Hot Air Balloons:

Not many people know but the hot air ballooning capital of the world, is Cairns/Palm Cove. Up to 12 balloons a morning go floating over the Atherton Tablelands. Even better, balloon rides here are up to 48% cheaper than Syd/Melb/Canberra at only $175pp including flight, return transfers, full hot brekkie & champagne toasts. Seeing all the balloons inflating is an AMAZING way to start the day. Mention STAYZ & get a FREE Boxed Set of Champagne Flutes.

Contact Details
Web: www.hotair.com.au
Email: cairns@hotair.com.au
Phone: + 61 7 4039 9900

Barron River Gorge:
The Barron River Gorge is located 10 minutes' drive from Palm Cove and lies along a traditional pathway used by the original indigenous Djabugay people. The spectacular Barron Falls, further upstream, are considered a sacred site. The famous Kuranda Railway and Skyrail Cableway also traverse sections of the gorge. Stoney Creek on the southern side of the Gorge is home to one of North Queensland's most beautiful national parks, complete with isolated waterfalls and swimming holes in a tropical wonderland.

Contact details
Web: www.wanggulay.com
Phone: +61 7 4039 1461

LOCAL RESTAURANTS

Casmar Restaurant & Bar
If you are in the Palm Cove/Port Douglas/Cairns area and looking for seafood, then the Casmar cannot be surpassed. With a Seafood Platter for 2 at $90 this is one of the cheapest in the area and certainly worth every cent. With prawns, Barramundi, bugs, calamari and oysters, it is spectacular.
Address: Cr Harpa St & Williams Esplanade Palm Cove
Ph: (07) 4059 0013
Web: www.casmar.com.au

Nu-Nu Restaurant
Recline on oversized banquettes and watch the sheer silver and ice blue curtains waft in the breeze against a backdrop of glistening sea views. If that isn't enough to put you in a peaceful frame of mind, the professional and polished service and delicious taste sensations certainly will be. For a unique and delicious breakfast, try the 'toastie' of poached rhubarb and apple on sweet challah bread with vanilla cream. Lunch and dinner options are no less appealing. Among them, blue swimmer crab and avocado sandwiches, roasted Spring Bay scallops or pork and bean-shoot egg-nets with pink pomelo (grapefruit) and a chilli coconut caramel sauce.
Address: 123 Williams Esplanade, Palm Cove QLD 4879
Phone: (07) 4059 1880
Web: www.nunu.com.au

Apres Beach Bar and Grill
The friendly and inviting atmosphere of Apres Beach Bar & Grill has earned us the reputation of being one of Cairns and North Queensland's premier meeting places, for both locals and visitors alike. Overlooking beautiful Palm Cove beach, you can meet for a meal, or mingle over a drink and soak up the buzz that defines the Apres style.
Address: 119 Williams Esplanade Palm Cove Queensland 4879 Australia
Ph: (07) 4059 2000
Web: www.apresbeachbar.com.au

Vivo Bar and Grill
Surrounded by elegant palms and majestic mellaleuca trees, the graceful white walls and turrets of Vivo's Queensland colonial exterior provide a stunning, cool contrast to the warm, aromatic and colourful vibrance of the interior. In the heart of the restaurant, the chic, stylish sunken bar forms a vibrant, animated hub. Vivo's sparkling stainless steel open plan kitchen enables Head Chef Russell Molina to oversee the whole restaurant, and also allows the delicious aromas of their gourmet cooking to waft tantalisingly on the gentle Coral Sea breezes.
Address: 49 Williams Esplanade, Palm Cove QLD 4879
Phone: (07) 4059 0944
Web: www.vivo.com.au

Bella Baci
Bella Baci is and Italian style, seafood resataurant situated on Williams Esplanade, Palm Cove. The restaurant boasts some of the finest food Palm Cove has to offer along with a fully licensed bar and the most stunning ocean views across the Esplanade.
Address: 123 Williams Esplanade, Palm Cove QLD 4879
Phone: (07) 4055 3186
Web: www.bellabaci.com.au

PROGRAM

Friday, 24 June 2011

Registration Opens
7:00 AM - 8:00 AM Temple 1 & 2 Courtyard

ISDS2011 Conference Scientific Program Start
8:00 AM - 8:00 AM Temple Rooms 1 & 2

Poster Session I with Breakfast
8:00 AM - 10:00 AM Sea Temple Restaurant

Lanie Alcausin

Clinical variability in *Osteogenesis Imperfecta* with calicification of interosseous membranes (OI Type V) *abs#051*

Elena Andreucci

Rhole of the COL11A1 gene in hereditary arthro-ophthalmopathies. *abs#052*

Michael Bober

Clinical Management of patients with Majewski Osteodysplastic Primordial Dwarfism, Type II (MOPDII). *abs#053*

Luisa Bonafe

Spondylo-Megaepiphyseal-Metaphyseal Dysplasia: severe neurologic manifestations from cervical spine instability *abs#054*

Erin Carter

Identification of Skin Abnormalities in Osteogenesis Imperfecta Patients by Magnetic Resonance Imaging: A Pilot Study *abs#055*

Denise Cavalcanti

Birth prevalence rates of osteochondrodysplasias (OCD) in South America (SA): an epidemiologic study in a large population *abs#056*

Jacqueline Cramb

“Let's Get Cracking”: Participation of children with *osteogenesis imperfecta* in extra-school physical activity *abs#057*

Sandeep Das

Growth and Body Proportions in Children with Achondroplasia and their Association with Adverse Health Outcomes. *abs#058*

Jane Estrella

Natural history of untreated Maroteaux-Lamy syndrome: Skeletal complications *abs#059*

Maha Faden

Mutation of CANT1 causes Desbuquois Dysplasia *abs#060*

Anita Inwood

Sibling comparison study of 7 years of enzyme replacement therapy for mucopolysaccharidosis type VI starting at 8 weeks and 3.5 years of age. *abs#063*

Penny Ireland

Functional performance in young Australian children with achondroplasia *abs#064*

David Tunkel

Hearing loss in skeletal dysplasia patients *abs#065*

Tiong Tan

Infantile systemic hyalinosis presenting as multiple joint pain *abs#097*

Welcome
10:00 AM

Ravi Savarirayan Temple Rooms 1 & 2

Invited Speaker Presentation I
10:00 AM - 11:00 AM Temple Rooms 1 & 2

Jim McGill
Current status and future challenges in the treatment of lysosomal storage diseases *abs#001*

Platform session I (Clinical/Translational Science)
11:00 AM - 12:30 PM Temple Rooms 1 & 2

11:00am **Luisa Bonafe**
Cleft palate, chondrodysplasia and abnormal joint development associated with recessive mutations in IMPAD1, the gene coding for the Golgi-resident nucleotide phosphatase, gPAPP *abs#002*

11:30am **Carlos Bacino**
FLNA mutations in terminal osseous dysplasia with pigmentary defects (TODPD) *abs#003*

11:45am **Sarah Smithson**
Cantú Syndrome: Skeletal and other clinical features in 11 new patients *abs#004*

12:00pm **George Tiller**
A novel syndrome with characteristic facial features, skeletal dysplasia and developmental delay. *abs#005*

12:15pm **David Rimoin, MD**
Dynamic cervicomedullary cord compression and alterations in CSF fluid dynamics in children with achondroplasia *abs#006*

Lunch Break
12:30 PM - 3:00 PM Sea Temple Restaurant

Platform Session II Part A (Clinical/Translational Science)
3:00 PM - 4:00 PM Temple Rooms 1 & 2

3:00pm **Stuart Tompson**
Dominant and recessive forms of fibrochondrogenesis resulting from defects in type XI collagen *abs#007*

3:30pm **Shiro Ikegawa**
CANT1 is also responsible for Desbuquois dysplasia, type 2 and Kim variant and has a founder mutation common in Korean and Japanese *abs#008*

3:45pm **Elisabeth Jameson**
A multicenter phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of BMN 110 treatment for mucopolysaccharidosis IVA (Morquio Syndrome) – clinical study design *abs#009*

Afternoon Tea/Coffee Break
4:00 PM - 4:30 PM Temple 1 Courtyard

Platform Session II Part B (Clinical/Translational Science)

4:30 PM - 5:30 PM Temple Rooms 1 & 2

4:30pm **Elena Andreucci**
TRPV4 related skeletal dysplasias: a phenotypic spectrum highlighted byclinical, radiographic, and molecular studies in 22 new families. *abs#010*

4:45pm **Roberto Mendoza-Londono**
Novel Ehlers-Danlos Syndrome caused by mutations in the *CHST14* gene - Expanding the Phenotype *abs#011*

5:00pm **Gen Nishimura**
Cole-Carpenter syndrome as a severe skeletal dysplasia *abs#012*

5:15pm **David Sillence**
Osteogenesis Imperfecta 2011 understanding a genetically heterogeneous disorder – a clinical and molecular synthesis *abs#013*

Welcome Reception function

6:00 PM - 7:30 PM Lagoon Bar

Registration Opens
7:00 AM - 8:00 AM Temple 1 & 2 Courtyard

Poster Session II with Breakfast
8:00 AM - 10:00 AM Sea Temple Restaurant

Michelle Fink

Fetal brain anomalies in skeletal dysplasias: "the brain predicts the dysplasia"? *abs#061*

Elena Andreucci

Genotype-Phenotype correlations in type II collagenopathies: analysis of 51 families. *abs#066*

Michael Bober

Safety of flexion extension cervical MRI under anesthesia in children with skeletal dysplasia *abs#067*

Erin Carter

Case Report: Fraternal twins with Kniest dysplasia *abs#068*

Denise Cavalcanti

Birth prevalence rates of osteochondrodysplasias (OCD) in South America (SA): an epidemiologic study in a large population *abs#069*

Sandeep Das

Head circumference for age curves in Australian children with cchondroplasia and the association between head circumference and cervicomedullary compression. *abs#070*

Penny Ireland

Population-based analysis of development of infants and young Australian children with Achondroplasia *abs#071*

Ok-Hwa Kim

CODAS (Cerebral, Ocular, Dental, Auricular, Skeletal) Syndrome: Detailed description of radiological findings and new feature on brain MRI *abs#072*

Carrie Kollias

Coxa Vara and associated Salter Harris II fractures of the femoral neck in osteopetrosis: A report of two cases requiring Valgus osteotomies *abs#073*

Shih-Chia (Jason) Liu

Orthopaedic management in Mucopolysaccharidosis paitents *abs#074*

Christine Loo

Liver and pancreatic lesions in a case of short-rib polydactyly type 3. *abs#075*

Roberto Mendoza-Londono

Expanding the phenotype of Perlecan disorders *: De-novo* microdeletion of chromosome region 1p36.12 involving *HSPG2* with hemizygous *HSPG2* mutation in a patient with spondyloepimetaphyseal dysplasia *abs#076*

Elena MONTI

A novel splicing mutation in FKBP10 in a patient with a moderate osteogenesis imperfecta histologically classificable as Type VI *abs#077*

Elena MONTI

Hypercalciuria and renal function in children affected by Osteogenesis Imperfecta *abs#078*

Sarah Nikkel

Thanatophoric dysplasia at 26 years of age *abs#079*

Gael E Phillips

The utility of fetal autopsy in the diagnosis of skeletal dysplasias *abs#080*

Invited Speaker Presentation II

10:00 AM - 11:00 AM Temple Rooms 1 & 2

John Bateman

Endoplasmic reticulum stress: A new player in the pathophysiology of skeletal dysplasias *abs#014*

Platform Session III (Basic science/Human/animal models)

11:00 AM - 12:30 PM Temple Rooms 1 & 2

11:00am **Michael Briggs**
The unfolded protein response in chondrodysplasias; old friends and new players *abs#015*

11:30am **Antonio Rossi**
Defective proteoglycan sulfation of the growth plate zones in the *dtd* mouse causes reduced chondrocyte proliferation via an altered Indian hedgehog signalling *abs#016*

12:00pm **L. Legeai-Mallet**
BMN 111, a CNP analogue, rescues femur growth and growth plate architecture in a severe model of Fgfr3-related chondrodysplasia. *abs#017*

Lunch Break

12:30 PM - 3:00 PM Sea Temple Restaurant

Platform Session IV (Basic Science/Human/animal models)

3:00 PM - 4:30 PM Temple Rooms 1 & 2

3:00pm **Paul Lockhart**
Loss of function of WDR35 causes short-rib polydactyly syndrome due to abnormal ciliogenesis *abs#018*

3:30pm **C. O'Neill**
BMN 111, a CNP analogue, promotes skeletal growth and rescues dwarfism in two transgenic mouse models of Fgfr3-related chondrodysplasia *abs#019*

4:00pm **Yewande Alade**
Surgical history, pain and function in skeletal dysplasia patients *abs#020*

4:15pm **David Coman**
Primary and secondary defects in of post-translational modification and the skeleton. *abs#021*

ISDS Membership meeting

4:30 PM - 5:15 PM Temple Rooms 1 & 2

ISDS2011 Conference Dinner

6:45 PM - 10:00 PM Cairns Night Zoo

Registration Opens
7:00 AM - 8:00 AM Temple 1 & 2 Courtyard

Poster session III with Breakfast
8:00 AM - 10:00 AM Sea Temple Restaurant

Michael Bober

Upper cervical fusion in children with morquio's syndrome: Medium and long-term results *abs#081*

Tim Cundy

Variable osteogenesis imperfecta phenotype resulting from a founder mutation in *FKBP10* in Samoa *abs#082*

Julie Hoover-Fong

Cardiopulmonary phenotype of achondroplasia adults *abs#083*

Penny Ireland

Medical management of children with Achondroplasia: Evaluation of an Australasian cohort aged 0-5 years. *abs#084*

Se-Hwa Kim

MPS screening in patients with orthopaedic problems *abs#085*

Ok-Hwa Kim

Leg duplication with ipsilateral renal agenesis: A spectrum of congenital acrorenal Malformation Syndrome *abs#086*

Elena Monti

Vitamin d levels in idiopathic juvenile osteoporosis *abs#087*

Elena Monti

Children and adolescents treated with neridronate for osteogenesis imperfecta: No evidence of any osteonecrosis of the jaw *abs#088*

Sulekha Rajagopalan

A new Australian case of raine syndrome *abs#089*

Peter Simm

Report of infantile hypophosphatasia and possibility for enzyme replacement therapy *abs#090*

Sarah Smithson

Phenotypes in a mother and baby with campomelic dysplasia caused by a SOX9 splicing mutation *abs#091*

Reid Sutton

The OI foundation linked clinical research centers longitudinal study *abs#092*

Elizabeth Thompson

A family with an Arg134Cys mutation in COL1A1 and overlapping phenotypes of osteogenesis imperfecta and ehlers-danlos syndrome. *abs#093*

Meow-Keong Thong

Raine syndrome: case report and delineation in a Malaysian infant *abs#094*

Peter Turnpenny

Short stature, clavicular hypoplasia, mild microcephaly and learning difficulties in a family with deletion 17q21.32-17q21.33, giving rise to haploinsufficiency of the *HOXB* gene cluster *abs#096*

Invited Speaker Presentation III
10:00 AM - 11:00 AM Temple Rooms 1 & 2

Sally Dunwoodie
Notch signalling makes its mark on spondylocostal dysostosis *abs#022*

Platform Session V (mixed topics/late breaking news)
11:00 AM - 12:30 PM Temple Rooms 1 & 2

11:00am **Melita Irving**
Mutations in NOTCH2 cause Hajdu Cheney syndrome *abs#023*

11:30am **Bernhard Zabel**
Genetic deficiency of tartrate-resistant acid phosphatase is associated with skeletal dysplasia, cerebral calcifications and autoimmunity *abs#024*

12:00pm **Peter Turnpenny**
Spondylothoracic dysostosis, spondylocostal dysostosis type 2, and the mutational spectrum of *MESP2* *abs#025*

12:15pm **Andreas Zankl**
The SKELETOME Project: Towards a community-driven knowledge curation platform for Skeletal Dysplasias *abs#026*

Maroteaux Award Presentation (sponsored by Biomarin)
12:30 PM - 1:00 PM Temple Rooms 1 & 2

ISDS2011 Conference Scientific Program End

Lunch Break
1:00 PM - 2:00 PM Sea Temple Restaurant

SPONSORS & SUPPORTERS

BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949
Contact: Kathie J. Ward, CMP
Phone (415) 506-6781
Email: kward@bmrn.com
Web: www.BMRN.com

BioMarin develops and commercializes innovative biopharmaceuticals for serious diseases and medical conditions. Approved products include the first and only enzyme replacement therapies for MPS I and MPS VI and the first and only FDA-approved medication for PKU. Visit www.BMRN.com to learn more.

Genzyme
Level 1 Building C, 12-24 Talavera Road
North Ryde
NSW 2113
Contact: Katerina Galluzzo
Ph: 02 9978 3900
Email: katerina.galluzzo@genzyme.com
Web: http://www.genzyme.com

One of the world's leading biotechnology companies, Genzyme has grown from a small start-up to a diversified enterprise serving patients in 80 countries throughout the world. Genzyme has businesses focused on the needs of patients seen by both private practice and hospital based specialists, including Enzyme replacement therapies for lysosomal storage disorders, Renal and Transplant Medicine, Haematology/Oncology, Endocrinology and Orthopaedics.

Enobia
Contact: Julie Anne Smith
Phone: (001) 609-516-2400
Email: JSmith@Enobia.com
Web: www.enobia.com

Enobia Pharma Inc. is a private Montreal-based company focused on the development of therapeutics to treat serious bone disorders for which there are no drug therapies currently approved. ENB-0040, an investigational drug for the treatment of hypophosphatasia, is the Company's lead program. For more information, please visit www.enobia.com.

POSSUMweb
Murdoch Childrens Research Institute
Contact: Dr Cathie Rose
Email: possum@mcri.edu.au
Web: www.possum.net.au

POSSUMweb is a dysmorphology database that can help with diagnosis of syndromes in patients and teaching about syndromes. By providing a flexible search facility, POSSUMweb saves time and effort in researching and cross-referencing syndrome information. The POSSUMweb database contains information on over 4000 syndromes, including skeletal dysplasias and chromosomal disorders. There are over 30,000 images including photos, Xrays, diagrams, and histology, with an extensive trait dictionary and atlas. POSSUMweb is available by annual subscription, with automatic monthly data updates, and images updated annually. The images are downloaded on to your hard-drive, and data accessed over the internet using a secure hardware key.

Short Statured People Of Australia
Contact: Rosemary Hobbs
Email: rosehobbs47@gmail.com
Web: www.sspa.org.au/

The Short Statured People of Australia (S.S.P.A.) is a non-profit, self-help organisation that provides support and information for people of short stature (dwarfs) who don't (or won't) reach the height of 150 cm. (4"11") at maturity, parents of short-statured people, siblings of short-statured people, and other interested members of the community. Our main aim is to assimilate people of short stature into society with the goal of equality of education and social status, and of employment opportunities. In 1981, the S.S.P.A. formed the National Medical & Scientific Advisory Board consisting of medical specialists from both the Bone Dysplasia Clinics in Melbourne, Victoria and Sydney, New South Wales. In subsequent years, the Board's membership has been extended to medical specialists from genetics clinics in other states of Australia. Members of the Board make themselves available to S.S.P.A. members for expert advice as new knowledge on the causes and management of bone dysplasias becomes known.

ABSTRACTS

ORALS

001

CURRENT STATUS AND FUTURE CHALLENGES IN THE TREATMENT OF LYSOSOMAL STORAGE DISEASES

J. McGill

Dept of Metabolic Medicine, Royal Children's Hospital, Herston, Australia

The lysosomal storage disorders (LSD) are a group of disorders resulting from impaired lysosomal enzyme function or transport. LSD are progressive, multisystem disorders with onset in utero. A skeletal dysplasia is part of the clinical spectrum of many of the disorders, including the Mucopolysaccharidoses (MPS) which I will use to illustrate the progress of therapy. The earliest therapy aimed at altering the disease phenotype was bone marrow transplantation then later haemopoietic stem cell transplantation (HSCT), particularly for Hurler syndrome (MPS IH).While successful in correcting or improving many of the clinical features of MPS IH, a new set of skeletal problems were created. Enzyme replacement therapy (ERT) has similarly significantly improved many of the clinical features of the MPS disorders but poorly vascularised tissues such as bone and cartilage have responded suboptimally because much higher levels of circulating enzyme are required to ameliorate bone pathology. Immune tolerance improves the tissue levels of enzyme. Animal studies indicate that neonatal onset of therapy and higher doses improves the skeletal response. Although neonatal onset of therapy has been demonstrated to be the optimal time to start, skeletal responses remain disappointing. Attempts to modify the enzyme so that bone tissue is targeted have encountered difficulties. To enable neonatal ERT, techniques have been developed to diagnose the LSD by newborn screening but it remains difficult to predict the disease severity in many of the disorders. Combined ERT and HSCT have improved the outcome for individuals with MPS IH and recent murine MPS I research demonstrated normalization of skeletal pathology with combined neonatal HSCT and gene therapy. More recent approaches to therapy of the LSDs include substrate inhibition, chaperone, stop-codon read-through and gene therapies; however the problem of delivering the therapy to cartilage and bone applies for all of these therapies.

002

CLEFT PALATE, CHONDRODYSPLASIA AND ABNORMAL JOINT DEVELOPMENT ASSOCIATED WITH RECESSIVE MUTATIONS IN IMPAD1, THE GENE CODING FOR THE GOLGI-RESIDENT NUCLEOTIDE PHOSPHATASE, GPAPP

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We used whole exome sequencing to study three individuals with a distinct condition characterized by short stature, cleft palate and facial dysmorphism, congenital joint dislocations, and chondrodysplasia with brachydactyly and a peculiar lateral deviation of the fifth toes. Previous diagnostic hypotheses had included diastrophic dysplasia and Desbuquois syndrome, but DTDST and CANT1 mutation analysis was negative. Affected individuals carried homozygous missense mutations in IMPAD1, the gene coding for gPAPP, a Golgi-resident nucleotide phosphatase that hydrolyzes phosphoadenosine-phosphate (PAP), the byproduct of sulfotransferase reactions, to AMP. The mutations affected residues in or adjacent to the phosphatase active site and are predicted to impair enzyme activity. A fourth unrelated patient was subsequently found to be homozygous for a premature termination codon in IMPAD1. Impad1 inactivation in mice has previously been shown to produce chondrodysplasia with abnormal joint formation and impaired proteoglycan sulfation. This condition (that we propose to call chondrodysplasia with joint dislocation, gPAPP type, or palato-gono-dactylic dysplasia) joins a growing number of skeleto-articular conditions associated with defective synthesis of sulfated proteoglycans, highlighting the importance of proteoglycans in the development of skeletal elements and joints.

003

FLNA MUTATIONS IN TERMINAL OSSEOUS DYSPLASIA WITH PIGMENTARY DEFECTS (TODPD)

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Terminal osseous dysplasia with pigmentary defects (TODPD) is an X-linked syndrome with distal limb anomalies and pigmentary skin defects. We have previously described this syndrome in several females from a large, four-generation pedigree. This condition appears to be male lethal. The clinical presentation consists of multiple limb anomalies including brachydactyly, syndactyly, camptodactyly, and distal digital fibromatosis. Other clinical features include hypertelorism, multiple frenula, and characteristic punched-out pigmentary abnormalities over the face, temporal regions, and scalp. The skeletal involvement is generalized with osteopenia, methapyseal involvement, vertebral flattening, carpal coalition, and brachydactyly. The molecular defect of TODPD has been recently identified and it involves the gene encoding for filamin A (FLNA). Affected patients have been found to harbor a unique splicing mutation (c.5217G>A) which activates a cryptic splice site, resulting in a loss of 16 amino acids at the protein level. The mutant allele is not expressed in patient fibroblasts and it has been only detected in fibroma cells. We have identified the c.5217G>A mutation in affected members from the original family in which TODPD was described. In addition, we have detected the same mutations in three additional patients from two independent pedigrees. Interestingly, the mutation was absent in both mothers, who either exhibited signs of the disease or generated two affected daughters both carrying the c.5217G>A mutation. These findings support in these two pedigrees the hypothesis of mosaicism for the mutated FLNA allele. In summary, we confirm that TODPD patients carry the c.5217G>A mutation in the FLNA gene and we also found high prevalence of mosaicism in this disorder. TODPD thus represents yet another filamin A disorder, a gene associated with great genetic heterogeneity.

004

CANTÚ SYNDROME: SKELETAL AND OTHER CLINICAL FEATURES IN 11 NEW PATIENTS

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Cantú syndrome, a rare disorder of congenital hypertrichosis, characteristic facial anomalies, cardiomegaly and osteochondrodysplasia was first described in 1982 by J Cantú. The pathogenesis of this rare autosomal dominant condition is unknown. In his original report Cantú described two siblings and two other unrelated patients. The radiological findings included broad ribs, platyspondyly, wide metaphyses, ischiopubic hypoplasia, small obturator foramen, bilateral coxa valga and generalised osteopenia. Subsequent reports have shown marked variability in the skeletal features.

We present the findings of a UK based study of Cantú syndrome, comparing the skeletal features of our new cases, with the 23 previously reported. We show progressive macrocephaly in our patients associated with thickening of the calvarium, prominent occiput and sclerosis of the skull base. Skeletal surveys at different ages show the most consistent finding is broad ribs and variable findings include coxa valga, broad femoral necks, wide ischiopubic synchondrosis and delayed bone age.

We describe how the distinctive facial appearance evolves with time and report several new findings including recurrent infections with low immunoglobulin levels and gastric bleeding in some of our patients. The cardiac manifestations include patent ductus arteriosus, septal hypertrophy, pulmonary hypertension and pericardial effusions. They may follow a benign course but of the 11 patients, 5 required surgical closure of the patent ductus arteriosus and 1 patient pericardectomy. Long term follow up of some of our patients has shown a reassuring neuro-developmental outcome and the emergence of an interesting behavioural phenotype.

005

A NOVEL SYNDROME WITH CHARACTERISTIC FACIAL FEATURES, SKELETAL DYSPLASIA AND DEVELOPMENTAL DELAY.

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We describe three male patients with a distinctive syndrome encompassing a skeletal dysplasia, characteristic facial features, and developmental delay. Skeletal findings include patellar dislocation, short tubular bones, mild epiphyseal and metaphyseal changes, mild vertebral endplate irregularity, exaggerated lumbar lordosis, brachydactyly, short femoral necks and shallow acetabular roofs. Facial features include epicanthal folds, hypertelorism, malar hypoplasia with broad nasal bridge, anteverted nares, cleft palate or bifid uvula, and synophrys. All of the patients demonstrated pre-school onset of cognitive developmental delay and an engaging personality. The phenotype closely resembles that of four unrelated males described by Bober et al (2008). We propose that the constellation of findings reported herein constitutes a novel syndrome which appears to exhibit an X-linked recessive inheritance pattern.

(1) Bober MB, Mackenzie W, Nicholson L, Scott CI. Three unrelated patients with a unique spondylo-epi-metaphyseal dysplasia. 30th annual meeting, Soc Bone Mineral Res, Montreal, Sept 2008.

006

DYNAMIC CERVICOMEDULLARY CORD COMPRESSION AND ALTERATIONS IN CSF FLUID DYNAMICS IN CHILDREN WITH ACHONDROPLASIA

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Introduction: In patients with achondroplasia, cervicomedullary junction compression may result in sleep apnea or sudden dearth. In the past we had presented four patients with worsening cervicomedullary compression with their cervical spine in flexed position. In a retrospective review, we evaluated 20 children for symptomatic cervicomedullary cord compression, presence of dynamic alterations in canal diameter, and assess outcomes following decompression.

Methods: Pediatric patients with achondroplasia and central sleep apnea were referred for evaluation to the pediatric neurosurgery program at Cedars-Sinai for possible cervicomedullary decompression. All patients underwent pre-operative MR imaging of the skull base and cervicomedullary junction, with all patients seen from 2006 and beyond undergoing preoperative and postoperative cervical spine MRI with flexion/extension CSF flow studies.

Results: Over a 11-year period, 20 patients with a diagnosis of achondroplasia (mean age 77.3 months) were found to have symptomatic cervicomedullary compression. Pre- and post-operative MRI studies in flexion/extension with CSF flow studies were completed in 14 out of 20 of these patients. Foramen magnum stenosis was demonstrated in all 14 (100%) in the flexed position, but with significant stenosis in only 9 out of 14 patients(64.2%) with the cervical spine in either the neutral or extended position.

Post-operatively, all 14 patients had re-establishment of CSF flow ventral to the cord at the level of the foreamen magnum in the neutral, flexed, and extended positions. At follow-up (mean time 3.4 years), all patients reported significant improvement in pre-operative symptoms and were found to have moderate to complete resolution of central sleep apnea. One patient was taken back for wound exploration, but no post-operative infection or CSF leak was detected in this or any other patient in our series.

Conclusion: There is a risk of dynamic cord compression and alterations in CSF dynamics in children with achondroplasia. Cervicomedullary decompression may be accomplished safely with significant clinical benefit and low morbidity.

007

DOMINANT AND RECESSIVE FORMS OF FIBROCHONDROGENESIS RESULTING FROM DEFECTS IN TYPE XI COLLAGEN

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Fibrochondrogenesis is a severe recessively inherited skeletal dysplasia that can be caused by mutations in the gene encoding the proα1(XI) chain of type XI collagen, *COL11A1*. The first of three cases reported here was the affected offspring of first cousins of Saudi Arabian descent. Whole-genome SNP genotyping excluded homozygosity at the *COL11A1* locus, however the gene encoding the proα2(XI) chain of type XI collagen, *COL11A2*, was present in the largest region of homozygosity. Sequence analysis identified homozygosity for a splice site change that resulted in exon skipping and implied deletion of 18 amino acids within the triple helical domain of proα2(XI). In cases two and three, sequence and high-density targeted array analyses were performed for *COL11A1* and *COL11A2*. In case two, heterozygosity for a 9-bp deletion in exon 40 of *COL11A2* was identified, which predicted a Gly-X-Y triplet deletion within the triple helical domain of the proα2(XI) chain. Neither parent carried the change and microsatellite analysis was consistent with parentage, which suggested the change was a *de novo* dominant mutation. In the third case, heterozygosity for a 9-bp deletion was identified in exon 44 of *COL11A1*, which predicted a deletion of a triplet within the triple helical domain of the proα1(XI) chain. Mass spectrometry of cartilage ECM proteins identified proα1(XI) chains that harbored the triplet deletion, showing that some mutant chains were incorporated into type XI collagen molecules and secreted. However, electron microscopy showed RER inclusions as well as sparsely distributed and abnormally frayed collagen fibrils. These and previously published results show that the phenotype results from a combination of reduced type XI collagen synthesis/secretion as well as incorporation of structurally abnormal type XI collagen into the cartilage ECM. The data further demonstrate that fibrochondrogenesis can result from either recessively- or dominantly-inherited mutations in either *COL11A1* or *COL11A2*.

008

CANT1 IS ALSO RESPONSIBLE FOR DESBUQUOIS DYSPLASIA, TYPE 2 AND KIM VARIANT AND HAS A FOUNDER MUTATION COMMON IN KOREAN AND JAPANESE

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Desbuquois dysplasia (DD) is a recessively inherited condition characterized by short stature, generalized skeletal dysplasia and advanced bone maturation. DD is clinically heterogeneous and at least two subtypes have been distinguished based on the presence (type 1) or absence (type 2) of accessory metacarpal bone. In addition, we have recently described an apparently distinct variant without additional metacarpal bone but with short metacarpals and long phalanges (Kim variant) (ref. 1). By the frontier study of the Paris group (Ref. 2), mutations in the gene CANT1 encoding calcium-activated nucleotidase 1 was identified in DD type I. We tested for CANT1 mutations in 11 subjects with DD from eight families (one type 1, two type 2, five Kim variant). We identified eight distinct mutations in seven families (one type 1, one type 2 and all five Kim variant): three were nonsense and five missense, all at highly conserved amino acids in the nucleotidase conserved regions. Measurement of nucleotidase activity in vitro showed that missense mutations were all associated with loss-of-function. Two mechanisms were considered for the loss-of-function, failure of secretion and loss of enzyme activity. Our results indicate that the clinical spectrum produced by CANT1 mutations must be extended to include distinct variants. While additional metacarpal ossification centre has been used to distinguish subtypes of DD, this sign is not a distinctive criterion to predict the molecular basis of DD. Our results also revealed c.676G>A in five families, which were all East Asians (Japanese or Korean). To examine a common founder in the two populations, we genotyped dense SNP markers of chromosome regions around the CANT1 mutation for the families. We identified in all families a common haplotype that ranged up to 550 kb. The two unrelated carriers of the mutation in general populations in Korea and Japan could also have the haplotype. We estimated the age of the founder mutation as ~1,400 years.

(1) Kim et al. Am J Med Genet 2010
(2) Huber et al. Am J Hum Genet 2009

009

A MULTICENTER PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BMN 110 TREATMENT FOR MUCOPOLYSACCHARIDOSIS IVA (MORQUIO SYNDROME) – CLINICAL STUDY DESIGN

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Introduction: MPS IVA is an inherited multi-systemic disorder caused by deficient activity of *N*-acetylgalactosamine 6-sulfatase (GALNS) which leads to excessive and pathologic lysosomal storage of keratan sulfate (KS). Skeletal and joint abnormalities, cardio-pulmonary complications, plus hearing and visual impairments are common, resulting in decreased endurance and impaired quality of life for patients. Enzyme replacement therapy (ERT) with recombinant human GALNS (BMN 110) may provide treatment benefit. A Phase 1/2 study with BMN 110 dosed at 0.1, 1.0, and 2.0 mg/kg/week for 3 consecutive 12-week periods, has been completed in MPS IVA patients; it is now in a continuation phase (maximum: 84 weeks of treatment). Improved performance on endurance assessments (6 Minute Walk Test [6MWT] and 3 Minute Stair Climb Test [3MSCT]), most respiratory function tests, and reduced urinary KS excretion were observed. Additionally, pharmacokinetic results and *in-vitro* studies using human Morquio fibroblasts suggest potential utility of an every-other-week dosing regimen.

Objective: To evaluate the relative safety and efficacy of BMN 110 when compared to placebo in MPS IVA patients.

Methods : Patient eligibility criteria include at least 5 years of age, ambulatory, and a confirmed MPS IVA diagnosis. Patients will be randomized to receive BMN 110 or placebo. Assessments of endurance (6MWT and 3MSCT), urinary KS levels, and safety (adverse events, immunogenicity, tolerability) will be performed. Additional assessments include cardiorespiratory function, hearing, quality of life, and biomarkers of bone/cartilage metabolism.

Discussion: BMN 110 treatment, if proven safe and effective, may provide substantial clinical benefit since endurance and mobility can be severely impaired in MPS IVA patients.

Conclusion: To date, this is the largest ERT trial in MPS patients, with expected enrollment of over 160 patients from EU, Middle East, Asia, and North and South America. The first patient was enrolled in February 2011. Specific study details will be provided.

010

TRPV4 RELATED SKELETAL DYSPLASIAS: A PHENOTYPIC SPECTRUM HIGHLIGHTED BYCLINICAL, RADIOGRAPHIC, AND MOLECULAR STUDIES IN 22 NEW FAMILIES.

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Background: The *TRPV4* gene encodes a calcium-permeable ion-channel that is widely expressed, responds to many different stimuli and participates in an extraordinarily wide range of physiologic processes. Autosomal dominant brachyolmia, spondylometaphyseal dysplasia Kozlowski type (SMDK) and metatropic dysplasia (MD) are three distinct skeletal dysplasias which share common clinical features, including short stature, platyspondyly, and progressive scoliosis.

Recently, mutations in *TRPV4* have been found to be responsible for these three skeletal phenotypes.

Methods and Results: We critically analysed the clinical and radiographic data on 27 subjects from 22 families, all of whom had a clinical diagnosis of one of the conditions described above: 16 with MD; 9 with SMDK; and 2 with brachyolmia. We sequenced *TRPV4* and identified 9 different mutations in 23 patients, 4 previously described, and 5 novel. There were 4 mutation-negative cases: one with MD and one with SMDK, both displaying atypical clinical and radiographic features for these diagnoses; and two with brachyolmia, with isolated spine changes and no metaphyseal involvement.

Conclusions: Our data confirm autosomal dominant brachyolmia, MD, and SMDK as allelic *TRPV4* skeletal dysplasias, and suggest that these conditions represent a continuum of severity with areas of phenotypic overlap, even within the same family. We propose that AD brachyolmia lies at the mildest end of this spectrum and, since all cases described with this diagnosis and *TRPV4* mutations display metaphyseal changes, we suggest that is not a distinct entity but represents the mildest phenotypic expression of SMDK.

011

NOVEL EHLERS-DANLOS SYNDROME CAUSED BY MUTATIONS IN THE *CHST14* GENE - EXPANDING THE PHENOTYPE

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Ehlers-Danlos Syndrome (EDS) is a heterogenous group of disorders characterized by varying degrees of connective tissue hyperextensibility. In 2010 a new type of EDS was described in patients of Japanese and of Turkish descent presenting with craniofacial characteristics, contractures and joint and skin laxity. All patients had mutations in the *CHST14* gene coding for the enzyme dermatan 4-O-sulfotransferase.

We present the detailed clinical findings in 2 sisters of Afghani descent born to consanguineous parents. The patients presented with multiple contractures, progressive joint and skin laxity and hemorrhagic diathesis following minor trauma. Prenatal evaluation of patient 2 identified possible Dandy-Walker variant, prominent amnion-chorionic separation, bilateral club feet and clenched hands. Platelet aggregometry and electron microscopy revealed normal function and ultrastructure. Cultured fibroblasts produced normal amounts of fibronectin and elastin but demonstrated lack of collagen III production, lack of extracellular deposition of collagen I fibers and a peculiar intracellular retention of Collagen I. Both patients were found to be homozygous for a novel missense mutation in the *CHST14* gene.

The identification of two additional patients with this disorder raises awareness of the pan-ethnicity of the condition and expands our knowledge regarding the clinical manifestations. Our studies show that the condition has to be considered in cases presenting prenatally with clenched fists and amnion-chorion separation, that the facial features are characteristic regardless of ethnicity and the bleeding diathesis in these patients are not the result of thrombocytopathy. We also expand the knowledge regarding the collagen abnormalities in this condition.

012

COLE-CARPENTER SYNDROME AS A SEVERE SKELETAL DYSPLASIA

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Cole-Carpenter syndrome (CCS; MIM 112240) is a rare disorder characterized by bone fragility and craniosynostosis with striking proptosis. Only a handful of cases have been reported 1), 2), 3). It was initially designated as ga newly recognized type of osteogenesis imperfecta h. However, type 1 collagen analysis was normal. We previously reported three sporadic patients, one boy and two girls with a presumably lethal form of CCS (outcomes: pregnancy interruptions, neonatal death) 4). Two identical cases were also found in Prof. Spranger fs personal archive. The phenotype was initially mistakenly reported as osteoglophonic dysplasia 5). The consistent picture of the skeletal changes included not only craniosynostosis and generalized osteopenia with mid-shaft femoral fractures or bowing and bowed tibiae and fibulae, but also beaded ribs, misshapen clavicles, abnormally wide sacrosciatic notches, and angel-shaped phalanges of the hands. We report here three additional cases with the severe CCS phenotype h. The three babies required intensive respiratory care in the neonatal period and subsequent tracheostomy, but all survived and were successfully weaned from assisted ventilation. One boy was treated with bisphosphonate. Unfortunately, he fell into a vegetative state as a result of rapidly progressive increased intracranial pressure with tonsillar herniation at age 6 months. The other patients, a 1-year-old girl and a 3-month-old girl have been relatively well. With age, the distinctive findings of the clavicles, ribs, and ilia have been gradually remodeled into a relatively normal shape.

(1) Amor DJ, et al. 2000. Am J Med Genet (A) 92: 273-277
(2) Cole DEC and Carpenter TO. 1987. J Pediatr 110: 76-80
(3) Macdermot KD, et al. 1995. Clin Genet 48: 217-220
(4) Nishimura G, et al. 2006. Annual Meeting of ASHG, New Orleans
(5) Stöss, et al., 1991. Pathologe 12: 161-166

013

OSTEOGENESIS IMPERFECTA 2011 UNDERSTANDING A GENETICALLY HETEROGENEOUS DISORDER – A CLINICAL AND MOLECULAR SYNTHESIS

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Osteogenesis Imperfecta in 2011 is confirmed as a genetically heterogeneous group of disorders. As at January 2011, various phenotypes had been discovered to result from mutations in at least 12 different gene loci. The International Nomenclature Committee(2009, published 2011) recommended that to ensure ready understanding by both clinicians and scientists it would group the OI Syndrome into 5 clinical categories plus a number of rare specific syndromes, some of which including *OI with Calcification in Interosseous Membranes* are presently of unknown pathogenesis.

Two phenotypes, *Non-deforming OI with Blue Sclerae* (OI type I) and *Common Variable OI with Normal Sclerae* (OI type IV) are most frequently encountered in European populations. The 'classic' disorder OI type I, which results from truncation mutations in COLIAI or COLIA2 and activation of nonsense mediated decay, is highly associated with progressive mixed (normally conductive) hearing loss. As may be expected, patients with Common Variable OI, where the majority patients have missense mutations in type I collagen genes, the unfolded protein response (UPR) is activated to varying degrees.

Missense and structural mutations in type I collagen genes result in phenotypes which fall into three clinical categories *Common Variable OI, Progressively Deforming OI* and *Perinatally Lethal OI*. However with the latter two groups of disorders, autosomal recessive subtypes contribute to the population frequency and recurrence risks. In Africa and parts of South Asia, over 50% of newborns with OI have one of these autosomal recessive disorders. Mutations in loci which interfere with prolyl – 3' hydroxylation are prevalent in African and Middle Eastern populations. Mutations in genes coding for several distinct collagen chaperone processes interfere with intracellular trafficking and mutations in OSX/SP7 with mineralization.

Finally early treatment with Cyclic Intravenous Bisphosphonates shows an almost compete preservation of skeletal growth in some patients, and biomechanical studies all indicate that quality rehabilitation has a major role in countering adverse outcomes such as skeletal deformity.

014

ENDOPLASMIC RETICULUM STRESS: A NEW PLAYER IN THE PATHOPHYSIOLOGY OF SKELETAL DYSPLASIAS

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Tissue-specific extracellular matrices (ECM) are crucial for normal cartilage and bone development and function, and mutations in ECM genes result in a wide range of skeletal dysplasias. Mutations cause dysfunction by combinations of two mechanisms. Firstly, secretion of the mutated ECM components can be reduced by mutations affecting synthesis or structural mutations causing cellular retention and/or degradation. Secondly, secretion of mutant protein can disturb crucial ECM interactions, structure and stability. Moreover, recent experiments suggest that endoplasmic reticulum (ER) stress, caused by mutant misfolded ECM proteins, contributes to the molecular pathology. The relative contribution of each of the intracellular and extracellular components to the pathophysiology will depend on the mutation and will be context dependant. In most cases it would seem likely that both gain-of-function unfolded protein response (UPR) consequences and alterations to the ECM, either by reduced secretion, altered interactions or composition will contribute to the disease mechanism. Developing a detailed understanding of ER-stress/UPR networks activated in chondrodysplasias may provide a basis for new therapeutic strategies. Schmid chondrodysplasia is an autosomal dominant disease caused by mutations in the hypertrophic chondrocyte marker *Col10a1*, and characterized by dwarfism and hypertrophic zone (HZ) elongation. We previously reported two mouse models bearing the phenotypic hallmarks of Schmid chondrodysplasia, and exhibiting endoplasmic reticulum (ER) stress in the HZ due to constitutive expression of misfolding proteins by hypertrophic chondrocytes (Rajpar et al., PLoS Genetics 5(10):e1000691) . The first (Schmid) bears a disease-causing N617K mutation in *Col10a1*. The second (Cog) carries a *Col10a1* promoter-driven transgene encoding a misfolding form of thyroglobulin. That both models exhibited identical phenotypes demonstrated the central importance of ER stress in the disease pathology. Here, we took a holistic approach to study the signaling networks involved in responding to hypertrophic chondrocyte ER stress. We microdissected HZs from Schmid, Cog, and wildtype mice, and amplified and interrogated the RNA by microarray analyses. In both mutants, these analyses revealed strikingly similar UPRs, involving upregulation of molecular chaperones and foldases to enhance ER folding capacity, upregulation of ER associated degradation (ERAD) to enhance disposal of misfolded proteins, and downregulation of secreted proteins to reduce ER protein load. Chop/Cebpb signaling, often a marker of apoptosis, was upregulated in both models. TUNEL-positive hypertrophic chondrocytes were detected in the Schmid and Cog growth plates, although active Bax and Bim (cell death executioners) were not detected by immunohistochemistry. To examine the effects of ER stress on chondrocyte differentiation, we analyzed the expression of genes identified by further microarray analyses as defining the wildtype proliferative zone (PZ), in the Schmid and Cog HZs. These analyses revealed that chondrocytes in the mutant growth plates fail to undergo complete hypertrophy due to partial retention of the PZ phenotype, accounting for the HZ elongation characteristic of Schmid chondrodysplasia.

015

THE UNFOLDED PROTEIN RESPONSE IN CHONDRODYSPLASIAS; OLD FRIENDS AND NEW PLAYERS

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Growth plate chondrocytes undergo a highly coordinated process of proliferation, hypertrophy and apoptosis and disruptions to this process lead to a heterogeneous group of genetic diseases known as the chondrodysplasias. At each stage of maturation chondrocytes synthesise and secrete structural proteins that are incorporated into the extracellular matrix. The expression of mutant forms of these proteins, such as COMP and matrilin-3, in pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED), causes endoplasmic reticulum stress and can induce an unfolded protein response (UPR).

We have shown using genetically engineered mouse models of PSACH-MED that the induction of ER stress, through the expression of mutant COMP and matrilin-3, can directly affect chondrocyte phenotype, cause growth plate dysplasia and dwarfism. Interestingly, although these mouse models all exhibit ER stress, different UPR pathways are activated that appear to be gene and/or mutation specific.

The expression of mutant matrilin-3 causes protein retention and a classical UPR characterised by the up-regulation of BiP and members of the protein disulphide isomerase family including two novel genes, CRELD2 and ARMET, which have only recently been implicated in ER stress. Similarly, the expression of a mutated, but secreted form of COMP (p.T585M) also causes conventional BiP-mediated UPR.

In contrast, the expression of a retained form of mutant COMP (p.D469del) causes increased chondrocyte apoptosis that is not associated with a conventional UPR or CHOP-mediated apoptosis. Instead, the accumulation of mutant COMP causes upregulation of *Igfbp3* and down regulation of *Prdx2*, suggesting that oxidative stress and mitochondrial-mediated apoptosis are important disease-causing mechanisms.

It is not clear in these archetypal examples of prolonged ER stress, whether the UPR is chondrocyte protective or a significant cause of distress. Answering this fundamental question will explain the initiation and progression of skeletal dysplasias, provide essential insight into disease mechanisms and identify potential therapies.

016

DEFECTIVE PROTEOGLYCAN SULFATION OF THE GROWTH PLATE ZONES IN THE *DTD* MOUSE CAUSES REDUCED CHONDROCYTE PROLIFERATION VIA AN ALTERED INDIAN HEDGEHOG SIGNALLING

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Mutations in the sulfate transporter gene, *SCL26A2*, lead to cartilage proteoglycan undersulfation resulting in chondrodysplasia in humans; the phenotype is mirrored in the diastrophic dysplasia (*dtd*) mouse. It remains unclear whether bone shortening and deformities are caused solely by changes in the cartilage matrix, or whether proteoglycan (PG) undersulfation affects also signalling pathways involved in cell proliferation and differentiation. Therefore we studied macromolecular sulfation in the different zones of the *dtd* mouse growth plate and these data were related to growth plate histomorphometry and proliferation analysis.

A 2-fold increase of non-sulfated disaccharide in *dtd* animals compared to wild-type littermates in the resting, proliferative and hypertrophic zones was detected indicating chondroitin sulphate PG undersulfation; among the three zones the highest level of undersulfation was in the resting zone. The chondrocyte proliferation rate, measured by bromodeoxyuridine labelling, was significantly reduced in mutant mice. To further characterize the proliferation defect expression levels of the main genes involved in the cell cycle were considered and sulfation studies of femoral head cartilage demonstrated that the sulfation defect affects chondroitin sulphate PGs, but heparan sulphate PGs, which are often involved in cell signalling, were normally sulphated. Immunohistochemistry of the *dtd* growth plate demonstrated that PG undersulfation in the extracellular matrix alters the distribution pattern of Indian hedgehog (Ihh), a long range morphogen required for chondrocyte proliferation and differentiation; in fact incubation of dtd chondrocytes with recombinant Ihh *in vitro* rescued the normal proliferation phenotype.

These data suggest that chondroitin sulphate PG undersulfation causes reduced chondrocyte proliferation in the proliferative zone via the Ihh pathway, therefore contributing to reduced long bone growth in *dtd* mice.

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017

BMN 111, A CNP ANALOGUE, RESCUES FEMUR GROWTH AND GROWTH PLATE ARCHITECTURE IN A SEVERE MODEL OF FGFR3-RELATED CHONDRODYSPLASIA.

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Achondroplasia, the most common form of dwarfism in humans, is characterized by a defect in endochondral bone growth due to an activating mutation in the Fibroblast Growth Factor Receptor 3 (Fgfr3), a transmembrane tyrosine kinase receptor. Fgfr3 activation decreases chondrocyte proliferation and differentiation leading to a growth deficit. The proximal bones, such as the femurs, are most severely affected. C-type natriuretic peptide (CNP), a member of the natriuretic peptide family, regulates endochondral bone growth by inhibiting Raf-1, a Fgfr3 downstream signaling mediator. Targeted *in vivo* overexpression of CNP or continuous infusion of CNP were shown to rescue the impaired bone growth observed in a mouse model of achondroplasia. However, CNP short half-life hampered its use as a therapeutic agent. To overcome the short half-life of native CNP, BioMarin developed a CNP analogue, BMN 111, with increased half-life allowing daily subcutaneous administration. BMN 111 pharmacological activity was characterized in an *ex vivo* model of severe achondroplasia ($Fgfr3^{Y367C/+}$ mice[1]). Femurs were isolated from wild-type and $Fgfr3^{Y367C/+}$ embryos (embryonic age E16.5) and were incubated for 6 days with BMN 111 (right femur, 10^{-6} to 10^{-10}M) or with vehicle (left femur). Culture media were replaced every two days. A significant increase in bone length was observed at the 10^{-6} to 10^{-9}M ($p < 0.01$) dose concentration range along with a restoration of the proliferative and hypertrophic zones of the growth plate. In addition, significantly greater bone length gain was observed at the 10^{-6} and 10^{-7}M concentrations in the $Fgfr3^{Y367C/+}$ femurs in comparison to the wild-type femurs (+71-86% for the $Fgfr3^{Y367C/+}$ femurs and +51% for the wild type femurs, respectively). BMN 111 incubation rescued the endochondral ossification process of proximal bones with a severe achondroplastic phenotype.

(1) Pannier S, Couloigner V, Messaddeq N, Elmaleh-Bergès M, Munnich A, Romand R, Legeai-Mallet L. Activating Fgfr3 Y367C mutation causes hearing loss and inner ear defect in a mouse model of chondrodysp

018

LOSS OF FUNCTION OF WDR35 CAUSES SHORT-RIB POLYDACTYLY SYNDROME DUE TO ABNORMAL CILIOGENESIS

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The short rib-polydactyly (SRP) disorders are a heterogenous group of autosomal recessive lethal skeletal dysplasias characterised by short ribs and limbs. The presence of additional clinical features such as abnormal viscera, cranium and palate can be used to classify the disorders into specific subtypes. We previously identified a family with an unclassifiable SRP that displayed laterality defects suggestive of ciliary dysfunction (1). We performed linkage and SNP analysis on five family members and identified a single region at chromosome 2p24.1 that was homozygous by descent in affected family members. CNV analysis identified a homozygous deletion within the linkage peak that disrupted the WDR35 gene. *WDR35* encodes a novel highly conserved protein with homology to known cilial proteins. Immunocytochemical analysis localised WDR35 to the cilial axoneme and basal body of control fibroblasts, however cilia were completely absent in fibroblasts derived from SRP patients. Targeted disruption of *wdr35* in the mouse resulted in abnormal cilia, randomised laterality, polydactyly and neural tube defects.

Mammalian cilia transduce essential signals during embryonic patterning and the mutant phenotype suggested deficits in hedgehog (Hh) signalling contributed to disease pathogenesis. Quantitative real-time PCR analysis confirmed that downstream effector genes, such as *Ptch1* and *Gli1*, were not responsive to Hh signalling in either MEFs derived from mutant mice or patient fibroblasts. In addition, ultrastructural analysis indicated an additional role for WDR35 in regulating ciliary membrane trafficking during mammalian development. Homology modelling revealed striking similarities in the protein structure of WDR35 and the coat complexes COPI, COPII and clathrin. This analysis suggested a molecular basis for the observation that mutations in *WDR35* can give rise to the distinct clinical phenotypes of short rib-polydactyly and Sensenbrenner syndrome.

(1) Kannu P et al (2007) AJMG Part A 143:26073

019

BMN 111, A CNP ANALOGUE, PROMOTES SKELETAL GROWTH AND RESCUES DWARFISM IN TWO TRANSGENIC MOUSE MODELS OF FGFR3-RELATED CHONDRODYSPLASIA

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Although FGFR3-related chondrodysplasia were identified more than 20 years ago, no effective treatments are available and therapeutic interventions are limited to surgical procedures. Achondroplastic patients display a short stature with disproportionate shorter proximal bones, narrow trunk and macrocephaly. The severity of the phenotype ranges from mild (hypochondroplasia) to severe (achondroplasia) and lethal (thanatophoric dysplasia) depending on the point mutation. C-type natriuretic peptide (CNP) is considered to be a potential therapeutic agent because of its inhibition of Fgfr3 downstream signaling. Targeted *in vivo* overexpression of a CNP transgene or continuous infusion of native CNP were shown to rescue the impaired bone growth in a mouse model of achondroplasia. To overcome the short half-life of native CNP, BioMarin developed a CNP analogue, BMN111, with an increased half-life allowing daily subcutaneous administration. BMN111 pharmacological activity was characterized in two transgenic mouse models of Fgfr3-related chondrodysplasia. In the $Fgfr3^{G380R}$ mouse model[1], the transgene expression is restricted to the chondrocytes while it is ubiquitously expressed in the $Fgfr3^{Y367C/+}$ mouse model[2]. A more severe phenotype is observed with the $Fgfr3^{Y367C/+}$ (shorter bones, pronounced prognathism and reduced lifespan). The mice received daily subcutaneous administrations of BMN111 from 6 days of age in the $Fgfr3^{Y367C}$ mice and three weeks of age in the $Fgfr3^{G380R}$ mice, supporting both achondroplastic and hypochondroplastic pediatric populations. The $Fgfr3^{Y367C}$ mice were treated for 10 days at dose levels up to 800 ug/kg. The $Fgfr3^{G380R}$ mice were treated for 5 weeks at dose levels up to 280 ug/kg. Overall, the treatment was well tolerated. A dose related increase in the axial and appendicular skeletons was measured in both models (~5-10% increase in the high dose groups). Normalization of bone age and growth plate architecture was observed in the $Fgfr3^{Y367C}$ mice. Based on these data, BMN111 is a potential therapeutic agent for achondroplasia and hypochondroplasia.

(1) Naski MC, Colvin JS, Coffin JD, Ornitz DM. Repression of hedgehog signaling and BMP4 expression in growth plate cartilage by fibroblast growth factor receptor 3. Development. 1998 Dec;125(24):4977-88

(2) Pannier S, Couloigner V, Messaddeq N, Elmaleh-Bergès M, Munnich A, Romand R, Legeai-Mallet L. Activating Fgfr3 Y367C mutation causes hearing loss and inner ear defect in a mouse model of chondrodyspla

020

SURGICAL HISTORY, PAIN AND FUNCTION IN SKELETAL DYSPLASIA PATIENTS

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Background: A cross-sectional survey was designed to assess the relationship between surgical history, pain and physical function in skeletal dysplasia patients.

Methods: This online, anonymized survey was advertised to 3000+ Little People of America member households.

Results: 417 individuals (277 adults, 140 children; 167 males, age 27.1(19.7) yrs; 250 females, 32.4(19.1) yrs) participated. 89.2% had 1 of 9 common diagnoses; 54.4% with achondroplasia (138 adults, 89 children). 76.5% could climb 1 flight of stairs and 73.6% walk 1 city block. Of 135 achondroplasia adults, 83.7% could climb 1 flight and 77.9% walk 1 block. Of 230 adults, 22.6% walked for <10 min. By the Bleck Scale, walking was impossible/not functional in 11.2% of adults and 10.5% were homebound. 3.9% of adults were non-mobile/unable to move around and 9.2% were limited to the immediate area. 90.6% of adults could toilet independently, 90.3% bathe and dress, 82.3% cook/do housework, and 79.4% grocery shop. By the Brief Pain Index, 71.1% of adults had more than mild pain with an average (i.e. least/worst in 24 hrs, overall, now) pain score of 3.5 (2.0) (0=none, 10=worst imaginable). Pain interfered with sleep in 61.3% and life enjoyment in 69.1%. Pain score increased with decreasing mobility and walking ability. There were 2.29 (achon), 2.19 (hypo), 2.11 (pseudo), 2.63 (DD) and 3.80 (SEDC/Kniest) back surgeries per 100 patient-years, and 4.16 (achon), 5.00 (hypo), 3.03 (pseudo), 4.00 (DD), and 3.95 (SEDC/Kniest) tympanostomy tubes placed per 100 patient-years. More spine and extremity surgeries were associated with decreased mobility and walking ability, and increasing age was inversely correlated with walking ability. Age and weight were also statistically significantly higher in those with poor mobility.

Conclusion: This survey suggests some short stature skeletal dysplasia patients have considerable physical limitations, pain, and a relatively high prevalence of surgical intervention. A longitudinal study is needed to ascertain the chronology of events in the complex interplay among surgery, pain and physical function.

021

PRIMARY AND SECONDARY DEFECTS IN OF POST-TRANSLATIONAL MODIFICATION AND THE SKELETON.

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Post-translational modification (PTM) of proteins is essential for normal cellular function. Primary and secondary defects in glycosylation result in various skeletal phenotypes. This paper reviews these phenotypes and their mechanisms. Defects in glycan assembly and processing, (congenital disorders of glycosylation CDG), are a protrean group of conditions. The skeletal involvement is under-diagnosed and ranges from osteopenia to primary skeletal dysplasias (resembling Kniest). This is expected given that many key celluler components of bone and connective tissue undergo glycosylation e.g. pro-collagen, and the SIBLING (Small Integrin-Binding Ligand, N-linked Glycosylation) family. Elevated lysosomal enzymes have been observed in the serum of CDG-Ia patients perhaps reflecting missorting, defective uptake, or reduced stability of the enzymes as a secondary consequence of the defective glycosylation thus contributing to the reported dysostosis multiplex phenotype of CDG.

Galactosaemia is another inborn error of metabolism in which osteopenia is common place among teenagers and adults irrespective of pubertal function. Secondary defects in glycan processing occur in galactosaemia and have been postulated to modulate the neurological phenotype, and perhaps also the bone disease. Mutations in the *FGFR-3* receptor underlie primary skeletal dysplasia phenotypes eg hypochondroplasia. Mutations affecting the intracellular domain induce premature receptor phosphorylation and inhibit receptor glycosylation, suggesting that premature receptor tyrosine phosphorylation of the native receptor inhibits its glycosylation. Abnormal glycosylation in Galactosaemia triggers an unregulated unfolded protein response, which in turn modifies the cellular and biochemical phenotype.

Aberrant golgi trafficking mechanisms have also been discovered in primary skeletal dysplasia phenotypes including achondrogenesis type 1A (GMAP-210: is required for the efficient glycosylation and cellular transport of multiple proteins), spondyloepiphyseal dysplasia tarda (TRAPPC2; a component of the trafficking protein particle (TRAPP) vesicle tethering complex) and osteoarthritis (matrilin-3; mutations lead to disturbed golgi trafficking). This work suggests that retention of proteins in the endoplasmic reticulum plays a role in skeletal dysplasia pathogenesis.

022

NOTCH SIGNALLING MAKES ITS MARK ON SPONDYLOCOSTAL DYSOSTOSIS

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Somites are the precursors of the vertebral column. They segment from the presomitic mesoderm (PSM) that is caudally located and newly generated from the tailbud. Somites form in synchrony on either side of the embryonic midline in a reiterative manner. A molecular clock that operates in the PSM drives this reiterative process. Genetic manipulation in mouse, chick and zebrafish has revealed that the molecular clock controls the activity of the Notch signalling pathway in the PSM. Disruption of the molecular clock impacts on somite formation causing abnormal vertebral segmentation (AVS). A number of dysmorphic syndromes manifest AVS defects. Spondylocostal dysostosis (SCD) is caused by mutation in genes associated with the Notch signaling pathway: SCD type1 is caused by mutation in the Notch inhibitory ligand DLL3; SCD type2 by mutation in the Notch target gene MESP2; and SCD type3 by mutation in the Notch target gene and Notch-modifying glycosyltransferase LFNG. Most recently autozygosity mapping identified mutation in another Notch-associated gene, HES7. HES7 is a direct target of Notch signalling and functions as a transcriptional repressor to indirectly inhibit Notch signalling during somite formation. Analysis of mutant proteins is undertaken to define the functional consequences of mutations. In conclusion, defects in Notch signalling are at the forefront of AVS and this has been established using a combination of human genome mapping and mutagenesis in mouse.

023

MUTATIONS IN NOTCH2 CAUSE HAJDU CHENEY SYNDROME

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Hajdu Cheney syndrome (HCS) is a rare, autosomal dominant, multisystem disorder of progressive bone loss with characteristic physical features including craniofacial and dental abnormalities, renal tract anomalies and mild to moderate short stature. In addition, there are consistent radiographic findings, most notably progressive acro-osteolysis. Significant morbidity arises secondary to generalised osteoporosis of childhood onset. Using an exome sequencing strategy in three unrelated HCS kindreds, sequence variants were identified in the terminal exon of *Notch2*. By direct sequencing, disease causing mutations, all confined to the terminal coding *Notch2* exon were identified in a further 11/12 unrelated HCS families. All mutations are predicted to lead to premature truncation of Notch2 with either disruption or loss of the C-terminal PEST proteolytic recognition sequence, the absence of which has previously been shown to increase Notch signalling. Indeed, a protein of the size of the predicted truncated NOTCH2 intracellular domain in primary skin fibroblasts from an affected individual heterozygous for the mutation F2091SfsX4 was detected. The significance of these findings in further understanding bone development and maintenance, as well as the wider implications of the molecular contribution to the aetiology of osteoporosis will be discussed.

024

GENETIC DEFICIENCY OF TARTRATE-RESISTANT ACID PHOSPHATASE IS ASSOCIATED WITH SKELETAL DYSPLASIA, CEREBRAL CALCIFICATIONS AND AUTOIMMUNITY

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Vertebral and metaphyseal dysplasia, spasticity with cerebral calcifications, and strong predisposition to autoimmune diseases are the hallmarks of the genetic disorder spondyloenchondrodysplasia (SPENCD). We mapped a locus in five consanguineous families to chromosome 19p13 and identified mutations in *ACP5*, which encodes tartrate-resistant phosphatase (TRAP), in 14 affected individuals and showed that these mutations abolish enzyme function in the serum and cells of affected individuals. Phosphorylated osteopontin, a protein involved in bone reabsorption and in immune regulation, accumulates in serum, urine and cells cultured from TRAP-deficient individuals. Patient-derived dendritic cells exhibit an altered cytokine profile and are more potent than matched control cells in stimulating allogeneic T cell proliferation in mixed lymphocyte reactions. These findings shed new light on the role of osteopontin and its regulation by TRAP in the pathogenesis of common autoimmune disorders. Pharmacologic modulation of osteopontin may thus provide a novel therapeutic angle for diseases like systemic lupus erymathosus and multiple sclerosis.

025

SPONDYLOTHORACIC DYSOSTOSIS, SPONDYLOCOSTAL DYSOSTOSIS TYPE 2, AND THE MUTATIONAL SPECTRUM OF *MESP2*

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The mesoderm posterior 2 (*MESP2*) gene (MIM 605195) is a key component of the Notch signalling pathway and is integral to the determination of segmental boundary formation in axial skeletal development. It is a small gene of 2 exons with a bHLH transcription domain located within the first exon. There are two main phenotypes associated with recessive mutations in the *MESP2* gene that affect all vertebral segments. Firstly, a mild form of spondylocostal dysostosis type 2 (SCD02, MIM 608681), with limited truncal shortening and good lung capacity. Secondly, the severe phenotype of spondylothoracic dysostosis (STD), giving rise to the crab-like radiological appearance of the chest, sometimes lethal in early childhood. We here describe a full range of published (*Am J Hum Genet* 2004;74:1249-54; *Am J Hum Genet* 2008;82:1334-41) and unpublished mutations alongside the phenotypes, where detail is available. Two SCD02 cases were shown to have the same 4 bp duplication mutation (c.500_503dup, p.Gly169fs) in exon 1 which results in an altered reading frame and a premature termination codon in exon 2, whilst the other case is a compound heterozygote for missense mutations within the bHLH domain. STD cases generally had frameshift or nonsense mutations in exon 1 that result in a truncated protein that is susceptible to degradation by the nonsense-mediated decay (NMD) pathway. In general, therefore, there appears to be a genotype-phenotype correlation depending on the mutational site and whether NMD occurs. However, one severe but non-lethal phenotype is homozygous for a deletion (c.776delC, p.Pro259fs) that results in an altered reading frame with a termination codon at 480 in exon 2 . This new *MESP2* data in man extends our understanding of the role of this developmental gene and aids recognition of the SCD/STD axial skeletal phenotypes.

(1) Am J Hum Genet 2004;74:1249-1254
(2) Am J Hum Genet 2008;82:1334-1341

026

THE SKELETOME PROJECT: TOWARDS A COMMUNITY-DRIVEN KNOWLEDGE CURATION PLATFORM FOR SKELETAL DYSPLASIAS

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The Nosology of Genetic Skeletal Disorders represents the main hub for structuring and retrieving key information about skeletal dysplasias. It provides a classification of the disorders, based upon a shared understanding among the experts, in addition to a shallow grouping by common clinical-radiographic characteristics and/or molecular disease mechanism. In parallel, several systems enabling case studies management and fostering knowledge exchange between domain experts have been developed (e.g., ESDN). Their main role is to promote diagnosis support via interactive discussions. However, their functionalities rise only to the level of a discussion forum and lack any real support for advanced features, like, retrieving information about similar cases. In addition, while the knowledge is intrinsically present in the communication process, novel findings cannot be directly reflected in the Nosology, due to its inflexible nature.

The continuous adoption of Semantic Web technologies now allows us to transform the Nosology into a more dynamic and well-grounded formalism. In this new context, the SKELETOME project aims at developing an ontology for the bone dysplasias domain, to enable knowledge consolidation and to create a comprehensive overview of the domain by adjoining several aspects describing its inherent complexity.

The SKELETOME project also plans to build an ontology-based community-driven knowledge curation platform that will enable collaborative input, sharing and re-use of data and information among experts. The goal is to provide a central access point to a rich skeletal dysplasia knowledge base, supported by low-level features, such as user and group-based access and privacy control. At the same time, from a high-level perspective, the anonymised pool of case studies will enable statistical inference for knowledge discovery purposes or computer-assisted diagnosis. Finally, the use of the ontology as foundational building block will lead a more straightforward and quicker incorporation of novel discoveries into the overall bone dysplasia domain knowledge.

POSTERS

051

CLINICAL VARIABILITY IN OSTEOGENESIS IMPERFECTA WITH CALICIFICATION OF INTEROSSEOUS MEMBRANES (OI TYPE V)

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The association of Osteogenesis Imperfecta with hyperplastic callus following a fracture was first described by Battle and Shaddock in 1908. In the intervening years this type of OI has been redescribed by independent groups resulting in a number of proposed names for the disorder. At the 2009 International Nomenclature Committee, the entity was named Osteogenesis Imperfecta with Calcification of Interosseous Membranes.

Three children have been referred in the past 10 years, and four other patients are known through consultation. The three Australian children had their first fractures prenatally in cases 1 and 2 and at 3 years. The diagnosis of OI type V was suspected on radiographic finding of exosteal hyperostosis of the medial border of the radius and ulna in all cases and confirmed in one by iliac crest histomorphometry. Contracture of the elbows was apparent in 2 patients from a young age (< 1 year). Bilateral dislocation of the radial heads was noted in all three patients. Two children developed explosive hyperplastic callus (hc) *(case 1: diagnosed birth, hc at 6 y 9 mo) and (case 2: diagnosed at birth, hc at 7 years)*. All 3 patients had normal sclerae and normal teeth. COL1A1 and COL1A2 molecular testing was performed in case 1 and was normal. There was no family history of an affected in these 3 cases. In case 3, the patient's father has a similar elbow dislocation but otherwise no other clinical or radiologic features.

The explosive hyperplastic callus bears a striking similarity to the explosive new bone formation seen in patients with Fibrodysplasia Ossificans Progressiva. The endosteal hyperostosis on the medial borders of radius and ulna also appears on the medial borders of tibia and fibula as seen in our two older patients. These families shed new light on the clinical variability, pathogenesis and medical management of this often missed type of OI.

052

RHOLE OF THE COL11A1 GENE IN HEREDITARY ARTHRO-OPHTHALMOPATHIES.

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Type XI collagen is one of the elements which constitute the fibrils in cartilage and many other tissues. It is an heterotrimer, made of three different chains, encoded by genes COL2A1, COL11A1 and COL11A2.

Mutations in the COL11A1 gene have been described as cause of type 2 Stickler syndrome and Marshall syndrome. They are both autosomal dominant disorders with many common features: ocular involvement, with a very high grade myopia and an augmented risk of retinal detachment; joint hypermobility and arthropathy; typical facial features and hearing loss of a variable degree of severity.

We analysed the COL11A1 gene in18 patients with an arthro-ophthalmopathy and a negative COL2A1 analysis. We identified 5 new variants, never described in literature, which were not present in 150 control DNAs, and 2 new exonic SNPs.

The data confirm that in patients with an arthro-ophthalmopathy and negative COL2A1 analysis, COL11A1 is the candidate gene to be analysed. The choice between these two genes should be made on the basis of an accurate ophthalmologic assessment, since we know that slightly different features of the vitreous can orient towards a specific diagnosis; unfortunately, though, this is not always possible, especially after a retinal detachment has already occurred.

053

CLINICAL MANAGEMENT OF PATIENTS WITH MAJEWSKI OSTEODYSPLASTIC PRIMORDIAL DWARFISM, TYPE II (MOPDII).

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Microcephalic primordial dwarfism (MPD) is a class of disorders characterized by IUGR, poor postnatal growth and microcephaly. Majewski osteodysplastic primordial dwarfism type II (MOPD II) is one of the more common conditions within this group. Aside from the classic features of MPD, individuals with MOPD II have an increased risk for cerebrovascular disease and insulin resistance. MOPD II is caused by mutations in the pericentrin (PCNT) gene and is inherited in an autosomal recessive manner. To help determine associated medical problems, an IRB approved Primordial Dwarfism Registry at the duPont Hospital for Children was created. This registry has thus far enrolled 50 participants, in whom a subset have confirmed PCNT mutations.

Specialized growth curves from individuals enrolled in the registry with confirmed PCNT mutations have been constructed. Expected average gains have also been calculated. These data suggest growth rates are at least half of those expected for a typical child.

Cerebrovascular disease, including moyamoya disease and aneurysms, are common. Screenings with MRA/CTA of the brain should begin at diagnosis and continue every 12 to 18 months thereafter to permit early detection of these conditions. If diagnosed in the early stages, revascularization and aneurysm treatment can be performed safely and effectively.

Insulin resistance is associated with MOPDII and can often progress to frank diabetes. Yearly screening labs should begin by 5 years of age and include: hemoglobin A1C, insulin levels, fasting blood sugars, liver functions and lipid profiles. If changes are present, appropriate follow-up and management plans can be implemented. It does appear that these patients respond well to an oral antihyperglycemic medication like metformin.

A yearly CBC should also be obtained as some children, especially post-pubertal girls, have developed anemia. Furthermore, it does appear that baseline platelet counts may be elevated. The clinical significance of this remains to be determined.

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054

SPONDYLO-MEGAEPIPHYSEAL-METAPHYSEAL DYSPLASIA: SEVERE NEUROLOGIC MANIFESTATIONS FROM CERVICAL SPINE INSTABILITY

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In Spondylo-Megaepiphyseal-Metaphyseal Dysplasia (SMMD; MIM 613330), there is overgrowth of the limbs, fingers and toes that contrasts with progressive shortening of the neck and trunk. The combination of radiographic findings - large epiphyses of the long bones, supernumerary epiphyses at the phalanges, absent ossification of the pubic bones, and underossified vertebrae with sagittal clefting - is pathognomonic and explains the clinical phenotype of long limbs and short trunk. We report here on the incidence of severe neurologic manifestations in SMMD. Of six patients whom we surveyed, five had neurologic disease including spasticity or tetraplegia, finger contractures and delayed motor development. Four patients had severe swan-neck deformity of the underossified cervical spine ("kyknodysostosis"), and a further patient had cervical myelopathy acquired at birth because of cervical instability. SMMD is caused by recessive mutations in the BAPX1 (NKX3-2) homoebox gene. All patients included in our study (three previously reported, Hellemans et al, Nat Genet. 2009; and four new ones) were homozygous for mutations in BAPX1 (NKX3-2) that caused either frameshift and premature terminations, or, in one family, an amino acid substitution within the highly conserved homeodomain, confirming that SMMD is associated with loss of function of BAPX1. The diagnosis of SMMD should alert about the risk of severe complications from cervical spine instability and deformation.

055

IDENTIFICATION OF SKIN ABNORMALITIES IN OSTEOGENESIS IMPERFECTA PATIENTS BY MAGNETIC RESONANCE IMAGING: A PILOT STUDY

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Osteogenesis imperfecta (OI) is a group of genetic disorders characterized by bone fragility and frequent fractures. Diagnosis is based on clinical and radiological criteria and increasingly through genetic test results. Most individuals have a type I collagen abnormality.

Our hypothesis is that magnetic resonance imaging (MRI) can detect skin abnormalities that correlate with OI genotype and phenotype. We collected data with the objectives of determining whether 1.MRI can differentiate between skin from OI and control subjects, and 2.MRI analysis is supported by compositional analysis by Fourier transform infrared imaging spectroscopy (FT-IRIS) and dermis phenotype across patients of all ages.

Three mm full-thickness forearm skin biopsies from human OI (n=10) and control (n=9) subjects were analyzed by MRI (T_1, T_2 and magnetization transfer ratio (MTR), and apparent first order rate, k_m); FT-IRIS (proteoglycan, collagen); and histological measurements (major collagen fiber bundle length, width, and angle relative to the epidermis).

Qualitative findings within the OI group correlated with the severity of clinical phenotype for all imaging modalities. Epidermal and dermal layers were thinner in OI patients compared to controls. Averaged univariate MRI parameters for the entire skin depth were dominated by heterogeneity within the dermis, with no significant differences seen between OI and controls. FT-IRIS revealed qualitative differences in the dermis of OI compared to controls; however, quantitative values for proteoglycan and collagen tended to decrease with age in all samples. Histological measurements showed no significant differences between OI and controls.

We conclude that FT-IRIS is sensitive to the presence and severity of OI in human skin. There is an age-related change in FT-IRIS parameters in both OI and controls. Non-destructive univariate MRI analysis did not distinguish between groups based on full-thickness parameter averages. However, further more sensitive multivariate analyses may detect differences between OI and control samples.

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056

BIRTH PREVALENCE RATES OF OSTEOCHONDRODYSPLASIAS (OCD) IN SOUTH AMERICA (SA): AN EPIDEMIOLOGIC STUDY IN A LARGE POPULATION

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The osteochondrodysplasias (OCD) birth prevalence rate of 2.0/10,000 is underestimated. This study aimed to assess OCD epidemiology using a large population in SA with the ECLAMC (a case-control, collaborative hospital-based program for birth defects) data. All OCD cases from ECLAMC files born between 2000-2007 were revised and diagnosis ranked in five evidence levels, taking level 1 as gold-standard, having available X-rays or DNA test. GraphPad InStat™3.0 was used for statistical analysis, and significance was defined as p value < 0.05. For comparative analysis all controls born in the same period were used. Prevalence rates are shown by 10,000 births. After excluding 45 from 536 ascertained cases, the prevalence in 1,544,496 births was 3.2 (CI 2.9 - 3.5). Lethal cases were 50% (245/491 – 65 stillbirths plus 180 cases with early neonatal death). Prenatal diagnosis was made in 73% cases. Among the 210 cases from level 1, the main OCD groups according the ISDS were: G-24(OI) – 33% (59% OI-II); G-1(FGFR3) – 29.5% (56% Thanatophoric D); G-2(Collagen 2) – 6.7% (29% Achondrogenesis 2); G-17(Bent bones) – 8% (71% Campomelic D); G-7 (SRP) – 5.7%. The prevalence of the main OCD types were: OI – 0.72 (0.59 – 0.87); Thanatophoric D – 0.47 (0.36 – 0.59); and Achondroplasia – 0.45 (0.34 – 0.56). Paternal age (31.2 yo), parity (2.6) and consanguinity rate (5.4%) were all increased in cases ($p < 0.001$). Birth weight (2,498 g) was lower in cases, however differences were found just for gestational age over 31 weeks ($p < 0,001$). In conclusion, the OCD overall prevalence rate of 3.2 per 10,000 found seems to be more real than the usually cited value of 2.0. This study also indicates a high rate of prenatal OCD diagnosis in SA, confirmed the overall high infant morbimortality, and the association with paternal age. Finally, a high parity and rate of parental consanguinity was observed.

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"LET'S GET CRACKING": PARTICIPATION OF CHILDREN WITH OSTEOGENESIS IMPERFECTA IN EXTRA-SCHOOL PHYSICAL ACTIVITY

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Physical activity is important for cardiovascular fitness, bone health, weight control, and psychosocial well-being. The Australian Physical Activity Guidelines for Children and Youth recommend at least an hour per day participating in moderate to vigorous physical activity, and not more than two hours playing computer games, watching TV, or non-educational internet use.

Children with osteogenesis imperfecta (OI) can have significant impairments in all domains – body functions and structures, activity, and participation according to the International Classification of Function. Many children with OI receive bisphosphonate therapy to reduce fracture rate and pain and increase bone density, cortical bone width, and porosity. The treatment should also facilitate improvement in their physical function and activity, though parents may still restrict their child's activity to reduce the risk of fracture.

A pilot study was undertaken to explore the participation of Queensland children with OI in recommended extra-curricular physical activity. Fifteen children (9 female) were included in the study (mean age 10.7; range 6-16 years). Participation was measured using the Children's Assessment of Participation and Enjoyment (CAPE), designed to assess participation in leisure activities for children with and without disabilities aged 6 to 21 years.

The children engaged in a broad range of activities with a median CAPE diversity score of 25. There was more involvement in recreational, social, and skill-based activities than physical and self-improvement activities. The intensity of participation ranged from a median of 4.0 (physical activities) to 5.5 (recreational activities) on a 1-7 scale. High levels of enjoyment for all types of activity were recorded. However, there were major differences between children in all scored items, related to OI type, age, sex, and family factors.

The study provides a foundation for understanding participation of children with OI which can assist their families and service providers in planning activities that encourage active participation.

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GROWTH AND BODY PROPORTIONS IN CHILDREN WITH ACHONDROPLASIA AND THEIR ASSOCIATION WITH ADVERSE HEALTH OUTCOMES.

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Introduction: The adverse effects of overweight and obesity have been well described for the general population. We are unable to use this knowledge to improve the health of people with Achondroplasia due to the lack of a definition of overweight and obesity, with current definitions based on Body Mass Index (BMI) being inappropriate to apply because of the differences in growth and body proportions in Achondroplasia. Excess body weight not only poses a risk for obesity related complications such as hypertension, dyslipidaemia and insulin resistance, but also Achondroplasia specific complications including spinal canal stenosis, knee pain, osteoarthritis, lower back pain and obstructive sleep apnoea [1, 2].

Methods: We conducted a retrospective chart review to produce weight for age and BMI for age growth curves for Australian children with Achondroplasia, and to determine the association between weight or BMI and complications of Achondroplasia.

Results: 126 medical records were reviewed which included 63 males and 63 females with Achondroplasia. Growth measurements, complications and additional descriptive data were extracted. A total of 1204 weight for age points and 1109 BMI for age points were obtained, and the LMS method used to produce the smoothed percentile curves. Statistical correlation between weight and/or BMI and medical complications will be performed.

Conclusion: It is important that the relationship between excess body weight and complications in children with Achondroplasia is defined to allow us to determine values for overweight and obesity in the population. A threshold weight for age or weight for height/BMI at which risk of adverse health outcomes increases needs to be determined through prospective studies.

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059

NATURAL HISTORY OF UNTREATED MAROTEAUX-LAMY SYNDROME: SKELETAL COMPLICATIONS

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Mucopolysaccharidoses (MPS) type VI (Maroteaux-Lamy Syndrome) is due to mutations in the gene encoding for arylsulfatase B leading to reduced or absent enzyme activity. Maroteaux-Lamy Syndrome may present from birth (severe form) through to later life. Patients with attenuated forms of MPS VI are probably more common than previously thought and have chronic musculoskeletal disability plus a variety of non-skeletal complications. We describe a patient who was diagnosed with an intermediate late onset form of mucopolysaccharidoses at the age of seven as a result of later investigation of mild joint contracture and chest deformity. Her diagnosis was later confirmed as MPS Type VI. Her adult height was 147 cm. She had mild skin thickening and did not have corneal clouding. She was a university graduate in Psychology and had worked as a counsellor. She developed cervical myelopathy with spinal canal stenosis necessitating decompression at the age of 35 years. A further posterior fossa decompression was needed at 43 years. By the age of 45 she had severe dysplastic changes in both hips with avascular necrosis and required a right total hip replacement. The spine was remarkable for multiple vertebral endplate irregularities and dysplastic changes. There was marked limitation of movement of all joints but she was independently mobile. Significant valvular heart disease required replacement of her aortic and mitral valves at the age of 36 years. She underwent comprehensive review at the age of 49 to assess suitability for enzyme replacement therapy but she passed away unexpectedly prior to initiation of therapy at 51 years of age.

060

MUTATION OF CANT1 CAUSES DESBUQUOIS DYSPLASIA

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Desbuquois dysplasia is an autosomal recessive dysplasia characterized by severe growth restriction and distinct hand and proximal femur appearance in addition to cognitive impairment. The critical interval for this disease has been mapped to 17q25.3 using homozygosity mapping. We have identified a newborn with classical features of the disease whose parents are first cousins. Assuming genetic homogeneity of this disorder, we were able to narrow the critical interval to a region that only contained 10 annotated genes by combining the results of our homozygosity mapping with those of others. Serial sequencing of the genes contained within the interval revealed a 5 bp duplication in Calcium-Activated Nucleotidase 1 gene (CANT1), consistent with the very recent report by Huber et al. [Huber et al. (2009); Am J Hum Genet 85:706–710]. This report cements the role of CANT1 in the causation of this dysplasia and demonstrates the high value of even single cases in the setting of genetically homogeneous disorders when homozygosity mapping is used .

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FETAL BRAIN ANOMALIES IN SKELETAL DYSPLASIAS: "THE BRAIN PREDICTS THE DYSPLASIA"?

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The diagnosis of skeletal dysplasias is largely based on imaging the skeleton. When a fetal skeletal dysplasia is suspected on ultrasound, the definitive diagnosis is usually not made until after delivery. More recently imaging and genetics both have highlighted the systemic manifestations of skeletal dysplasias. In particular, the presence of brain anomalies in skeletal dysplasias has been described, however the imaging thereof has seldom been reported, in particular antenataly. We present the brain anomalies detected on antenatal imaging in four fetuses with different skeletal dysplasias (thanatophoric, Apert syndrome, short rib polydactyly syndrome type IV, and infantile osteopetrosis) in order to illustrate the specific findings in each. Sophisticated fetal neurosonography and MR imaging capable of diagnosing these anomalies is currently available in tertiary referral centres. Using the additional neuro-anatomical information will allow clinicians to refine the differential diagnosis antenataly beyond the issue of lethality. This will assist the counselling of prospective parents. We propose that detailed evaluation of the brain be part of the assessment of any fetus with a suspected skeletal dysplasia.

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SIBLING COMPARISON STUDY OF 7 YEARS OF ENZYME REPLACEMENT THERAPY FOR MUCOPOLYSACCHARIDOSIS TYPE VI STARTING AT 8 WEEKS AND 3.5 YEARS OF AGE.

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Two siblings with mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) have had seven years treatment with enzyme replacement therapy (ERT) using galsulfase (*Naglazyme*) weekly at a dose of1mg/kg starting from 8 weeks of age and 3.5years of age respectively. Treatment has been well tolerated by both siblings with no infusion associated reactions recorded. In the younger sibling ERT has preserved joint movement, cardiac valves, liver and spleen size, height (10th centile) and facial morphology. He has mild scoliosis (23 degrees), stable mild corneal clouding but has recently developed evidence of carpal tunnel syndrome and has significant skeletal disease with a waddling gait from avascular necrosis of the hips. The older sibling initially had a marked improvement in joint and scoliosis mobility which have been maintained and has softening of her facial features and stabilised cardiac valve pathology and corneal clouding. Her height is 6 cms below the 1st centile after correcting for scoliosis which has progressed. Rodding of her spine, which was considered necessary prior to initiating ERT, has been deferred until completion of growth. She has required surgery for severe pes cavus. This paper adds further evidence that early initiation of ERT will slow or prevent the natural pathological progression of MPS VI.

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FUNCTIONAL PERFORMANCE IN YOUNG AUSTRALIAN CHILDREN WITH ACHONDROPLASIA

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Background: Achondroplasia, the most common form of chondrodysplasia, is known to be characterised by delays in basic gross motor, fine motor, oral motor (feeding) and communication skills, however no population specific milestones have been documented for the impact this has on more complex function in areas such as self-care, mobility and social cognition. Condition specific information regarding the acquisition of independence in functional skills is required for clinicians to identify children developing more slowly than their peers and implement appropriate management.

Method: A multi-centre, population-based, cross-sectional study was performed to measure the functional performance of Australian children with Achondroplasia. The study was led by the Royal Children's Hospital, Brisbane and involved The Royal Children's Hospital, Melbourne; The Children's Hospital at Westmead, Sydney; Princess Margaret Hospital, Perth and the Women's and Children's Hospital, Adelaide. Participatns were parents of all known Australian children with Achondroplasia aged three, five or seven years. Parents were interviewed using the Functional Independence Measure for Children (WeeFIM ^{TM}) to gather information about their child's performance on 18 common daily functional activities under the domains of self-care, mobility and social cognition. With author permission, this data was compared to WeeFIM ^{TM} norms.

Results: Thirty-five families participated representing fourteen 3-year-olds, twelve 5-year-olds and nine 7-year-olds. Children with Achondroplasia showed delayed development of independence in functional tasks across all domains and in all age groups compared to normative data.

Recommendations: The need for additional support to complete self care, mobility and social cognition tasks suggests an increased burden of care extending later into childhood for families, teachers and carers of children with Achondroplasia. Access to physical, occupational and speech therapists skilled in assessment and management of Achondroplasia may assist families to identify strategies and environmental devices to support their children to become more independent, particularly at time of school commencement.

065

HEARING LOSS IN SKELETAL DYSPLASIA PATIENTS

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Purpose: To determine the prevalence of hearing loss and abnormal tympanometry in a volunteer population of short stature children and adults attending a national support group meeting, and to assess the feasibility of hearing screening in a non-clinical environment.

Methods: Hearing screening was performed with behavioral audiometry and/or otoacoustic emissions. A failed hearing screen was defined as hearing at 35dB or worse at one or more frequencies tested or by a “fail” response with otoacoustic emissions. Tympanometry and otoscopy were performed on a subset of the group.

Results: 112 subjects were enrolled, and 110 completed the screening. 58(51.8%) were children. 73(65.2%) had achondroplasia, 34(30.4%) had one of 11 other diagnoses, and 5(4.4%) were undiagnosed. 25.8% of children failed hearing screening in one or both ears, while 46.3% of adults failed in one or both ears. Similarly, 54.1% of adults and 25.0% of children with achondroplasia failed screening. Abnormal hearing was also found in the small subpopulations of patients with SEDC (75%), diastrophic dysplasia (66%), and Morquio (66%). Hearing was normal in those with hypochondroplasia, pseudoachondroplasia, and primordial dwarfism. Tympanometry was abnormal in at least one ear in 53.3% of children and 38.5% of adults who had this testing. Abnormal tympanometry in the absence of functioning tympanostomy tubes was associated with a 1.9 times greater risk of hearing loss in the total cohort and a 6.7 times greater risk of hearing loss in children compared to those with normal tympanograms. Only 3(2.7%) reported hearing aid use.

Conclusions: Hearing loss and middle ear disease is common in both children and adults with skeletal dysplasia. Adults were more likely to fail hearing screening than children. Abnormal tympanometry is associated with hearing loss. Intervention is underutilized. Hearing screening with appropriate intervention is recommended for all individuals with short stature skeletal dysplasias.

066

GENOTYPE-PHENOTYPE CORRELATIONS IN TYPE II COLLAGENOPATHIES: ANALYSIS OF 51 FAMILIES.

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Type II collagenopathies are a group of skeletal dysplasias due to mutations in the COL2A1 gene. They show autosomal dominant inheritance and involve mainly the spine and the epyphisis of the long bones. The bone abnormalities are also associated with alterations in the vitreous, typical dysmorphic features and hearing loss with a variable degree of severity.

We analysed 51 italian families and identified 32 mutations: 21 were new, never discribed in litarature and 11 were known mutations.

The phenotype was quite variable among our patients: 19 pazienti had a diagnosis of Sticlkler syndrome, due mainly to nonsense and splice-site mutations; among the more severe phenotypes we had 8 cases of SEDC and SMEDC, which are usually due to mutations with a dominant negative effect. An interesting case was that of a boy with atypical radiographic features, in which we found a de novo variant, D1301E, in the C-terminal region of the protein. We also found many new SNPs. Our data confirm the genotype-phenotype correlations described in literature and shows how on the one hand, sometimes, specific clinical or radiographic features can orient the diagnosis towards a specific mutation; on the other hand, also some patients with a typical features may have a mutation in COL2A1.

067

SAFETY OF FLEXION EXTENSION CERVICAL MRI UNDER ANESTHESIA IN CHILDREN WITH SKELETAL DYSPLASIA

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Introduction: Upper cervical instability and stenosis are common findings in children with skeletal dysplasia. Initial evaluation of the upper cervical spine is with flexion and extension lateral radiographs. If the spine is well ossified the radiographs provide information about stability but no information about the degree of upper cervical cord compression. In young children sedation or general anesthesia is required to achieve satisfactory imaging. Many institutions are uncomfortable with passive positioning for flexion and extension MRI because of the potential for injury to the upper cervical cord. The purpose of this study was to review flexion and extension cervical MRI's under anesthesia to determine if there has been a neurological injury resulting from this procedure.

Method: A retrospective review identified 40 patients with the diagnosis of skeletal dysplasia requiring a cervical MRI in flexion and extension. The procedure was performed in the MRI imaging suite under anesthesia. The protocol followed by the MRI technician included placing the neck in a neutral position by putting a support under the trunk. Cervical extension and subsequently flexion is imaged if the cervical spine in neutral does not demonstrate any cord compression. Changes in vital signs were also monitored to determine safety of the procedure.

Results: All patients had satisfactory flexion and extension MRI imaging. No patients had a change in their baseline neurological status after the MRI procedure.

Conclusions: The cervical flexion and extension MRI is extremely valuable in the diagnosis of upper cervical instability, cord compression and myelopathy. These children can be imaged safely in the MRI suite by a Radiology Technician under anesthesia.

Summary: 40 flexion and extension cervical MRI's under anesthesia in children with skeletal dysplasia were done safely without change of neurological status.

Key Words: Pediatric, cervical instability, skeletal dysplasia, neurologic injury

068

CASE REPORT: FRATERNAL TWINS WITH KNIEST DYSPLASIA

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Background: Kniest dysplasia is characterized by short trunk and limbs, kyphoscoliosis, midface hypoplasia, hearing loss, and severe myopia. Dominant mutation of Col2α1 has been detected in a number of cases. Severely-affected individuals die from respiratory failure shortly after birth whereas mildly-affected individuals can have mild short stature, scoliosis and/or craniofacial manifestations. Cleft palate, club feet, prominent knees, and short stature may be noted at birth in more severe cases.

History: This is a set of fraternal twins conceived with assistance (IVF) using germ cells from nonconsanguineous parents. Family history is negative for skeletal dysplasia or metabolic bone disease. The twins were born at 34 weeks gestation. Twin A (male) weighed 4lbs5oz and was 16.75" long at birth. He spent 3 weeks in the NICU. At 12months his height was in the 0.01st%ile. Radiographic evaluation of a pectus deformity revealed abnormal vertebrae; a skeletal survey showed findings we interpreted as Kniest dysplasia. Ophthalmology and audiology evaluations were normal. He is normocephalic. Twin B (female) weighed 4lbs2oz and was 18" long at birth. A skeletal survey at 14months revealed similar findings to her brother's. Height at 14 months was 26" (0.09th%ile) and weight 20lbs14oz (26th%ile). She has no medical problems, regular facial features with hypertelorism, genu varum, and no pectus deformity.
Radiographic Findings: Kniest is distinguishable from other type II collagenopathies by coronal clefts of the vertebrae and dumbbell-shaped femora. Epiphyses and metaphyses are dysplastic. Platyspondyly with some wedging and anterior beaking. Tubular bones are shortened with narrowed joint spaces.

Summary: We present a set of dizygotic twins with radiographic findings of Kniest dysplasia, first picked up at 14months of age when twin A underwent radiographs for evaluation of a pectus deformity. Subsequent radiographic analysis of twin B revealed similar findings. Molecular genetic analysis of Col2α1 detected no mutation in either twin.

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069

BIRTH PREVALENCE RATES OF OSTEOCHONDRODYSPLASIAS (OCD) IN SOUTH AMERICA (SA): AN EPIDEMIOLOGIC STUDY IN A LARGE POPULATION

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Background : Osteochondrodysplasias (OCD) birth prevalence has been considered underestimated. This study aimed to assess OCD epidemiology using a large population in SA with the ECLAMC (a case-control, collaborative hospital-based program for birth defects) data during 2000-2007 period. Methods: OCD cases were selected through two codes. All cases were revised and diagnosis ranked in five evidence levels, being level 1 (gold-standard) cases with available X-rays or DNA test. Excell™ 2007, EpiInfo™ 5.3.1 and GraphPad InStat™ 3.0 were used for statistical analysis and significance was defined as p value < 0.05. For comparative analysis all controls born in the same period were used. Prevalence rates are shown by 10,000 births. Results: After excluding 45 cases from 536 ascertained, the prevalence in 1,544,496 births was 3.2 (CI 2.9 - 3.5). Lethal cases were 50% (245/491 – 65 stillbirths plus 180 cases with early death). Prenatal diagnosis was related in 73% cases. Among the 210 cases from level 1, the main OCD groups according the ISDS were: OI – 33% (59% OI-II); FGFR3 – 29.5% (56% Thanatophoric D); Collagen 2 – 6.7% (29% Achondrogenesis 2); Bent bones – 8% (71% Campomelic D); SRP – 5.7%. The prevalence of the main OCD types were: OI – 0.72 (0.59 – 0.87); Thanatophoric D – 0.47 (0.36 – 0.59); and Achondroplasia – 0.45 (0.34 – 0.56). Paternal age (31.2yo), parity (2.6) and consanguinity rate (5.4%) were all increased in cases ($p < 0.001$). Birth weight (2,498 g) was lower in cases, however differences were found just for gestational age over 31 weeks ($p < 0,001$). Conclusions: The OCD overall prevalence found in this study seems to be more real. This study also indicates a high rate of prenatal OCD diagnosis in SA, confirmed the overall high infant morbimortality, and the association with paternal age. Finally, it was found a high parity and rate of parental consanguinity.

070

HEAD CIRCUMFERENCE FOR AGE CURVES IN AUSTRALIAN CHILDREN WITH ACHONDROPLASIA AND THE ASSOCIATION BETWEEN HEAD CIRCUMFERENCE AND CERVICOMEDULLARY COMPRESSION.

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Introduction: Children with Achondroplasia require unique head circumference for age growth curves as their head size is generally much larger than children of average stature. These curves are used to screen for progressive hydrocephalus, as well as other general paediatric abnormalities. If the head is abnormally large or crosses to a higher percentile, neuroimaging is often considered to investigate possible obstructive hydrocephalus and the need for shunting. There is also some concern that head size in Achondroplasia may also be related to cervicomedullary compression, a very serious medical complication that can require surgical decompression in infancy or early childhood.

Methods: We conducted a retrospective chart review to produce head circumference for age growth curves for Australian children with Achondroplasia, and to determine the association between head circumference and neurological complications including hydrocephalus and cervicomedullary compression.

Results: 126 medical records were reviewed which included 63 males and 63 females with Achondroplasia. Growth measurements, complications and additional descriptive data were extracted. A total of 905 head circumference for age data points were obtained, and the LMS method used to produce the smoothed percentile curves. Statistical correlation between head circumference and neurological complications will be performed.

Conclusion: Local head circumference for age growth curves will be presented from our Australian cohort. If an association between head circumference and cervicomedullary compression is indicated, this may suggest that measurement of head circumference in children with Achondroplasia may help identify individuals not only at risk of progressive hydrocephalus, but also cervicomedullary compression.

071

POPULATION-BASED ANALYSIS OF DEVELOPMENT OF INFANTS AND YOUNG AUSTRALIAN CHILDREN WITH ACHONDROPLASIA

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Achondroplasia is the most common form of chondrodysplasia, characterised by significant delays in development of communication and motor skills, particularly during the first two years. Despite this, there is little population specific data available to guide assessment of gross motor, fine motor or communication skills, and no information for feeding skills. Without condition specific developmental profiles, it is difficult for clinicians to identify children developing more slowly than their peers in order to initiate therapy intervention. To address this problem, a multi-centre, population based, combined retrospective and prospective audit of developmental milestone data for Australian children with Achondroplasia was undertaken. Lead by the Royal Children's Hospital, Brisbane, the study also included: The Royal Children's Hospital, Melbourne; The Children's Hospital at Westmead, Sydney; The Princess Margaret Hospital, Perth; and the Women's and Children's Hospital, Adelaide. Participant were parents of all known Australian children with Achondroplasia aged from 0-5 years. Parents completed a questionnaire to report their child's acquisition of 41 gross motor, fine motor, communication and feeding skills. Items were drawn from the Australian Personal Health Record Book, standardised developmental assessments and activity limitations highlighted in Achondroplasia literature. Data from families of 20 children in the retrospective arm indicate that developmental delays are present across gross motor, communication and feeding skills but not fine motor skills. Data also identifies two previously unreported and distinctive methods of transitioning between static positions for this population group. Forty five families are still reporting prospectively. Multi-centre research provides important population based information for clinicians and families particularly when considering low incidence, low-prevalence conditions.

072

CODAS (CEREBRAL, OCULAR, DENTAL, AURICULAR, SKELETAL) SYNDROME: DETAILED DESCRIPTION OF RADIOLOGICAL FINDINGS AND NEW FEATURE ON BRAIN MRI

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CODAS syndrome is a very rare constellation of congenital anomalies with only four cases reported to date. The characteristic features are craniofacial anomalies, congenital cataracts, dental anomalies, malformed ears, and multiple epiphyseal dysplasia. We present a case and discuss in detail the radiological manifestations. A 3.5 year old Korean boy was referred because of waddling gait. At age of 3 months bilateral cataracts with strabismus had been discovered. He had evidence of developmental delay. Thyroid function test and cardiovascular and abdominal ultrasound examinations were normal. He attended rehabilitation clinic for psychomotor delay without a convincing diagnosis. A recent clinical evaluation showed a hyperactive boy with slight intellectual impairment and normal height. Facial features showed a flat mid-face, short nose with anteverted nares, and a vertical groove of the nasal tip. Ears appeared to be normal. Radiographs taken at age 2 years showed non ossification of femoral heads, short and broad femoral neck with notch-like depression at the metaphyses. The knees showed non ossification of the distal femoral epiphyses, V-shaped deep indentation of the femoral metaphyses, and horizontally straight metaphyses of the tibias. Lateral spine radiograph showed coronal cleft-like lucent lines were seen through T5-T8. Follow-up radiographic examination at age of 3.5 year showed small and dysplastic femoral heads and persistent notches at the proximal femoral metaphases. The epiphyseal ossifications of the distal femur were not ossified and the deep notches at distal femoral metaphyses persisted. Brain MRI showed marked cerebellar hypoplasia with prominent cerebellar folia. No abnormal finding was seen in the cerebrum. Upon review of the literature and with the inclusion of our case, a consistent pattern is evident with epiphyseal dysplasia, metaphyseal notches seen of the proximal and distal femur, and spinal changes and thus, we suggest that CODAS syndrome is a distinct spondylo-epi-metaphyseal dysplasia.

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073

COXA VARA AND ASSOCIATED SALTER HARRIS II FRACTURES OF THE FEMORAL NECK IN OSTEOPETROSIS: A REPORT OF TWO CASES REQUIRING VALGUS OSTEOTOMIES

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Two patients with osteopetrosis presented to orthopaedic care with Salter Harris II fractures of the femoral neck and associated coxa vara at ages 6 and 7. Each child received subtrochanteric valgus osteotomy with a dynamic hip screw; one of these required revision surgery as a result of loss of fixation in the femoral head. Both healed successfully. One of the children received prophylactic pinning of the asymptomatic contralateral hip as the physis appeared to be widened. Both children have had good outcomes at 1 and 2 years post-op, respectively.

074

ORTHOPAEDIC MANAGEMENT IN MUCOPOLYSACCHARIDOSIS PAITENTS

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Unavailable at time print

075

LIVER AND PANCREATIC LESIONS IN A CASE OF SHORT-RIB POLYDACTYLY TYPE 3.

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Liver and pancreatic lesions are known to occur in some types of short rib polydactyly (SRP) syndromes. We present autopsy findings of a 32 week gestational fetus with SRP type 3 showing ductal plate malformation in the liver and irregular dilatation of pancreatic ducts, paucity of acini and increase in stroma, occurring in the uncinate process of the pancreas but not in the pancreatic body or head. It has been suggested that the underlying abnormality in SRP type 3 is a disorder of primary cilia. In our case, no mutation of DYNC2H1 (cytoplasmic dynein 2 heavy chain 1) was found, but other genes for primary cilia have not yet been investigated. We have performed immunoperoxidase stains for myofibroblasts / activated stellate cells (αSMA - alpha-smooth muscle actin) and stellate cells (cRBP-1 - cellular retinol binding protein-1) on liver and pancreatic tissue. Many stromal cells expessed α-SMA and cRBP-1 in the pancreatic uncinate region but only few stromal cells in the body expressed these antigens. The cRBP-1 stain showed a mild increase in hepatic stellate cells in the SRP fetus, compared to a control fetus of 29 weeks gestation without malformations. The hepatocytes showed abnormal differentiation, with increased cRBP-1 and cytokeratin 19 staining compared to the control fetus. α-SMA showed an increase in portal tract myofibroblastic cells, especially around the edges of the tracts. We suggest that abnormal mesenchymal development may also have contributed to liver and pancreatic malformations. We discuss our findings in relation to data on liver and pancreatic development from other studies reported in the literature. Primary cilia and mesenchymal development may be linked for example through the Hedgehog signalling pathway so that these mechanisms are not necessarily mutually exclusive. We plan to perform immunoperoxidase stains using acetylated tubulin antibody to investigate primary cilia formation.

076

EXPANDING THE PHENOTYPE OF PERLECAN DISORDERS *: DE-NOVO* MICRODELETION OF CHROMOSOME REGION 1P36.12 INVOLVING *HSPG2* WITH HEMIZYGOUS *HSPG2* MUTATION IN A PATIENT WITH SPONDYLOEPIMETAPHYSEAL DYSPLASIA

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HSPG2 is a ubiquitous heparan sulfate proteoglycan that is an integral component of basement membranes. In an autosomal recessive state, it has been implicated in Schwartz-Jampel syndrome type 1 (SJ) and Silverman-Handmaker type of dyssegmental dysplasia (SHDD). We present the clinical, radiologic and cytogenetic findings in a female with a de-novo microdeletion of chromosome 1p36.12 involving HSPG2. Sequencing of HSPG2 revealed a base pair deletion in the other allele.

The patient was born at 38 weeks gestation with a birth weight of 2.6 kg (5-10th centile) and length of 48cm (25th centile). Postnatally she was diagnosed with a form of spondyloepimetaphyseal dysplasia. She developed progressive limitation of the range of motion of multiple joints and became wheelchair bound by 4 years of age. At age 14 she was significantly short at 122 cm (50th centile for a 7 year old). Her bone mineral density was found to be low at -3.8. Her intellectual development has been normal.

Skeletal survey at 12 years of age showed irregularity of the endplates of the cervical spine, fusion of the bodies of C2-C3 and kyphoscoliosis. She has small iliac wings and shortening of the pelvic bones. The femoral heads are irregular, sclerotic with broadening of the femoral neck. The epiphyses of the distal femur and tibia are enlarged. There is generalized long bone shortening. Her elbow joints are disclocated bilaterally.

Array CGH identified a deletion of chromosome region 1p36.12 with an estimated size of 1.357 Mb. This deletion results in the loss of 17 UCSC RefSeq genes, which include 6 OMIM genes: HSPG2 , WNT4, three complement genes and EPHB2. FISH analysis of parental bloods was normal. This case highlights the importance of considering a recessive phenotype when a microdeletion is found and expands the phenotype of skeletal disorders associated perlecan deficiency.

077

A NOVEL SPLICING MUTATION IN FKBP10 IN A PATIENT WITH A MODERATE OSTEOGENESIS IMPERFECTA HISTOLOGICALLY CLASSIFICABLE AS TYPE VI

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BACKGROUND: Osteogenesis imperfecta (OI) is a group of hereditary disorders characterized by bone fragility and osteopaenia, with a broad spectrum of clinical severity. The majority of cases are dominantly inherited and due to mutations in type I collagen genes, whereas recessive forms are less frequent and attributable to mutations in different genes involved in collagen I post translational modifications and folding (prolyl-3-hydroxylase complex, SERPINH1, FKBP10). CASE REPORT: We report the case of a patient with an initially mild and then increasingly moderate-severe form of osteogenesis imperfecta due to a novel homozygous splicing mutation in FKBP10 (intron 8 c.1399+1G>A), which results in aberrant mRNA processing and consequent lack of FKBP65 chaperone. DISCUSSION AND CONCLUSION: Although the biological data differ from the typical hallmarks of type VI such as increased serum alkaline phosphatase the histomorphometric pattern of our patient's bone sample are similar to that previously described as OI type VI and the clinical features seem milder than those described in some newly described FKBP10 mutated patients.

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078

HYPERCALCIURIA AND RENAL FUNCTION IN CHILDREN AFFECTED BY OSTEOGENESIS IMPERFECTA

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INTRODUCTION: Osteogenesis Imperfecta (OI) is an heterogeneous group of inherited disorders of connective tissue characterized by bone fragility, reduced bone mass, laxity of ligaments, blue sclera and different levels of low stature. Hypercalciuria is a condition characterized by an increased urinary calcium excretion without hypercalcemia. It is characterized by an urinary calcium concentration >4mg/kg/die or urinary Ca/Cr ratio >0,21. OBJECTIVE: the aim of this study is to observe the incidence of hypercalciuria among patients affected by OI and the possible correlation with the severity of the underneath condition. We also want to verify the presence of any kidney damage related with the increased urinary calcium or with the ongoing treatment with bisphosphonates. METHODS: we have recruited 36 patients, followed at our clinic, treated with bisphosphonates. We collected, in a period of 3 months (T0-T1), auxological, clinical and laboratory parameters. All patients performed an abdominal ultrasound. In T0 we have investigated the patients' alimentary habits with a questionnaire. Results: the average calcium intake with diet in these patients is lower than the levels indicated by LARN normalized for age. Through urinary Ca/Cr ratio we have identified 11 hypercalciuric patients in T0, 15 in T1. We didn't found any alterations in kidney function both in biochemical and in imaging data. But estimating the urinary calcium in mg/kg/die in T1, we've also observed that hypercalciuric patients were only 6. CONCLUSION: we haven't found correlation between hypercalciuria and severity of OI. Urinary Ca/Cr ratio is not specific enough to detect hypercalciuria in our patients, maybe because of low creatinine levels as a consequence of OI. Hypercalciuria and the treatment with bisphosphonates do not cause any significant kidney alteration. The next studies with DXA are going to make a better evaluation of the influence of hypercalciuria on bones of patients affected by OI.

079

THANATOPHORIC DYSPLASIA AT 26 YEARS OF AGE

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We present an update on a patient with thanatophoric dysplasia (TD) who was first described by MacDonald et al. (1989) and was mentioned in the discussion in the paper by Baker et al. (1997). She is now 26 years of age and is one of the oldest individuals with this diagnosis. She has had a number of complications due to the skeletal manifestations: craniocervical spinal stenosis resulting in high cervical myelopathy, ventilator dependency due to progressive restrictive lung disease, and decreased bone density, as there are no weight bearing activities. There was evolution of the radiologic findings. The diaphyses became gracile with marked flaring at the metaphyses. The pubic bones are quite thin and the vertebral bodies in the lumbar region appear tall. Her tongue has become hypertrophied; as for many years she has used it as an extra appendage. She has had episodes of bradycardia, although an echocardiogram and Holter monitoring have been unremarkable. She has an "active" EEG with a febrile seizure in infancy followed by nonfebrile seizures developing at age 15. In 2010, Nakai et al. reported a 23-year-old woman with TD and described her dermatological features with seborrhoeic keratosis and acanthosis nigricans. The clinical pictures demonstrated that she was intubated and ventilated, but there were no comments on her other health and developmental issues. Individuals with SADDAN are the one patient group where clinical comparisons may be made, but this too is a limited population. There are consistent features seen in SADDAN and TD survivors, but are less common with other *FGFR3* conditions: the dermatological issues, the cognitive impairment, and the presentation of seizures. Our patient provides further information on the natural history of TD.

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(2) Baker KM, Olson DS, Harding CO, Pauli RM (1997): Long-Term Survival in Typical Thanatophoric Dysplasia Type 1. Am J Med Genet 70:427-436.

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080

THE UTILITY OF FETAL AUTOPSY IN THE DIAGNOSIS OF SKELETAL DYSPLASIAS

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Fetal autopsy examination plays a vital role in the investigation and diagnosis of skeletal dysplasias. The macroscopic examination, with detailed photographic images and specialised skeletal radiology, along with histopathological examination of various bone types is essential for accurate diagnosis which enables the correct genetic advice to be given to parents. In addition to histopathology, tissue obtained at autopsy enables molecular genetic testing to be undertaken.

The authors present a series of cases encountered in a major tertiary / quaternary referral hospital where permission for autopsy examination of a number of fetuses with skeletal dysplasia was obtained. The cases include osteogenesis imperfecta types II and III, chondrodysplasia, hypophosphatasia and thanatophoric dysplasia. Macroscopic pathology as well as histopathological features will be demonstrated, correlated with genetic testing.

The importance of counselling parents to give permission for detailed autopsy examination is emphasized.

081

UPPER CERVICAL FUSION IN CHILDREN WITH MORQUIO'S SYNDROME: MEDIUM AND LONG-TERM RESULTS

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Objective: To assess the medium and long-term clinical and radiological outcomes of upper cervical fusion in patients with Morquio's syndrome.

Summary of Background data: Patients with Morquio's syndrome have a high incidence of upper cervical instability, which can lead to compression of the spinal cord resulting in progressive neurological deterioration, quadriplegia, and even death. Upper cervical fusion has been used to prevent this instability and neurological deterioration.

Material and Methods: The medical charts and radiographs of 13 patients with Morquio syndrome who had undergone upper cervical fusion to arrest upper cervical instability were reviewed to assess bony fusion, cervical spine sagittal alignment, neurological improvement, and complications.

Results: The average follow up was 127 months (range 49-194). All patients achieved solid fusion at the final follow up. Twelve (92%) of the patients achieved fusion by 6 months and the remaining patient developed a symptomatic pseudoarthrosis, which needed surgical revision 4 years after the index surgery. Four of the five patients with neurologic deficit preoperatively, improved after the upper cervical fusion and one patient showed no change in their neurologic status. Five patients experienced symptomatic instability below the fusion mass and needed extension of fusion level after an average of 57.8 months (range 18-109 months) follow-up. Three patients developed a second area of compression at cervico-thoracic or upper thoracic level after an average of 88.6 months follow-up (range 33-161 months).

Conclusion: Upper cervical arthrodesis is a safe and reliable procedure in children with Morquio's syndrome to arrest upper cervical instability and neurological deterioration. Long-term follow up is strongly recommended as these patients have a propensity to develop late complications (instability below the fusion level) and second area compression.

082

VARIABLE OSTEOGENESIS IMPERFECTA PHENOTYPE RESULTING FROM A FOUNDER MUTATION IN *FKBP10* IN SAMOA

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Mutations in *FKBP10*, which encodes the collagen prolyl *cis-trans* isomerase chaperone protein FKBP65, have recently been discovered as a cause of a recessively-inherited variant of osteogenesis imperfecta (1,2). We have identified 17 individuals in 10 independent families that originate from the Southern Pacific islands of Samoa and share one mutation. There is remarkable phenotypic variation, even within the same family.

One group presents at birth with Bruck syndrome-like features of talipes and flexion contractures; these patients may also have fractures; their growth is slow and they do not attain independent mobility. In the second group, affected individuals become ambulatory at the normal time but present in childhood or adolescence with difficulty walking due to progressive acetabular protrusion and may also suffer femoral or tibial fractures. Skull changes include macrocephaly, Wormian bones and platybasia. Short stature is common to all, and is exacerbated by progressive scoliosis, which causes restrictive lung disease and is a major cause of reduced life expectancy. In limbs that are not immobile, bone mass appears normal.

The Samoan mutation [c.948_949insT] in *FKBP10* creates a frameshift with a premature stop codon in exon 7 and results in mRNA instability so that no protein is produced. In all but one of these families, affected individuals are homozygous for this mutation. Two affected siblings from a family with one Samoan parent were compound heterozygous for the Samoan mutation and the previously described c.831_832insC mutation (1) that also results in very unstable mRNA and no protein production.

We estimate that the c.948_949insT mutation has a frequency of 1 in 50 - 100 in the Samoan population, and think it is a founder mutation carried by the early migrants to Samoa ~1000 BCE.

(1) Alanay et al AJHG 2010 86: 1-9
(2) Shaheen et al AJHG 2010 87: 306-8

083

CARDIOPULMONARY PHENOTYPE OF ACHONDROPLASIA ADULTS

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Background: Little is known about cardiovascular disease (CVD) risk factors (e.g.obesity, hypertension, glucose intolerance, dyslipidemia, sedentary lifestyle, obstructive sleep apnea (OSA)) in achondroplasia. This pilot will establish the feasibility, tolerability and effectiveness of measures to assess the cardiopulmonary phenotype of achondroplasia adults and justify a longitudinal study.

Methods: Ambulatory non-pregnant achondroplasia adults (18-50 yrs) were recruited. Study activities include: anthropometry, DEXA, past medical, surgical and family history and physical exam, 6 minute walk test (6MWT), fasting labs, overnight standard polysomnography and simultaneous portable ARES + at home ARES, 5 day accelerometry, 3 day diet record, bioelectrical impedance (BIA), resting energy expenditure by indirect calorimetry, and validated questionnaires pertaining to pain (Brief Pain Index), function (SF-36, Bleck scale) and sleep (Berlin).

Results: 15 of 20 projected achondroplasia subjects have participated: 9 females (mean 37.9 yrs+6.2) and 6 males (37.7yrs+9.2). Average female height was 123.5+4.7cm and weight was 60.0+11.2kg; male was 124.8+5.6cm and 52.9+10.1kg. By DEXA, mean % body fat was 42.7% for females and 28.4% for males, and highly correlated with BIA (43.2 % females, 27.8% males); $r = 0.91$, $p<0.001$ for genders combined. Although pre-study diagnoses were not reported, 4/15 were hypertensive (systolic >140 or diastolic >90mmHg) and 7/15 were hypercholesterolemic (total chol >200mg/dl). ARES revealed OSA in 6/12 (RDI4% > 5). Of 7 positive OSA Berlin screens, ARES detected 5. Vitamin D deficiency (25OH vitamin D <30nmol/L) was nearly universal (14/15). All echocardiograms (n=5) have been normal without heart failure or pulmonary hypertension. Those with no prior spine or orthopaedic surgery walked further (382.8 m) on the 6MWT than those having >1 procedure (311.6 m), $p=0.1$. Average resting energy expenditure by indirect calorimetry (1257 kcal/24 hours) was comparable to average stature adults. Reported and measured physical activity was low.

Conclusion: Risk factors for CVD are common in achondroplasia adults. A longitudinal natural history study of CVD would delineate temporal links among risk factors and determine optimal preventative measures.

084

MEDICAL MANAGEMENT OF CHILDREN WITH ACHONDROPLASIA: EVALUATION OF AN AUSTRALASIAN COHORT AGED 0-5 YEARS.

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Background: Achondroplasia is the most common form of osteochondrodysplasia. It is associated with a number of life threatening complications and the complexity of managing these led to development of Health Supervision Guidelines by the American Academy of Pediatrics in 1995, with revisions in 2005. Despite these guidelines, there remains limited population-based information on referral to and utilisation of medical and therapy services for children with Achondroplasia. Better understanding of service utilisation and client outcomes is required to assist future service development.

Method: A multicentre, population-based study targeting all Australasian children with Achondroplasia aged 0-5 years was co-ordinated through the Royal Children's Hospital, Brisbane, Australia. Parent questionnaires repeated at 3-month intervals were used to gather comprehensive data regarding frequency and timing of key medical consultations (geneticist, paediatrician/rehabilitation physician, respiratory physician, orthopaedic consultant, neurologist, neurosurgeon), investigations (sleep study, MRI/CT), operative procedures (brainstem decompression, tonsillectomy/adenoidectomy, shunt insertion, shunt revision and grommet insertion) and allied health consultations (physiotherapist, occupational therapist, speech pathologist, dietician and orthotist) experienced by the cohort between birth and 5 years. Items were drawn from the AAP Health Supervision Guidelines, recommendations of an expert multi-disciplinary reference group, and a literature review targeting specific morbidities and frequently reported or recommended assessments or interventions.

Results: Parents of 53 Australasian children with Achondroplasia participated. Access to geneticists and paediatricians in the first year approached 2005 AAP recommendations. Frequency of polysomnography studies and speech pathology assessment appeared lower than Guideline recommendations, however grommet insertion, tonsillectomy/adenoidectomy and cervicomedullary decompression rates were similar to previous reports. Despite absence of recommendations by the AAP, a significant proportion of children accessed physiotherapy and occupational therapy for developmental and orthopaedic management, warranting inclusion of these professionals in future guideline recommendations.

Conclusion: Australasian service utilisation approaches current AAP Guidelines. Addition of physiotherapy and occupational therapy to future Guidelines is recommended.

085

MPS SCREENING IN PATIENTS WITH ORTHOPAEDIC PROBLEMS

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Background: The mucopolysaccharidoses (MPSs) are a group of lysosomal storage disorders caused by deficiency in the enzymes catalyzing the degradation of glycosaminoglycans (GAGs). T he effect of storing GAGs in the body lead to many physical problems, including skeletal dysplasia. The newborn screening tests for MPS are seldom conducted. As a result, patients are diagnosed after symptoms are manifest. Because of progressive musculoskeletal problems, patients with MPS often seek evaluation at orthopaedic clinics for growth and developmental disturbances.

Objectives: To investigate the distribution of MPS in Korean patients who seek evaluation at orthopaedic clinics, we examined urine MPS screening and confirmation tests.

Methods: Patients with > 2 of 8 criteria, and 1 accompanying signs and symptom were enrolled in the current study. The inclusion criteria were as follows: 1) joint stiffness and contractures; 2) cervical myelopathy (C1-C2 subluxation and odontoid hypoplasia); 3) thoracolumbar kyphosis, lordosis, and scoliosis (beaking spine and vertebra plana); 4) petus carinatum; 5) waddling gait (hip dislocation and coxa valga); 6) genu valum; 7) enlarged and short hands; and 8) idiopathic carpal tunnel syndrome. Elevated urinary GAG levels were determined by the toluidine blue method a nd the c etylpyridinium chloride (CPC) turbidity test. If the urinary GAG concentration was increased compared to the age-specific reference range, a confirmation test were added to determine the MPS type.

Results: Approximately 200 patients were screened and 4 patients were diagnosed with MPS (2 patients had MPS type II and 2 patients had MPS type IVA). Case 1 had joint stiffness and a beaking spine and case 2 had joint stiffness involving the hands and lumbar lordosis. Cases 3 and 4 were siblings, both of whom presented with typical skeletal manifestations of MPS.

Conclusions: The early diagnosis of MPS is critical for early treatment. In this study, 4 of approximately 200 patients were diagnosed with MPS. We will continue to investigate the distribution of MPS in Korean patients using screening and confirmation tests.

086

LEG DUPLICATION WITH IPSILATERAL RENAL AGENESIS: A SPECTRUM OF CONGENITAL ACRORENAL MALFORMATION SYNDROME

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Duplication of a leg, either partial or total, is an extremely rare congenital anomaly that is characterized by supernumerary metatarsals, tarsals, and fibular or tibial dimelia as well as extra toes. Owing to its rarity, very little is known about associated internal organ anomalies and the anatomic morphology of the pelvic girdle in the duplicated leg. We report two patients with partial leg duplications associated with ipsilateral renal genesis. Patient 1 was an 18 months old girl who had eight toes of the right foot. Radiographs showed enlarged the right ischium and pubic bone. There was a small bony projection over the tilted acetabulum, which was verified as an accessory ilium on computed tomography (CT). The right fibula was duplicated and distally fused to the single shaft. The right foot showed a duplication of cuboid, seven metatarsals with eight phalanges. Because of urinary tract infection, renal ultrasound examination underwent and absence of the right kidney was observed. Renal agenesis was confirmed by subsequent CT scan. Patient 2 was one month old girl who presented with a supernumerary foot attached to the posterior aspect of the left thigh. Radiographs showed that the extra-foot was composed of hypoplastic fibula, deformed calcaneus and talus with 4 metatarsals and toes. The left leg showed an absence of fibula and short tibia as well as 3 metatarsals and 3 toes. MRI showed absence of the left kidney, which was confirmed by DMSA renal scan. This report emphasizes the association of duplication of the leg with ipsilateral renal agenesis. Malformation of the ipsilateral pelvic girdle also attracts attention. The spectrum of aberrant skeletal development in duplication of the leg should be meticulously assessed by using CT scan.

(1) Clin Genet 1988; 33:234-239
(2) J Bone Joint Surg 1978; 60-A:1143-1145
(3) Genet Counsel 1990; 1:265-272
(4) J Pediatr Ortho B 2000; 9:306-308

087

VITAMIN D LEVELS IN IDIOPATHIC JUVENILE OSTEOPOROSIS

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BACKGROUND: Idiopathic juvenile osteoporosis (IJO) is a rare form of childhood osteoporosis with an estimated incidence of 1:100.000. On the other side, vitamin D insufficiency can lead to bone loss, secondary hyperparathyroidism, and increased risk of fractures. In the literature few studies have considered vitamin D levels in osteoporotic young patients and none in patients affected by IJO. OBJECTIVE The purpose of this work is to evaluate the relationship between serum 25-hydroxyvitamin D (25OHD) levels and bone parameters in patients affected by IJO followed in our Paediatric Clinic. METHODS: We analysed 12 caucasian patients with IJO (9 males and 3 females; mean age 12.63 ± 4,3 years and 12.78 ± 3,9 years respectively): all the patients had a clinically significance fracture history and a lumbar BMD Z-score lower than -2.0, adjusted for age, gender and body size (mean Z-score -2.45 ± 0.9 SD). Pubertal stage, serum 25-hydroxyvitamin D, parathyroid hormone and BMD, as well as other bone markers, were obtained for all the patients. RESULTS: Vitamin D insufficiency (25OHD < 30 ng/m) was observed in the majority of patients (autumn: mean 27.68 ng/ml ± 11.8 SD; spring: mean 29.73 ng/ml ± 16,7 SD; summer mean 37,7 ng/ml ± 0 SD). CTX levels are increased (mean: 1.43 ng/ml ± 0,5 SD) compared to normal values (0.15-0.45 ng/ml). Total lumbar BMDs are significantly correlated with 25OHD levels ($p<0.02$). DISCUSSION: We demonstrated that vitamin D insufficiency is frequent in patients with IJO and we observed that lumbar BMDs are directly correlated with vitamin D levels. This suggests that in patients with JIO it is very important to dose 25OHD and we believe that vitamin D and calcium supplementations are preventive measure that in patients affectd by IJO must be use before any further treatment.

088

CHILDREN AND ADOLESCENTS TREATED WITH NERIDRONATE FOR OSTEOGENESIS IMPERFECTA: NO EVIDENCE OF ANY OSTEONECROSIS OF THE JAW

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BACKGROUND In recent years, several studies have been published on cases of osteonecrosis of the jaw (ONJ) in patients using second- and third-generation nitrogen-containing bisphosphonates, but no case has ever been reported in patients taking neridronate. Children and adolescents affected by osteogenesis imperfecta (OI) could belong to an high risk group for ONJ because in these patients bone fragility is associated with a connective tissue malfunction. The purpose of this study was to find the incidence of ONJ in a paediatric population treated with neridronate for OI. STUDY DESIGN This study is a retrospective survey of 52 paediatric patients with OI who took neridronate for a mean of 5.96 years (SD ± 2.47 years). Eligibility criteria for participation included patients between 2.2 and 22 years old who received cyclical neridronate infusions for at least 2 years. All the patients' conditions were reviewed to determine dosage and duration of their bisphosphonate therapy and were examined clinically to assess their oral health status. RESULTS We have not demonstrated evidence of ONJ as a side-effect of neridronate use in the paediatric population with OI analysed. CONCLUSIONS We reported the absence of ONJ in children and adolescents treated with neridronate, corroborating previous studies using other bisphosphonates which also failed to find any occurrence of ONJ in young patients. Probably, the lack of comorbidities and the lower doses used in children and adolescents reduce the risk of osteonecrosis. Nevertheless, other prospective studies are needed to determine the safety of neridronate both in adults and in children.

089

A NEW AUSTRALIAN CASE OF RAINE SYNDROME

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Raine Syndrome is a rare autosomal recessive osteosclerotic skeletal dysplasia associated with narrow thorax,distinctive craniofacial dysmorphic features and brain abnormalities including intracranial calcification. In 2007, mutations in the FAM20C gene were identified to cause the condition. Raine Syndrome appears to be neonatal lethal in the majority of cases,mainly due to respiratory failure from thoracic hypoplasia. Only 19 cases from 15 families have been described in the literature, and there is a high incidence of parental consanguinity. There is only one previously published case in Australia in 1992.

We present a female infant with the clinical diagnosis of Raine Syndrome,who died shortly after birth due to profound respiratory distress. She was the offspring of consanguineous (first cousin) parents. Antenatal ultrasound scan revealed polyhydramnios, in-utero growth retardation, lemon-shaped head, protuberant eyes, severe micrognathia and diffusely increased echogenicity of the periventricular white matter. Examination of the infant soon after death revealed the characteristic dysmorphic features of Raine Syndrome. The salient features included microbrachycephaly,wide fontanelles, marked proptosis and micrognathia, severly hypoplastic nose, carp-like mouth, midline gingival cleft,bell-shaped chest and telebrachyphalangy. Diagnostic findings on skeletal survey included diffuse osteosclerosis, subperiosteal new bone formation, pseudofractures of the ribs and striking ossification of the base of the skull and facial bones. MRI brain scan suggested the presence of multiple intracerebral calcifications. The parents declined an autopsy.Sequencing of the FAM20C gene did not identify a disease causing mutation. This may support the presence of genetic heterogeneity in this condition.

This case highlights that the diagnosis of Raine Syndrome may be made with a non-invasive post-mortem examination, with the aid of a skeletal survey and brain imaging, preferably CT.

090

REPORT OF INFANTILE HYPOPHOSPHATASIA AND POSSIBILITY FOR ENZYME REPLACEMENT THERAPY

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We report an infant with the severe infantile form of hypophosphatasia. The patient was the second child to consanguineous parents. She presented with severe femoral bowing on antenatal ultrasound (presumed osteogenesis imperfecta). Seizures in the first 24 hours post birth required treatment with a combination of phenobarbitone and pyridoxine. She had bowing of her limbs, especially her femori, a soft skull with apparent widening of the anterior fontanelle, and narrowing of the chest wall. Serum calcium was elevated with suppressed PTH. Serum alkaline phosphatase level was undetectable (<20 IU/L). Urinary phosphoethanolamine was elevated. Radiological investigation demonstrated widespread hypomineralisation, most marked in the skull. These features were all consistent with the diagnosis of hypophosphatasia.

Following discharge from the neonatal unit, the patient showed poor weight gain, with increasing vomiting episodes. She developed severe hypercalcaemia requiring hyperhydration, frusemide and prednisolone to settle. She had an acute respiratory collapse at the age of 4 months with secondary hypoxia and subsequent central diabetes insipidus and loss of central respiratory drive. At this point the decision was made to withdraw treatment and the infant passed away at 5 months of age.

There has been no previous treatment available for patients with the severe infantile form of this disorder. However, promising early results have been published in abstract form for the use of a modified version of tissue non-specific alkaline phosphatase, which is able to be retained in bone and improve mineralization. Thus far 10 patients have completed the 6 month study, with 9 showing substantial healing of rickets accompanied by improved respiratory and gross motor function. Ongoing recruitment and further longitudinal investigation of the existing cohort is continuing. Our patient deteriorated too rapidly to commence this treatment, but subsequent patients may be candidates for its use, ameliorating the otherwise bleak prognosis.

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PHENOTYPES IN A MOTHER AND BABY WITH CAMPOMELIC DYSPLASIA CAUSED BY A SOX9 SPLICING MUTATION

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We present the clinical, radiological and genetic findings in a mother and daughter with campomelic dysplasia. The mother, now aged 30 years, was recognized at birth to have a congenital malformation syndrome including a cleft palate, a short broad neck and positional talipes but no specific diagnosis was made. At the age of 19 she had a respiratory arrest following dislocation of her cervical spine. The patient required occipitocervical fusion, further staged neurosurgical procedures to achieve stabilization and long term nocturnal ventilation. Following the birth of her daughter, now aged 1 year, a diagnosis of campomelic dysplasia was recognised.

At 10 months of age the baby was short (length 0.4th centile), had a small chin but no cleft palate, bowed lower limbs with tethered dimples overlying the tibiae, talipes with tight Achilles tendons and apparently normal development. Clinical findings in the mother included disproportionate short stature with short spine (height 150 cm), relative macrocephaly (90th centile), short neck, nasal speech and normal intelligence.

Skeletal survey of the baby in the neonatal period showed typical radiological findings of campomelic dysplasia including angulated femora and tibiae, short fibulae, talipes, short phalanges of halluces, narrow iliac wings, absent ossification of pubic rami, 11 pairs of ribs, absent wings of scapulae, absent pedicles in the thoracic spine and cervical kyphosis. Review of the mother's past xrays showed cervical spine anomalies, pelvic hypoplasia with dysplastic acetabulae, bilateral subluxation of the femoral heads but minimal bowing of long bones. Molecular genetic investigation of both mother and daughter in DNA derived from peripheral lymphocytes showed the presence of a mutation (c.685+5G>A) in the SOX9 gene, predicted to affect splicing.

Campomelic dysplasia is often lethal in infancy with death typically resulting from respiratory complications. Several long-term survivors have been reported and in those patients cervical spine instability is an important complication.

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THE OI FOUNDATION LINKED CLINICAL RESEARCH CENTERS LONGITUDINAL STUDY

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The Osteogenesis Imperfecta Foundation Linked Clinical Research Centers is a collaborative consortium of seven sites across North America. Over 350 individuals with OI have been enrolled in our longitudinal study. To date, approximate enrollment numbers are: Type I - 150; Type III - 50; Type IV - 100 and approximately 25 individuals with Types V-VII. Approximately 250 participants are children and adults comprise nearly 100 study members. We will present data stratified by age and disease subtype that will include bone mineral density, level of function and mobility, pulmonary function, audiometry and surgical history.

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A FAMILY WITH AN ARG134CYS MUTATION IN COL1A1 AND OVERLAPPING PHENOTYPES OF OSTEOGENESIS IMPERFECTA AND EHLERS-DANLOS SYNDROME.

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The proband, a girl, presented at 10 months of age with a fractured femur after no known injury, vertebral crush fractures and wormian bones and was diagnosed with osteogenesis imperfecta. She had pale blue sclerae, normal teeth and skin and scored 6/9 on the Beighton scale of hyperextensibility. Her echocardiogram was normal. She was treated with regular intravenous bisphosphonate infusions resulting in a marked improvement in well being and development, and a reduced fracture frequency. From the age of 14 years, her father had had several fractures in his hands, feet, vertebrae and ribs but never the long bones, almost always the result of an injury. He had abnormal, wide, atrophic scars on his knees and shins, but not particularly stretchy skin. He scored 4/9 on the Beighton scale. He had normal sclerae and teeth but early otosclerosis. He had a long history of central chest pain and reported tachycardia while cycling but an echocardiogram, exercise stress test and Holter monitor test while out cycling on the road were normal. The pain is thought to be musculoskeletal in origin.

DNA from the proband was analysed at Matrix DNA Diagnostics, Tulane University, New Orleans. An Arg134Cys substitution mutation was identified in COL1A1, in the highly conserved Gly-X-Y triplet. The result is formation of abnormal aggregates of type 1 collagen molecules that cannot be secreted efficiently. The father also carries this mutation.

Mutations in type 1 collagen are mostly associated with a phenotype of osteogenesis imperfecta. However, this particular mutation was reported in two children with classical Ehlers-Danlos syndrome (Nuytinck et al., 2000) and in a woman with EDS and dissection of an iliac artery (Malfait et al., 2007). Our proband has a phenotype that is predominantly that of OI, whereas her father has some features of EDS and a history of minor fractures. Follow up regarding the risk of arterial rupture will be important for the girl and her father.

(1) Nuytinck L et al. American Journal of Human Genetics 66:1398-1402, 2000
(2) Malfait F et al. Human Mutation 28:387-395, 2007

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RAINE SYNDROME: CASE REPORT AND DELINEATION IN A MALAYSIAN INFANT

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Raine syndrome, an autosomal recessive disorder first described in 1989, is characterised by microcephaly, hypoplastic nose, exophthalmos, choanea atresia, cleft palate and osteosclerosis. The majority died during the neonatal period with pulmonary hypoplasia leading to respiratory insufficiency, There are altogether 15 reported cases in the world with limited information on this condition in the Asian population.

A one-day-old female infant was referred for severe respiratory distress and dysmorphic features. Both her parents are related (uncle-niece marriage). The antenatal history was uneventful and she was delivered post date with a birthweight of 3.3kg. Her mother had one previous miscarriage at 8 weeks gestation. Another child is currently well. There was no significant family history. Postnatally, the child was noted to have multiple birth defects and developed severe respiratory distress. She was resuscitated and stabilized.

She was noted to have a flat nasal bridge, hypoplastic nose and midface, exophthalmos, bilateral choanal stenosis (left more severe than the right), microstomia, micrognathia, low-set ears and prominent anterior fontanelle. There was no cleft palate or gum abnormalities. She had mild pulmonary hypoplasia and a soft systolic murmur at the parasternal edge. Her length was 49 cm and occipito-frontal circumference was 34 cm. The rest of the examination was unremarkable. Investigations showed she had a small atrial septal defect and patent ductus arteriosus on echocardiography. Skeletal survey showed generalized osteosclerosis and increased bone density. No fractures were seen. A cranial CT showed multiple calcifcations located in the brain parenchyma. Screening for intrauterine infections was normal. The full blood count and renal function test was normal. There was increased serum alkaline phosphotase of 1247 IU/L (normal range 50-136 IU/L). Chromosome analysis and metabolic studies were normal.

On the basis of the above findings, the diagnosis of Raine syndrome was made. Mutation study of the FAM20C was not done.

(1) Raine J, Winter RM, Davey A, Tucker SM. Unknown syndrome: microcephaly, hypoplastic nose, exophthalmos, gum hyperplasia, cleft palate, low set ears, and osteosclerosis. J Med Genet 1989;26:786-788.
(2) Shalev SA, Shalev E, Reich D, Borochowitz ZU. Osteosclerosis, hypoplastic nose, and proptosis (Raine syndrome): further delineation. Am J Med Genet 1999;86:274-277.

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SHORT STATURE, CLAVICULAR HYPOPLASIA, MILD MICROCEPHALY AND LEARNING DIFFICULTIES IN A FAMILY WITH DELETION 17Q21.32-17Q21.33, GIVING RISE TO HAPLOINSUFFICIENCY OF THE *HOXB* GENE CLUSTER

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Microdeletions of the 17q21.3 region have been reported regularly since the advent of microarray-CGH technology with a distinctive, recognisable phenotype associated with del 17q21.31. We here describe a family with an approximate 1 Mb deletion at 17q21.32-q21.33, which appears to be very rare. The proband was a 9-year old boy who presented with learning difficulties, short stature, microcephaly, a triangular face, prominent ears, broad nasal bridge, short fingers with 5th finger clinodactyly and incurled toes. Radiographs showed hypoplasia of the right clavicle. His mother had very similar features, as did his younger brother; his brother had a hypoplastic right clavicle whilst their mother had bilateral clavicular hypoplasia. Height and head circumference for all three were proportionate: 0.4th-1st percentile. In the wider family there are several individuals reported to have short stature but they have not been assessed. The proband and his mother were both positive for the ~1 Mb deletion at 17q21.32-17q21.33, which contains 24 annotated genes, including the entire *HOXB* cluster. In consideration of a possible coincidental association with cleidocranial dysostosis, mutation analysis of the *RUNX2* (6p21) gene in the proband did not identify a variant. Very few cases with confirmed molecular pathology at this precise locus have been reported. The features in this family raise the possibility that haploinsufficiency for the *HOXB* gene cluster causes a skeletal phenotype with clavicular hypoplasia and short stature.

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INFANTILE SYSTEMIC HYALINOSIS PRESENTING AS MULTIPLE JOINT PAIN

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Background: Infantile systemic hyalinosis (ISH) is a rare autosomal recessive disorder characterized by abnormal hyaline deposits in the papillary dermis and other tissues. It presents in early infancy with severe pain with movement, progressive joint contractures, thickened skin and hyperpigmented macules over bony prominences. Gingival hypertrophy, skin nodules, perianal masses are common but late findings.

Clinical information: The proband was the third child of a consanguineous Pakistani couple. She was born full term with normal growth parameters and APGAR scores. She presented with decreased limb movement at 3 months. Her limb movements were limited by severe pain; her ears were simple but prominent and there was hyperpigmentation over the knuckles and ankles. Skeletal survey showed metaphyseal/submetaphyseal widening with periosteal reaction. Bone marrow examination excluded myeloproliferative disorders. She had normal inflammatory markers and normal eye examination. At age 4 months, perianal papules were noted, and at 6 months she was tube fed, had occasional loose stool and was hypoalbuminemic requiring two albumin transfusions.

A known pathogenic homozygous mutation c.[652T>C] was found in the *ANTXR2* gene causing an amino acid substitution p.C218R, confirming the diagnosis of ISH. The parents were heterozygous carriers of the mutation.

Conclusion: ISH should be considered in infants presenting in early infancy with painful joint contractures, skin and skeletal abnormalities. Additional complications include protein-losing enteropathy, feeding issues, perianal masses causing pain with defecation, gingival hypertrophy, and pathologic fractures. The prognosis of patients with ISH is poor and they usually suffer from recurrent infections, enteropathy and progressive functional limitation, with death in childhood.

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