International Skeletal Dysplasia Society

ISDS

16th International SKELETAL DYSPLASIA SOCIETY MEETING

Madrid, Spain
18-21st September, 2024

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#ISDS2024

ABSTRACT BOOK

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ABOUT ISDS

The International Skeletal Dysplasia Society, ISDS is a non-profit organization, founded almost 30 years ago. The principal aim of the Society is to promote scientific progress in the field of skeletal dysplasias and dysostoses and related topics (which are genetic bone conditions).

To this aim, the society organizes meetings on a two-year basis. The meetings are conducted in a friendly and familial way to promote networking and exchange of expertise.

The scientific program of the meetings includes advances in the clinical, radiological, genetic, biochemical, and molecular characterization of skeletal dysplasias, as well as advances in management of individuals affected by skeletal dysplasia and dysostoses.

Since the beginning the meetings have been held in sites on different continents.

Welcome to 16th International Skeletal Dysplasia Society Iberian meeting held in Madrid (Spain).

COMMITTEES & CHAIRS

ISDS2024 CO-CHAIRS:

Name	Hospital	City, country
Karen E. Heath	Hospital Universitario La Paz (ERN BOND)	Madrid, Spain
Sergio B. Sousa	Hospital Pediatric Coimbra, Centro Hospitalar Coimbra (ERN BOND)	Coimbra, Portugal

ISDS2024 IBERIAN MULTIDISCIPLINARY ORGANIZING COMMITTEE:

Name	Hospital	City, country
Manuel Parrón-Pajares	Hospital Universitario La Paz (ERN BOND)	Madrid, Spain
André Travessa	Hospital Santa Maria (ERN BOND)	Lisbon, Portugal
Lucia Sentchordi Montané	Hospital Universitario Infanta Leonor	Madrid, Spain
Fernando Santos-Simarro	Hospital Universitario Son Espases	Palma, Mallorca
Cristina Alves	Hospital Pediatric Coimbra, Centro Hospitalar Coimbra (ERN BOND)	Coimbra, Portugal

SCIENTIFIC COMMITTEE

Yasemin Alanay

Cristina Alves

Alistair Calder

Valerie Cormier-Daire

Virginia Fano

Carlos Ferreira

Karen Heath

Melita Irving

Roberto Mendoza

Gen Nishimura

Manuel Parrón

Ravi Savarirayan

Lucia Sentchordi-Montané

Sergio Sousa

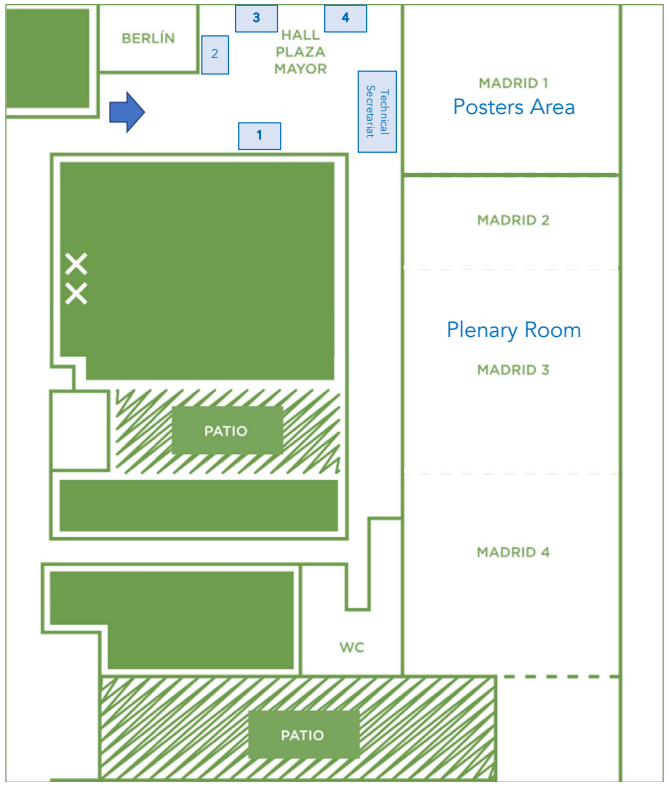
Andrea Superti-Furga

Sheila Unger

Matt Warman

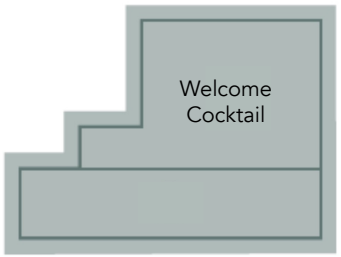
PRACTICAL INFORMATION

PC FLOOR: Plenary room, Posters Area, Exhibition Area

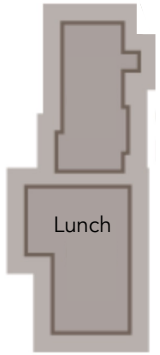


WIFI network: nh. Password: wifi
Elevators available in every floor.
You must carry your accreditation at all times.

PS FLOOR:
Florence Terrace



S-1 FLOOR:
Buffet Praga



SOCIAL PROGRAM

VENUE: NH Eurobuilding Hotel
(Calle del Padre Damián, 23, Chamartín, 28036 Madrid)

- Welcome Cocktail → Florencia Terrace Room **(PS Floor)**
- Plenary room → Madrid 2 + 3 + 4 Room **(PC Floor)**
- Posters Area → Madrid 1 Room **(PC Floor)**
- Exhibition Area → Plaza Mayor Hall Madrid **(PC Floor)**
- Lunch → Praga Buffet **(S-1 Floor)**

LOCAL VISITS OPTIONS Thursday 19 sept 2024

- **17:30**h Tour Madrid Center
- **17:30**h El Prado Museum

GALA DINNER
Friday 20 sept 2024 in "San Agustín" de Guadalix

- **18:30**h Transfer from NH Eurobuilding Hotel to the restaurant.
- **00:30**h Transfer from the restaurant to the NH Hotel.

SCIENTIFIC INFORMATION

INFORMATION FOR ORAL PRESENTERS

- Maximum time for presentation: 15 min including questions.
- PowerPoint format.
- All presentations must be in a pendrive.
- No personal computers will be allowed.
- You will be able to download the presentations with the technician in the same meeting room and check that everything is correct before your presentation.

INFORMATION FOR POSTER PRESENTERS

- We will provide you with all the necessary material to hang it in Madrid 1 room.
- The presenting author must be present in front of their poster at the scheduled poster presentation time during the meeting. We sent this information in June 2024. This will allow you the opportunity to talk with delegates about your poster and answer questions regarding your work.

SCIENTIFIC PROGRAM

Wednesday 18th September	
16:00 18:00	**Registration.**
16:00 17:30	**ISDS:ERN BOND workshop.** Discussion on the creation of an interactive online resource for ISDS nosology and how to reconciliate the ISDS nosology of genetic skeletal disorders with Orphanet grouping and coding. Open to all conference assistants.
18:30 20:30	**Welcome cocktail.**

Thursday 19th September		
08:45 10:30	**Session 1: Novel genes and phenotypes.** **Moderators: Yasemin Alanay & André Travessa**	
08:45	C-0041: Biallelic variants in *CCN2* underlie an autosomal recessive kyphomelic dysplasia in humans and zebrafish.	Katta Girisha
09:00	C-0020: Identification of *KIF22* homozygous variants in semd with joint laxity, lepdodactylic type and demonstration of proteoglycan biosynthesis impairment.	Valerie Cormier-Daire
09:15	C-0105 Autosomal dominant spondylocostal dysostosis in two unrelated families caused by the same heterozygous pathogenic variant in *MESP2*.	Aneta Malesa
09:30	C-0038 *SMAD7*: a novel gene in sclerosing bone dysplasia.	Corinne Collet
09:45	C-0098 The clinical and molecular spectrum of sclerosing bone dysplasias: experience from a tertiary care centre in india.	Neerja Gupta
10:00	C-0095 Mitochondrial skeletal disorders: a retrospective cohort of 9 French cases.	Caroline Michot
10:15	C-0073 Broader than bone fragility – the phenotypic spectrum of osteogenesis imperfecta type 15.	Alistair D. Calder

10:30 11:00	**Coffee break.**	
11:00 12:00	**Session 2: Functional characterization.** **Moderators: Carlos Ferreira & Fernando Santos**	
11:00	C-0047 Self replicating RNA for somatic reprograming fibroblasts to osteoblasts.	Asghar Fallah
11:15	C-0070 Utilizing urine-derived stem cells for disease modelling and drug screening in skeletal dysplasias.	Kazette Yuen Yu Chan
11:30	C-0078 Closing the data gap for skeletal dysplasias: a comprehensive multiomic expression atlas of the skeleton.	Ivan Durán
11:45	C-0042 Variants located throughout *IHH* lead to defective secretion, causing Short stature and/or brachydactyly and acrocapitofemoral dysplasia.	Francisca Díaz-González
12:00 12:30	**David Rimoin lecture.** Geert Mortier, Centre for Human Genetics, University Hospitals Leuven, Belgium.	
12:30 13:45	**Lunch.**	
13:45 14:05	**QED corporate symposium.**	
14:05 15:35	**Session 3: Mice models of skeletal dysplasias.** **Moderators: Matt Warman & Ivan Durán**	
14:05	C-0012: Adjuvant therapeutic enhances bone growth and quality in growing mice with moderate-to-severe osteogenesis imperfecta: exploration of a CNP analog.	Cathleen Raggio
14:20	C-0028: Small molecule inhibition rescues the skeletal dysplasia phenotype of *Trpv4* mutant mice.	Daniel Cohn
14:35	C-0052: Characterization of the skeletal phenotype in an adult murine model of diastrophic dysplasia.	Alessandra Leone
14:50	C-0007: Anti-Siglec 15 acts as an anti-resorptive and bone-formation agent in adult mice with moderate-to-severe osteogenesis imperfecta.	Cathleen Raggio
15:05	C-0040: A novel mouse model for acrodysostosis type 2 to enable the development of new treatments.	Melissa Bowerman
15:20 15:50	**Coffee break.**	
15:50 16:50	**Poster session 1.**	
C-0010	Biallelic loss of function variants in *FUZ* result in an orofaciodigital syndrome.	Katta Girisha
C-0023	European Achondroplasia Forum practical considerations for following adults with achondroplasia - a patient held checklist.	Svein O. Fredwall
C-0026	A novel genetic mechanism (for Schwartz-Jampel syndrome, SJS) to solve a difficult case: signal peptide variants – the “postage address” of gene instructions.	Ataf Sabir
C-0033	Examining the effect of vosoritide treatment on bone strength in children with achondroplasia.	Cathleen L. Raggio
C-0045	Negative nail patella syndrome, when to reconsider an established diagnosis.	Heather Wood
C-0050	Spinal surgeries in patients with B3GALT6-related disorders: a case series of four patients.	Kexin Xu
C-0056	Understanding observer-reported signs of achondroplasia: validation of the achondroplasia child experience measure–observable signs measure (ACEM-OSM).	Meryl Brod
C-0058	Achondroplasia and subdural bleeding: an under-recognised clinical finding and an erroneous suspicion of NAI.	Holly Pratt
C-0066	The Achondroplasia roadmap.	Susana Noval
C-0069	Split hand-foot malformation: challenges in the diagnosis and genetic counseling.	Debora Bertola

C-0084	3M syndrome: from phenotype to genotype.	Marzia Pollazzon
C-0086	Nociception and pain in osteogenesis imperfecta: approach from physiotherapy.	Miguel Rodriguez Molina
C-0088	A second patient of camptodactyly, tall stature, and hearing loss syndrome with a novel homozygous *FGFR3* variant.	Ozlem Akgun-Dogan
C-0090	Caregiver perspectives on vosoritide treatment: meaningful HRGOL improvements in children with achondroplasia	Ravi Savarirayan
C-0093	Girl with cutaneous skeletal hypophosphatemia syndrome treated with Burosumab: 2 years follow up.	Mariana del Pino
C-0097	Fatal pulmonary hypertension in an infant with severe osteogenesis imperfecta.	Janet M. Legare
C-0102	Intron retention: an emerging molecular mechanism which underlies rare skeletal dysplasia conditions and is a potential future therapeutic target.	Lucy Scrimshaw
C-0107	Prenatal genetic diagnosis through exome trio sequencing in foetuses with a suspected skeletal dysplasia.	Fernando Santos Simarro
C-0109	Atelosteogenesis type I: ultrasound, phenotypic, radiological and molecular features.	Marzia Pollazzon
C-0112	The current landscape in pharmacological treatments for skeletal dysplasia.	Isabela Dorneles Pasa
C-0116	Schwartz-Jampel syndrome with prenatal presentation: a case report with additional findings and review of the literature.	Maria Abreu
C-0122	Spondyloperipheral dysplasia caused by a non-coding 3-prime-UTR variant in the *COL2A1* gene molecularly characterized using prime editing.	Roberto Mendoza-Londono
C-0126	Perinatal lethal form of *IFITM5*-related osteogenesis imperfecta: case report.	Guillermo Lay-Son
C-0134	Autosomal recessive acromesomelic dysplasia Maroteaux type associated with a large intragenic duplication in *NPR2*.	Lucie Dupuis
C-0138	Characterization of patients with osteogenesis imperfecta from a Chilean tertiary care center: a retrospective database analysis.	Allisson Müller Delgado
C-0141	Full skeleton radiographic study: description of the experience in a skeletal dysplasia reference center over the past 10 years.	Javiera Vildoso
C-0143	Molecular findings in very rare skeletal dysplasias.	Virginia Fano
17:30	**Local visits**	

Friday 20th September		
08:30 10:30	**Session 4: Clinical and radiological aspects of skeletal dysplasias- cohorts and cases** **Moderators: Julie Hoover-King & Manuel Parrón.**	
08:30	C-0099: Perinatal outcome in 35 children with cartilage hair hypoplasia.	Ellamaija Kasanen
08:45	C-0128: *RMRP*-related spectrum: clinical, radiological and molecular characterization of a Portuguese cohort.	Mafalda Santos
09:00	C-0072: Epstein-Barr virus positivity in malignancy samples of patients with cartilage-hair hypoplasia.	Outi Mäkitie
09:15	C-0136: Multiple osteochondromas: clinical and molecular characterization of a Portuguese cohort.	Ana Mafalda Gonçalves
09:30	C-0132: Acromelic dysplasias: a series of eight patients and a long follow-up of a boy with acromelic dysplasia related to *FBN2*.	Denise P Cavalcanti
09:45	C-0129: Helical col1a1 variant in family with features of arthrochalasia-type Ehlers Danlos syndrome.	Shaimaa Helal
10:00	C-0024: Chondrodysplasia phenocopy and short stature in children after early haematopoietic stem cell transplant for non-oncologic and oncologic disorders.	Cheng Guang Gan
10:15	C-0101: Artificial intelligence in differential diagnosis, bone age assessment, and monitoring of skeletal dysplasias.	Behnam Javan-mardi
10:30 11:00	**Coffee break**	
11:00 12:00	**Poster session 2**	
C-0013	Natural history of the spine in achondroplasia and its management strategy.	Carmen Barreal Vega
C-0025	Trametinib effects on skeletal involvement in two children affected by oculoectodermal syndrome caused by *KRAS* mosaic mutations.	Massimiliano Rossi
C-0030	GH treatment in a Spanish cohort of 53 children with *SHOX/SHOX* enhancer alterations.	Ana Coral Barreda Bonis
C-0036	Starting a multidisciplinary dysplasia clinic during a pandemic: lessons, failures and plenty of coffee.	Catherine Gooch
C-0046	Catel-Manzke syndrome caused by compound heterozygosity in *TGDS*.	Stephen Miller
C-0054	Prenatal diagnosis of atypical Holt-Oram syndrome caused by a novel inherited intragenic *TBX5* duplication: a rare mechanism with variable expressivity.	David Chitayat
C-0057	Deep phenotyping of the spinal features in EDS: a study of 20 patients and review of the literature.	Nan Wu
C-0063	Fidelity of mouse models of human genetic skeletal disorders.	Robert Brommage
C-0068	Cases of survivorship; recommendations for prenatal genetic counseling with double skeletal dysplasias.	Angela Duker
C-0071	Antenatal diagnosis of cartilage-hair hypoplasia by rapid fetal whole exome sequencing - implications for neonatal management.	Deborah Shears
C-0085	Molecular and clinical characterization of a large cohort of patients with Ellis-Van Creveld syndrome and a family with Weyers acrofacial dysostosis.	Asier Iturrate
C-0087	Descriptive study of osteogenesis imperfecta in Spain.	Miguel Rodríguez Molina
C-0089	Expanding the phenotypic and genetic spectrum of Steel syndrome: novel *COL27A1* variants in three patients from Turkey.	Ozlem Akgun-Dogan
C-0092	Novel variant in the *GNAS* gene in a child with overlapping features of Progressive osseous heteroplasia (POH)	Merlene Peter

C-0096	Exploring gait diversity in adults with achondroplasia using wearable motion sensors.	Inês Alves
C-0100	*RUNX2*-related metaphyseal dysplasia with maxillary hypoplasia: a rare skeletal disorder resembling *SFRP4*-related Pyle disease.	Ewa Hordyjewska-Kowalczyk
C-0104	Undiagnosed despite trio WGS: a patient with spondyloepimetaphyseal dysplasia, lower extremity neuropathy and arterial tortuosity.	Rafael Adrian Pacheco-Orozco
C-0108	T1-T12 and T1-S1 length at maturity in skeletal dysplasia patients.	Zaid Elsabbagh
C-0110	Design and objectives of the ACORN study: a non-interventional study evaluating long-term safety in achondroplasia children treated with vosoritide.	Swati Mukherjee
C-0118	Towards creation and characterization of *COL2A1*-SEDC and *BGN*-SEMD IPSC-derived chondrocyte models.	Pauline De Kinderen
C-0123	Diagnosis and multidisciplinary management of trichorhinophalangeal syndrome type I: clinical and molecular description of a familial case.	Francesca Cartisano
C-0130	Type II collagenopathies: phenotypic variability.	Sara Franco Freire
C-0135	Van den Ende-Gupta syndrome: a clinical case with novel variants in *COL9A2* and *SCARF2* genes.	Sara Franco Freire
C-0140	Clinical spectrum of *PTH1R* gene variants: a case report of variable phenotypic presentation.	Javiera Vildoso
C-0142	Clinical and molecular features of a Portuguese cohort of osteogenesis imperfecta type V.	Catarina Macedo
C-0144	Phenotypic spectrum of *RMRP*-related disorders: a case report with moderate phenotype associated with a rare variant.	Allisson Müller
12:00 13:00	**ISDS Business meeting**	
13:00 14:00	**Lunch**	
14:00 14:20	**BioMarin corporate symposium - VOXZOGO® ▾ (vosoritide): A look beyond height.**	

14:20 16:10	**Session 5: Novel treatments and repurposing of treatments of skeletal dysplasias** **Moderators: Ravi Savarirayan & Sergio Sousa**	
14:20	C-0017: Vosoritide increases growth in children with hypochondroplasia: phase 2 trial results.	Andrew Dauber
14:35	C-0022: Vosoritide improves growth in Rasopathies, *ACAN* and *NPR2* deficiency: preliminary data from a phase 2 trial.	Andrew Dauber
14:55	C-0021: New treatments for children with achondroplasia.	Ravi Savarirayan
15:10	C-0133: TransCon CNP (Navepegritide) improves physical functioning and well-being in children with Achondroplasia (ACH) in the accomplish trial.	Ravi Savarirayan
15:25	C-0146: Tyra-300 demonstrates significant increases in bone length in two mouse models of FGFR3-related skeletal dysplasia.	Jacqueline Starrett
15:40	C-0015: Preclinical and clinical study of Umedaptanib pegol (anti-FGF2 aptamer) in achondroplasia.	Yoshikazu Nakamura
15:55	C-0076: Snail in the control of bone length: a new therapeutic target for achondroplasia.	Sonia Vega
16:10 16:40	**Coffee break**	
16:40 17:25	**Session 6: Other topics,** **Moderators: Virginia Fano & Cristina Alves**	
16:40	C-0039: Pain rehabilitation of patients with a skeletal dysplasia diagnosis – how to take care of their special needs and at the same time use existing programmes.	Ariane Kwiet
16:55	C-0083: Mindful self-compassion to reduce pain interference among adults with osteogenesis imperfecta: a pilot study.	V. Reid Sutton
17:10	C-0106: Skeletal dysplasia patients undergoing cervical spine fusions have similar re-operation rates regardless of post-operative bracing and fusion to the occiput.	John P. Avendano
18:30	**Conference dinner** **After dinner:** Maroteaux award	

Saturday 21st September		
09:00 10:45	**Session 7: Care and monitoring of skeletal dysplasia patients** **Moderators: Melita Irving & Lucia Sentchordi**	
9:00	C-0114: Real-world safety and effectiveness of vosoritide treatment in achondroplasia children: Portuguese experience.	Isabel Silva
9:15	C-0094: Early real-world experience with vosoritide treatment in achondroplasia: a single-center report from Turkey.	Saygin Abali
9:30	C-0055: Understanding the impact of achondroplasia on functioning and well-being: validation of the achondroplasia child experience measure–impact (ACEM–impact).	Alden Smith
9:45	C-0027: Body composition by bioelectrical impedance analysis (BIA) in adults with achondroplasia in clarity (The Achondroplasia Natural History Study).	Julie Hoover-Fong
10:00	C-0137: The prevalence of autism and neurodevelopmental disorders in a UK cohort of patients with achondroplasia.	Rhoda Akilapa
10:15	C-0145: Long-term impact of palovarotene treatment on heterotopic ossification volume in patients with fibrodysplasia ossificans progressiva: data from the phase III move trial.	Peter Kannu
10:30	C-0067: PIK3CA related overgrowth spectrum (pros): phenotypic variability in 16 molecularly proven patients and response to sirolimus.	Sheila Nampoothiri
10:45 11:15	**Coffee break**	
11:15 13:15	**Session 8: Genetic testing of Skeletal dysplasias** **Moderators: Valerie Cormier-Daire & Karen Heath**	
11:15	C-0044: 10 years experience in diagnosing skeletal dysplasias by Next-Generation Sequencing in Spanish and Portuguese patients.	Silvia Modamio Høybjør
11:30	C-0048 Systematic WES reanalysis and rapid functional studies in a skeletal dysplasia cohort yield new diagnoses.	Elsa Lucas Castro
11:45	C-0011: Rapid analysis of genomic data transforms management of infants with skeletal dysplasia.	Sarah Smithson
12:00	C-0064: Review of 400 genome analysis for patients with osteochondrodysplasia in the national French SEQOIA laboratory	Corinne Collet
12:15	C-0124: Molecular evaluation of patients with skeletal dysplasia and dysostosis through whole genome sequencing: a cohort from Brazilian rare genomes project.	Eduardo Perrone
12:30	C-0075: Prenatal exome sequencing in constitutional bone diseases: a series of 47 cases.	Roxa Borghese
12:45	C-0113: Genome sequencing in a cohort of 31 fetuses with genetic skeletal disorders.	Hillevi Lindelöf
13:00	**Awards and closing**	
13:30	**Lunch (Lunch box)**	

2024 ISDS

ISDS

International Skeletal Dysplasia Society

ORAL PRESENTATIONS

16th International
SKELETAL DYSPLASIA SOCIETY MEETING

Madrid, Spain
18-21st September, 2024

2024 ISDS

Session 1
Novel genes and phenotypes

Moderators
Yasemin Alanay & André Travessa

C0041 BIALLELIC VARIANTS IN *CCN2* UNDERLIE AN AUTOSOMAL RECESSIVE KYPHOMELIC DYSPLASIA IN HUMANS AND ZEBRAFISH.

Katta Girisha [1], Swati Singh[2], Sumita Danda[3], Neetu Sharma[4], Hitesh Shah[5], Vrisha Madhuri[6], Mir Tariq Altaf[6], Nadia Zipporah Padala[4], Raghavender Medishetti[4], Alka Ekbote[3], Gandham SriLakshmi Bhavan[5], Aarti Sevilimedu[4]

[1]Department of Medical Genetics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, India and Department of Genetics, College of Medicine and Health Sciences, Sultan Qaboos University Muscat, Sultanate of Oman [2]Department of Medical Genetics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, India [3]Department of Medical Genetics, Christian Medical College and Hospital, Vellore, Tamil Nadu, India [4]Dr. Reddy's Institute of Life Sciences, Hyderabad, Telangana, India [5]Department of Pediatric Orthopedics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India [6]Department of Pediatric Orthopedics, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

Introduction: Kyphomelic dysplasia is a rare, heterogeneous group of skeletal dysplasias characterized by severe bowing of the limbs (kyphomelia). The affected individuals demonstrate variable facial dysmorphism. *De novo* variants in *KIF5B* have recently been implicated in a subset of kyphomelic dysplasia. Here we report two unrelated families with six affected individuals with kyphomelic dysplasia resulting from biallelic loss of function variants in *CCN2*.
Aims: To describe human and zebrafish skeletal dysplasia phenotypes that result from biallelic loss of fuction variants in *CCN2*.
Cohort & methodology: We ascertained two unrelated consanguineous families from India and Bangladesh with four and two affected offsprings respectively. Exome sequencing was performed in the three probands.

Variants were segregated in the family members by Sanger sequencing. We generated G0 knockouts of ccn2 in zebrafish.
Results: The porbands have short stature and distinctive facial features that include bitemporal narrowing, posteriorly placed ears, deviated nasal septum, cleft palate, micrognathia, microstomia, and retrognathia. They all had kyphomelic femora. Additionally, radial head dislocation, bowing of long bone (radius, ulna, femur, tibia and fibulae) and broad great toes were noted. They had platyspondyly, and epi-metaphyseal dysplasia. Exome sequencing revealed two novel biallelic variants in *CCN2* (NM_001901.4, NP_001892.2): a missense variant c.443G>A; p.(Cys148Tyr) in exon 1 in the Indian family and a frameshift variant, c.779_786del; p.(Pro260LeufsTer7) in exon 5 in the Bangladeshi family. The variants segregated in autosomal recessive fashion in the available family members. These variants are absent in local and population databases and are predicted to result in loss of function of CCN2. *CCN2* encodes a multipotent factor that plays a crucial role in facilitating the proliferation and differentiation of chondrocytes. Initial studies have shown that CCN2-deficient mice exhibit several skeletal defects. The ccn2a crispant showed significant abnormalities including altered body curvature and either bent or missing tails. They displayed impaired cartilage formation in craniofacial region. Furthermore, a notable decline in levels of osteogenic markers such as *col2a1, sp7* and *runx2a* were observed cc2na crispant.
Conclusion: We thus confirm the role of biallelic loss of function variants in *CCN2* in an autosomal recessive kyphomelic dysplasia.

C0020 IDENTIFICATION OF *KIF22* HOMOZYGOUS VARIANTS IN SEMD WITH JOINT LAXITY, LEPDODACTYLIC TYPE AND DEMONSTRATION OF PROTEOGLYCAN BIOSYNTHESIS IMPAIRMENT.

Dubail Johanne[1], Rondeau Sophie[2], Michot Caroline[2], Baujat Genevieve[2], Capri Yline[5], Thevenon Julien[6], Charpie Maelle[2], Pejin Zagorka[8], Phan Gilles[9], Huber Céline[10], **CORMIER-DAIRE Valerie** [11]

[1]INSERM UMR 1163, Institut Imagine [2]reference center for skeletal dysplasia, Hôpital Necker [5]Genetics department, Hôpital Robert Debré [6]Genetics department, CHU Grenoble [8]orthopdic surgery department, hôpital Necker [9]Laboratoire CiTCoM, Faculté de Santé, Université Paris Cité, CNRS [10]Paris Cité University, INSERM UMR 1163, Imagine Institute, Paris, France [11]Université Paris Cité, Reference center for skeletal dysplasia, INSERM UMR 1163, Hôpital Necker Enfants malades and Institut Imagine

Introduction: Chondrodysplasias with multiple dislocations have been, for most of them, associated with mutations in genes encoding enzymes or transporters implicated in the synthesis or sulfation of glycosaminoglycan chains of the proteoglycans . They are characterized by joint laxity, multiple dislocations, short stature of pre- and post-natal onset, hand anomalies and/or vertebral anomalie. Lepto-SEMDJL presents a strong phenotypic overlap with chondrodysplasia with multiple dislocations. However, proteoglycan synthesis has never been investigated in patients with *KIF22* pathogenic variants.
Aims: Our aims were to further contribute to identify the molecular basis of chondrodysplasia with multiple dislocations.
Cohort & methodology: Patients included in the study were a part of a project dedicated to the identification of the molecular basis of chondrodysplasia with multiple dislocations. They all presented with multiple dislocations and benefited either from exome sequencing analysis or from a panel targeted sequencing analysis designed for skeletal dysplasias.
Results: By targeted gene sequencing analysis, we identified an homozygous *KIF22* variant (NM_007317.3:c.146G>A, p.(Arg49Gln)) in three patients from three unrelated families. The clinical features appeared similar to those of patients carrying heterozygous *KIF22* variant (c.443C>T or c.446G>A), although the spinal involvement appeared later and was less severe in patients with a recessive variant. Relatives harboring the c.146G>A variant at the heterozygous state were asymptomatic. The homozygous *KIF22* variant c.146G>A affected a conserved residue located in the active site and potentially destabilized ATP binding. RT-PCR and western-blot analyses demonstrated that both dominant and recessive *KIF22* variants do not affect *KIF22* mRNA and protein expression in patient fibroblasts compared to controls. We then analysed proteoglycan synthesis in patient skin fibroblasts. Compared to controls, DMMB assay showed a significant decrease of total sulfated proteoglycan content in culture medium but not in the cell layer and immunofluorescence

demonstrated a strong reduction of staining for chondroitin sulfates but not for heparan sulfates, similarly in patients with recessive or dominant *KIF22* variants.
Conclusion: These data identify a new recessive *KIF22* pathogenic variant, link for the first time *KIF22* pathogenic variants to altered proteoglycan biosynthesis and place the Lepto-SEMDJL in the CMD spectrum.

C0105 AUTOSOMAL DOMINANT SPONDYLOCOSTAL DYSOSTOSIS IN TWO UNRELATED FAMILIES CAUSED BY THE SAME HETEROZYGOUS PATHOGENIC VARIANT IN *MESP2*.

Aneta Malesa[1], Gabriela Andrade Vasques[2], Alexander A. L. Jorge[2], Wim Van Hul[3], Mortier Geert [4], Gretl Hendrickx[5]

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Introduction: Spondylocostal dysostosis (SCD) is a rare skeletal dysplasia characterized by multiple vertebral segmentation defects occurring during embryonic development. Affected individuals typically present with disproportionate short stature, scoliosis, vertebral (e.g. block vertebrae; hemivertebrae; butterfly vertebrae) and rib abnormalities. SCD usually has an autosomal recessive inheritance pattern, although one multi-generational family with an autosomal dominant TBX6-related form of SCD has been described. Disease-causing genes for SCD (DLL3, MESP2, LFNG, HES7, TBX6, RIPPLY2 and DLL1) are all involved in the Delta-Notch signaling pathway, which regulates the molecular segmentation clock which is crucial for the proper formation of the vertebral column.
Aims: To identify the molecular basis of autosomal dominant forms of SCD
Cohort & methodology: We have identified two unrelated families with an autosomal dominant form of SCD in whom we could not identify heterozygous pathogenic variants in TBX6.Family 1 originates from Belgium and includes four affected individuals with missing/fused ribs and multiple vertebral segmentation defects affecting the cervical and/or thoracic spine. Family 2 originates from Brazil and includes an affected father and daughter with congenital scoliosis, multiple vertebral segmentation defects and disproportionate short stature.
Results: Whole-genome sequencing in Family 1 led to the identification of a heterozygous MESP2 variant that segregates with the SCD phenotype. This variant has not been reported in gnomAD and prediction programs uniformly predict the variant to be disease-causing. Interestingly, the same MESP2 variant was also identified in a Brazilian family (Family 2) with SCD. This MESP2 variant is a missense variant affecting a highly-conserved amino acid residue in the basic helix-loop-helix (bHLH) domain of MESP2. Luciferase assays in HEK293T cells using a Lfng reporter were performed to investigate the regulation of LFNG expression by MESP2 as a transcription factor. Our data clearly suggest a dominant negative

effect by the missense variant, which was confirmed when wildtype MESP2 was co-transfected in the luciferase assays (to mimic the heterozygous state in the affected individuals).
Conclusion: In conclusion, we provide the first genetic evidence that a heterozygous missense variant in MESP2 can cause an autosomal dominant form of SCD. Additional studies are ongoing to further explore the functional effects of this variant on vertebral segmentation.

C0038 SMAD7: A NOVEL GENE IN SCLEROSING BONE DYSPLASIA.

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Introduction: Sclerosing bone dysplasias comprise a heterogeneous group of disorderscaused by different genes that lead to increased bone formation. Among them, Camurati–Engelmann disease characterized by progressive hyperostosis of long bones and skull is caused by a gain-of-function mutation in TGF-ß1(OMIM 131300). This disease is due to an overactivation of TGF-ß1 signaling pathways that leads to increased osteoblast function via SMADs proteins. We present here the case of a young woman who displays a severe facio-mandibular hyperostosis and diaphyseal sclerosis of the long bones. The first signs appeared in early childhood and worsen with age. Biochemical markers of bone turnover showed only a high level of ALPL activity.
Aims: to unravel the etiology of the atypical phenotype of the patient.
Cohort & methodology: A targeted genes sequencing panel for Sclerosing bone dysplasias was performed as well as array-CGH and WES. Functional studies to confirm the pathogenicity of the identified variant were then performed using primary fibroblast cells from the patient and controls.
Results: We have identified, by WES, compound heterozygous missense variants (NM_005904.3 c.232C> T p.(Pro78Ser) and NM_005904.3: c.812C>T NP_005895.1: p.(Thr271Met)) in SMAD7 gene, an inhibitor of SMADs pathways. From primary fibroblasts, we found that RNA and protein expressions of SMAD7 were decreased in the patient cells compared to control cells. Western-blot analysis showed that SMAD2/3 and p-SMAD3 levels were higher in mutated fibroblast cells than in control cells after TGF-β1 treatment. We tested transcript expression levels of osteoblast differentiation genes such as RUNX2, SP7, ALPL and COL1A1. Compared to control cells, SMAD7-mutated cells showed increased expression of ALPL, with reduced expression of RUNX2 and its target genes SP7 and COL1A1.The expression of β-catenin was not affected. Moreover, RANKL expression was abolished in SMAD7 mutated cells and OPG expression was slightly increased.
Conclusion: Functional studies support the pathogenicity of SMAD7 variants in the osteosclerosis phenotype.The higher expression of ALPL in the patient seems to be under the control of the SMAD pathways, but is not regulated by RUNX2 as expected. ALPL seems regulated by other signaling pathways that we are currently exploring.

C0098 THE CLINICAL AND MOLECULAR SPECTRUM OF SCLEROSING BONE DYSPLASIAS: EXPERIENCE FROM A TERTIARY CARE CENTRE IN INDIA.

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Introduction: Sclerosing bone dysplasias (SBDs) include a heterogeneous group of skeletal disorders characterized by increased bone density resulting from genetic or acquired etiologies causing disturbance of osteoblast or osteoclast regulation. Clinical, radiological, and genetic characterization of these disorders is important for accurate diagnosis and management.
Aims: To study the clinical and genetic spectrum of sclerosing bone dysplasias
Cohort & methodology: Retrospective (2014-2023) evaluation of patients with sclerosing bone dysplasia*
Results: Fifty-three unrelated families with 74 affected individuals (age range 2 months to 49 years) with sclerosing bone dysplasia including osteopetrosis (n=34), pycnodysostosis (n=15), dysosteosclerosis (n=2) and Ghosal hematodiaphyseal dysplasia (n=2) were identified. Consanguinity and family history were observed in 14 and 17 families respectively. Molecular testing strategies include targeted panel testing for one or more SBD-related genes (n=14) or exome sequencing (ES) (n=24) or both (n=1), and CTSK sequencing for pycnodysostosis (n=14). The overall diagnostic yield for pathogenic/ likely pathogenic variants was 72% (n=38/53) including osteopetrosis (25/34), pycnodysostosis (10/15), dysosteosclerosis (1/2) and Ghosal hematodiaphyseal dysplasia (2/2) respectively. Amongst osteopetrosis, 84% (21/25) had mutations in TCIRG1 (11/25) and CLCN7 (10/25), followed by OSTM1 (2/25), CA2 (1/25) and TNFRSF11A (1/25). Overall, a total of 17 novel variants were identified.
Conclusion: The study describes a large Indian cohort of SBDs and expands their clinical and molecular spectrum including rarer forms such as dysosteosclerosis. A molecular diagnosis could not be reached in one-third. Detailed clinic-radiological characterization and high throughput sequencing are vital for early diagnosis and in planning therapeutic interventions like HSCT and genetic counseling.
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Conflicts of interest: None
*including published cases

C0095 MITOCHONDRIAL SKELETAL DISORDERS: A RETROSPECTIVE COHORT OF 9 FRENCH CASES.

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Introduction: Mitochondrial disorders (MD) result from primary mitochondrial dysfunction. They are associated with oxidative phosphorylation and ATP production defects, leading to multisystemic manifestations. However, bones and joints disorders are uncommon in MD. A group of autosomal recessive skeletal dysplasias linked to mitochondrial dysfunction is yet emerging, involving LONP1 (mitochondrial protease), HSPA9 (mitochondrial chaperone), IARS2 (mitochondrial tTRNA synthetase), PAM16 (mitochondrial protein import), AIFM1 (mitochondria-associated apoptosis inducing factor) and PISD (inner mitochondrial membrane modification).
Aims: We aim to further describe and compare the skeletal presentation of these mitochondrial skeletal disorders (MSD).
Cohort & methodology: We recruited 9 cases from 6 families, including 5 females and 4 males of diverse ethnicities; 4 fetuses and 5 living patients (8 to 15 years old).
Results: We identified biallelic mutations of LONP1 in 1 fetus and 1 family (1 patient and 2 fetuses), AIFM1 (2 brothers) and PISD (3 cases including 1 fetus). Common symptoms include IUGR and short long bones for fetuses, growth retardation for living patients (-2 to -5 SD) and absence of microcephaly. The PISD fetus displayed neuronal alterations, platyspondyly, short ribs, curved femora, metaphyseal spurs and delayed bone maturation. All 3 LONP1 fetuses harbour multiple malformations including cardiopathies and diaphragmatic hernias, which do not affect the living patient (sibling of fetuses). The LONP1 fetuses and living patient share abnormal external ears, feet malposition and delayed bone maturation. All living MSD patients display motor developmental delay, eye abnormalities, spondyloepimetaphyseal dysplasia and maxillofacial anomalies. Epiphyseal dysplasia becomes complicated by distal femoral epiphysiodesis, genu valgum and patellar dislocation in LONP1. AIFM1 and PISD patients display brachymetacarpy and brachyphalangy. Marked metaphyseal alterations and enlarged knees are observed in AIFM1, whereas hip and elbow dislocations and progressive coxa vara are seen in PISD.

Conclusion: We confirms the existence of common skeletal signs among MSD with growth retardation, severe epiphyseal dysplasia, spine involvement and maxillofacial anomalies. Together with the shared extra-skeletal signs, this supports a common clinicoradiological presentation linked to genes involved in mitochondrial protein homeostasis and transport. However specific signs are observed for each genotype and we underline the importance of assessment of joint laxity in LONP1 and coxa vara in PISD.

C0073 BROADER THAN BONE FRAGILITY – THE PHENOTYPIC SPECTRUM OF OSTEOGENESIS IMPERFECTA TYPE 15.

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Introduction: Osteogenesis imperfecta (OI) type 15 is a rare autosomal recessive form caused by WNT1 gene variants. In addition to bone fragility, it may have extra-skeletal features including neurodevelopmental impairment. Whilst pathogenic mechanisms are not fully understood, the Wnt signalling pathway is a key regulator of bone homeostasis and osteoblast activity, and WNT1 variants may affect other signalling pathways critical for central nervous system development. We report three patients with OI type 15 across the NHS England Highly Specialised Childhood Complex Osteogenesis Imperfecta Service.
Results: All patients presented with peri- or neonatal fractures and were diagnosed with OI in infancy. Initial skeletal surveys revealed multiple clavicular, rib, and long bone fractures, without Wormian bones. Further long bone fractures and progressive vertebral compression fractures developed; the latter between 3–14 months old.
All patients commenced intravenous bisphosphonates between 1–12 months old, with uncertain response. Patient 1 showed improved vertebral modelling after 10 months of treatment despite ongoing long bone fractures, but now aged 7 years has little improvement in BMD, unchanged widespread thoracic vertebral height loss and recurrent upper limb fractures. Patient 2 continues to have severe vertebral fractures with no remodelling; multiple lower limb fractures have reduced after intramedullary rodding. Patient 3 developed vertebral compression fractures aged 12 months despite starting bisphosphonates aged 2 months. All patients have undergone lower limb rodding – 1 and 2 bilaterally. Patient 2's ptosis transiently improved with oral salbutamol.
Conclusion: In addition to bone fragility OI type 15 can be associated with neurodevelopmental impairment, ptosis, movement disorders and autism spectrum disorder. The extra-skeletal features may be most limiting in terms of participation and quality of life. Education of professionals caring for children with this condition is essential, to improve awareness of the phenotypic spectrum and identify associated co-morbidities. This also enables early intervention and multidisciplinary team input to achieve best possible developmental outcomes. All

patients have had uncertain benefit from intravenous bisphosphonates. Anti-sclerostin antibodies which activate Wnt signalling may be a more appropriate treatment option for children with OI type 15 and this requires further study.

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Session 2: Functional characterization

Moderators
Carlos Ferreira & Fernando Santos

C0047 SELF REPLICATING RNA FOR SOMATIC REPROGRAMING FIBROBLASTS TO OSTEOBLASTS.

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Introduction: Here, we introduce a novel method utilizing self-replicating RNA (srRNA) to directly convert fibroblasts into osteoblasts (OBs), the key cells involved in bone formation and mineralization.
Cohort & methodology: By delivering transcription factors OCT4, L-MYC, RUNX2, and OSX via srRNA, we induced fibroblasts to differentiate into OBs without genome integration, mitigating risks of genomic mutations and teratoma formation. Our approach incorporates mRNA-B18R, which blocks Toll-like receptor-mediated inflammatory responses, ensuring efficient reprogramming while preserving the srRNA replicon.
Results: Functional validation confirmed the osteoblastic identity of induced OBs, as evidenced by mineralized matrix production and expression of osteoblast markers such as alkaline phosphatase and osteocalcin.
Conclusion: This groundbreaking method offers a faster, safer, and more efficient alternative to traditional cell therapy approaches, with broad applications in regenerative medicine beyond bone regeneration. By addressing key challenges in cell therapy, our innovation holds immense potential to advance patient care and improve outcomes in various fields, paving the way for future clinical translation and therapeutic interventions.

C0070 UTILIZING URINE-DERIVED STEM CELLS FOR DISEASE MODELLING AND DRUG SCREENING IN SKELETAL DYSPLASIAS.

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Introduction: Diagnosing skeletal dysplasias (SDs) remains a challenge due to variants of uncertain significance (VUS) that impede accurate diagnosis. The acquisition procedure of affected tissues such as bones and cartilage for molecular diagnosis poses risks, hindering the study of rare variants and disease mechanisms in SDs. To address this challenge, we propose a non-invasive human-based modelling system utilizing urine-derived stem cells (UDSCs) to classify VUS and study the pathomechanism of SDs.
UDSCs, naturally present in human urine, exhibit mesenchymal characteristics. While existing studies demonstrate their regenerative ability, using UDSCs as an in vitro disease modelling system remains underexplored. This project aims to leverage the differentiation potential of UDSCs and extend their applications into the medical and academic fields.
Aims: 1. Using UDSCs to classify VUS and develop a disease modelling tool.
In the next phase of this project, I will compare the differentiation efficacy and morphology of UDSCs derived from SD patients against those from healthy individuals. This analysis aims to identify disease-specific phenotypes in vitro. I hypothesize that patient-derived UDSCs may exhibit reduced chondrogenic or osteogenic capabilities, phenocopying the donor's underlying conditions.
Cohort & methodology: We recruited healthy individuals without SDs, cultured cells derived from anonymized urine samples for 14 days and induced direct differentiation into osteogenic or chondrogenic lineage cells using specific media. The results of differentiation were examined 28 days after induction.
Results: Our preliminary results demonstrate the potential of UDSCs as an SD modelling system. The cells showed positive Alizarin Red staining for osteogenesis, indicating mineralized matrix deposition, and positive Safranin O staining for chondrogenesis, verifying glycosaminoglycan production.
Conclusion: In conclusion, our work holds significant potential for advancing the diagnosis, understanding, and therapy development in SDs. By utilizing UDSCs as a non-invasive disease modelling system for SDs, we aim to improve patient outcomes and quality of life.

C0078 CLOSING THE DATA GAP FOR SKELETAL DYSPLASIAS: A COMPREHENSIVE MULTIOMIC EXPRESSION ATLAS OF THE SKELETON.

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Introduction: Skeletal biomedicine covers the study of diverse human pathologies, ranging from prevalent conditions like osteoporosis and osteoarthritis to rare disorders such as skeletal dysplasias. However, accessing comprehensive gene and protein expression data from skeletal tissues remains a challenge, limiting our understanding of disease mechanisms and the search for new therapies. While the amount of big-data generated in skeletal research is on the rise, the field has yet to provide open access to skeletal "omics" results, unlike other areas of research that are well represented in public databases like the Human Protein Atlas and Mouse Genome Informatics resources.
Aims: To address this gap, we have developed a novel gene and protein expression atlas for skeletal tissues. Our atlas integrates our own with publicly available transcriptional (bulk and single-cell RNA-seq data) and proteomic data from human and mouse models into an interactive online interface. This tool is designed to provide a user-friendly platform for researchers and clinicians to comprehensively explore skeletal tissue expression profiles.
Cohort & methodology: Given that skeletal dysplasias research not only informs our understanding of rare skeletal conditions but also serves as a model for genetically more prevalent disorders such as osteoporosis and osteoarthritis, the published public data and our atlas are enriched with skeletal dysplasia expression information.
Results: Our group has meticulously curated and selected high-quality, comparable datasets from the literature, which have been integrated into simple matrices for skeletal tissues and cell types. This approach yields a graphical, intuitive representation for each gene and protein present in the skeleton.
Conclusion: We believe that this atlas will serve as a valuable resource for the skeletal biomedical community, empowering researchers and clinicians without extensive bioinformatics skills to access skeletal tissue data with ease and generate their own exploratory or publishable expression analysis.

Visit https://skeletalatlas.uma.es

C0042 VARIANTS LOCATED THROUGHOUT IHH LEAD TO DEFECTIVE SECRETION, CAUSING SHORT STATURE AND/OR BRACHYDACTYLY AND ACROCAPITOFEMORAL DYSPLASIA.

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Introduction: Background: Indian Hedgehog (IHH) is a morphogen essential for maintaining the growth plate length during long bone development. In humans, IHH variants have been associated with Brachydactyly type A1 (BDA1, AD), and Acrocapitofemoral dysplasia (ACFD, AR). Typically, these variants are located within the N-terminal domain of IHH (IHH-N), which, once secreted, constitutes the signaling molecule. However, an increasing number of heterozygous variants localized throughout the gene (mainly classified as variants of unknown significance (VUS)) are being identified in patients with/without short stature (SS) and variable brachydactyly. Additionally, nearly half of these variants are in the IHH C-terminal domain (IHH-C), which lacks signaling activity but is essential for IHH-N activation and function, though no functional characterization has been performed for these variants.
Aims: To develop a functional assay for determining IHH variant pathogenicity and secondly, to determine whether variants located in the C-terminal domain alter IHH function.
Cohort & methodology: Nine IHH variants (4 IHH-N, 5 IHH-C) detected in patients with SS and/or brachydactyly, the four reported ACFD variants and three coding variants with the highest MAF in gnomAD (1 IHH-N, 2 IHH-C) were introduced into pCMV6-IHH vector by site-directed mutagenesis and transiently transfected into HEK293T cells. Culture media and cell lysates were collected and the secreted-IHH and IHH peptides were analyzed by western blot. The variants were studied in the homozygous and heterozygous states.
Results: Secreted-IHH was undetectable or severely reduced in all studied mutants regardless of their location. Similarly, decreased intracellular levels of both IHH-N and IHH-C peptides were observed. Though secreted-IHH was higher in the heterozygous mutants, it remained significantly reduced compared to wild-type. Surprisingly, the C-terminal located gnomAD variants showed reduced secreted-IHH, IHH-N and IHH-C peptides.
Conclusion: 1) Regardless of variant location and zygosity, reduced availability of secreted IHH is likely to be the underlying disease mechanism in the IHH-associated phenotypes. 2) Our study provides the first insight into the functional consequences of IHH C-terminal variants. 3) This study highlights the importance of functional studies to confirm the pathogenicity of VUS. 4) Relatively frequent IHH variants in the general population may contribute to an individual's height and phenotype.

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Session 3: Mice models of skeletal dysplasias

Moderators

Matt Warman & Ivan Durán

C0012 ADJUVANT THERAPEUTIC ENHANCES BONE GROWTH AND QUALITY IN GROWING MICE WITH MODERATE-TO-SEVERE OSTEOGENESIS IMPERFECTA: EXPLORATION OF A CNP ANALOG.

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Introduction: Osteogenesis imperfecta (OI) is a heterogenous type 1 collagenopathy characterized by fragile bones, decreased bone mass, and shorter stature. Bisphosphonates are used to manage moderate-to-severe OI in children because they are known to reduce fracture incidence, but they do not increase growth velocity. C-type natriuretic peptide (CNP) is produced in the growth plate and positively regulates linear bone growth; an unpublished study by Bober found that people with OI have a reduced level of CNP.
Aims: This study evaluates if administering the CNP analog as adjuvant treatment with a standard bisphosphonate (alendronate (ALN)) will reduce fracture incidence and increase bone growth, strength, and bone mineral density (BMD) in growing oim/oim (oim) mice.
Cohort & methodology: Two week old oim mice (N=27) were divided into four dosage groups: controls (N=8) receiving saline and treated mice receiving weekly ALN with one of three CNP dosages: 10 ug/kg three days/week (10x3)(N=6), 20 ug/kg three days/week (20x3)(N=7), or 20 ug/kg five days/week (20x5)(N=7). Faxitron images were taken at two, eight, and 14 weeks (sacrifice) to assess fracture incidence and measure femoral length and vertebral height. Microcomputed tomography was used to assess bone microstructural parameters.

Results: The 20x5 group had no fractures post-sacrifice; there were two mice with one fracture each in the 10x3 and 20x3 groups. Femoral length was increased in all treated groups in comparison to saline mice; the 20x5 group had the largest increase and the 10x3 and 20x3 groups had comparable increases. Vertebral height was increased in all treated groups; the 10x3 and 20x5 groups had greater, comparable increases than the 20x3 group. All treated groups had an increase in trabecular BMD. All three treated groups had increased cortical TMD, BMD, and thickness.
Conclusion: CNP analog adjuvant treatment increased femoral length and vertebral height without compromising fracture reduction while also providing added benefits for trabecular and cortical bone (not observed with bisphosphonates alone). These results will be used to identify the optimal dose of the CNP analog; a full murine study will be conducted to investigate the potential for use in humans.

C0028 SMALL MOLECULE INHIBITION RESCUES THE SKELETAL DYSPLASIA PHENOTYPE OF TRPV4 MUTANT MICE.

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Introduction: The TRPV4 skeletal dysplasias are characterized by short stature, prominent large joints, and severe scoliosis and result from dominant missense mutations that activate the TRPV4 calcium permeable ion channel. Chondrocyte specific induction of the mutation, either embryonically using Col2a1-Cre or postnatally using Acan-CreER2 and tamoxifen, resulted in a skeletal dysplasia affecting the spine and long bones, consistent with the human skeletal dysplasia phenotypes produced by TRPV4 mutations. Cartilage growth plate histological abnormalities included disorganized proliferating chondrocyte columns and reduced hypertrophic chondrocyte development, reflecting abnormal endochondral ossification. In vitro studies in transfected HEK cells demonstrated that a TRPV4-specific small molecule, GSK2798745, inhibits p.R594H and other mutant TRPV4 channels. Subsequently, in vivo inhibitor treatment of affected mice significantly improved their radiographic skeletal phenotype and rescued the growth plate histological abnormalities. Single cell RNA-seq of chondrocytAs a platform to understand the mechanism of disease and to test the hypothesis that channel inhibition could treat these disorders, we developed a knock-in mouse that conditionally expresses the p.R594H Trpv4 mutation. es from affected mice identified calcium-mediated effects on multiple signaling pathways as potential mechanisms underlying the defects in linear and cartilage appositional growth observed in both mutant mice and human patients. These results provide preclinical evidence demonstrating that TRPV4 inhibition is a rational, mechanism-based therapeutic strategy to ameliorate disease progression and severity in the TRPV4 skeletal dysplasias.

C0052 CHARACTERIZATION OF THE SKELETAL PHENOTYPE IN AN ADULT MURINE MODEL OF DIASTROPHIC DYSPLASIA.

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Introduction: Diastrophic dysplasia (DTD) is a recessive chondrodysplasia caused by mutations in the SLC26A2 gene encoding for a sulfate/chloride antiporter. SLC26A2 impairment leads to low intracellular sulfate level causing proteoglycan under sulfation and alterations of cartilage extracellular matrix properties. In the patients, degenerative changes in the joints are progressive and accentuated with growth and age; joint deformities and premature osteoarthritis are the rule in DTD patients. To better characterize the bone and joint structure of DTD and to develop therapeutical approaches, a Slc26a2 knock-in mouse (dtd mouse) was generated and the phenotype during skeletal growth was studied.
Aims: In this work we investigated skeletal alterations in adult dtd mice of both genders at 1, 2 and 6 months of age.
Results: X-ray studies confirmed that dtd mice are characterized by a skeletal phenotype with significant growth retardation over controls at all the time points. Morphometric analysis of mutant mice showed that significantly higher values in the bone measurements are always found in males compared with females. The evaluation of bone quality and architecture through dual-energy X-ray absorptiometry (DEXA) and micro-computed tomography (micro-CT) demonstrated that bone mineral content and density alongside the trabecular and cortical bone parameters are altered in dtd compared with non-mutant mice for all age groups regardless the gender. To investigate the cartilage defects, safranin-O staining was performed in the knee. The assessment of OARSI (Osteoarthritis Research Society International) score revealed the presence of proteoglycan loss and surface discontinuity in the joint of dtd mice. Therefore, we investigated possible changes in subchondral bone since its remodeling is related to the initiation of cartilage loss. Micro-CT analysis showed a reduction in subchondral bone parameters in dtd mice compared with controls for both genders at all the time points, with significantly higher values in male mice compared with female littermates only at 1 month of age.
Conclusion: Overall, these results confirmed the presence of cartilage and bone impairment in adult dtd mice and demonstrated that the skeletal degeneration is progressive as it occurs in DTD patients.

C0007 ANTI-SIGLEC 15 ACTS AS AN ANTI-RESORPTIVE AND BONE-FORMATION AGENT IN ADULT MICE WITH MODERATE-TO-SEVERE OSTEOGENESIS IMPERFECTA.

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Introduction: Osteogenesis Imperfecta (OI) is a heterogeneous connective tissue disorder characterized by fragile bones and frequent fractures. Therapeutic treatments for adults with OI are not well-established due to the lack of efficacy with existing therapies. The sialic acid-binding immunoglobulin-like lectin 15 (Siglec 15) immunoreceptor plays a key role in modulating development of osteoclasts and bone resorption. NP159 (an antibody targeting Siglec 15) increases bone mass and improves mechanical properties of bone in fracture, OVX, and spinal-cord injury models in rodents.
Aims: We have previously shown that a low dosage (10mg/kg) of NP159 (antibody targeting Siglec 15) reduced fracture incidence and provided additive benefits to trabecular and cortical bone in an OI mouse model (oim/oim). This study investigates effects of a two-fold increase in the dose of NP159 (20mg/kg) on additional improvements in bone quality.
Cohort & methodology: 60 male and female oim/oim mice (20 saline and 10 NP159 each) were treated from age 14-26 weeks with weekly saline or 20 mg/kg NP159 s.c. Faxitron images were taken at 14 and 26 weeks to evaluate fractures. Post-sacrifice, femurs were analyzed by micro-CT for microarchitecture and biomechanical testing for bone strength. Tibias were analyzed for compositional changes using FTIR spectroscopy. Statistics were performed using two-way ANOVA; $p \leq 0.05$ was considered significant.
Results: 90% of treated males had no fractures post-sacrifice (85% in saline group), compared to 80% of treated females (55% in saline group). NP159-treated mice showed increased trabecular tissue mineral density, cortical TMD and porosity, and BMD. Only the males showed an increase in trabecular bone volume fraction and number, BMD, and decreased separation, along with increased cortical thickness. Both sexes showed increased Young's modulus (material stiffness); only males had increased max load to failure and stiffness. Both sexes showed increased collagen maturity by FTIR; only males had increased acid phosphate (new mineral formation).
Conclusion: NP159 reduced fracture incidence in both sexes and improved bone strength and quality to a greater extent in males than females. These results highlight the potential of NP159 as treatment for adult OI, and the need to consider sexual dimorphism in future research.

C0040 A NOVEL MOUSE MODEL FOR ACRODYSOSTOSIS TYPE 2 TO ENABLE THE DEVELOPMENT OF NEW TREATMENTS.

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Introduction: Acrodysostosis type 2 (ACRDYS 2) is a rare developmental skeletal dysplasia disorder characterised by a variety of skeletal, hormonal and cognitive symptoms. ACRDYS 2 is an autosomal dominant condition caused by single nucleotide polymorphism (SNP) missense mutations in the phosphodiesterase-4 subtype D (PDE4D) gene. Whilst the genetics behind ACRDYS 2 are well established, it is not clear how the mutations contribute molecularly and phenotypically to the range of symptoms observed in patients. Furthermore, there are several pharmacological PDE4D inhibitors that could be evaluated for their therapeutic potential in ACRDYS 2. Unfortunately, until very recently, there were no animal models of the disease to allow the undertaking of these fundamental and translational investigations.
Aims: Our aim was to generate a mouse model for ACRDYS 2 that would allow the assessment of pathological mechanisms that contribute to the condition as well as the evaluation of the therapeutic potential of novel treatments and repurposed drugs.
Results: We have recently generated a novel mouse model for ACRDYS 2 with a SNP reflecting the human PDE4D S190A mutation (S185A in mice) that displays phenotypes reflecting the human condition such as reduced size and weight, skeletal dysplasia as well as aberrant cognitive function. Isolation of primary fibroblasts from the ACRDYS 2 mice also shows an impact of the mutation on cellular growth and function. We are currently undertaking an in-depth characterisation of the ACRDYS 2 mouse model at cellular, tissue and behavioural levels.
Conclusion: We have successfully generated a new and unique ACRDYS 2 mouse model that will be an invaluable tool for researchers, clinicians and patients to help better understand the pathophysiology of ACRDYS 2 as well as identify treatment strategies for ACRDYS 2 and other conditions characterised by aberrant PDE4D activity.

Session 4:
Clinical and radiological aspects of skeletal dysplasias- cohorts and cases

Moderators
Julie Hoover-King & Manuel Parrón.

C0099 PERINATAL OUTCOME IN 35 CHILDREN WITH CARTILAGE HAIR HYPOPLASIA.

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Introduction: Cartilage-hair hypoplasia (CHH) is an autosomal recessive skeletal dysplasia caused by pathogenic variants in the RMRP gene. CHH is characterized by disproportionate short stature; average adult heights are 131.1 cm and 122.5 cm for males and females. Other manifestations include immunodeficiency, anemia, and increased malignancies. Very limited data are available on perinatal outcomes in CHH.
Aims: This study aimed to evaluate prenatal findings and the course of pregnancies and deliveries in newborns with CHH.

Cohort & methodology: We reviewed data for 35 children with CHH who were included in the Finnish Skeletal Dysplasia register and born between 2000 and 2023. Data about diagnosis, family history, pregnancy, delivery, and neonatal period were gathered from patient records.
Results: Of the 35 children, 34 had a genetically confirmed diagnosis of CHH and one was diagnosed based on phenotype and family history. Family history was available for 28 children; 8 (29%) had older siblings with CHH. In 8/35 (23%), a genetic diagnosis was made prenatally. Prenatal ultrasonography findings were available for 21 children. In 19/21 (90%), shortened long bones or abnormal growth was observed during pregnancy. Delivery data were available for 33 cases. Most of the children (82%) were born at term, 3 (9%) were born before 34 weeks of pregnancy and 3 (9%), between 34+0 and 36+6 weeks of pregnancy. The method of delivery was reported for 24 patients. Less than half (46%) were born by vaginal delivery. The others were born by elective C-section (5/24; 21%), urgent C-section (4/24; 17%), or emergency C-section (4/24; 17%). The average Apgar score at one minute was 7.4. The median length for those born at term was 44.5 cm (range 40.0–50.0 cm) for boys (N=10) and 44.0 cm (range 37.0–48.0 cm) for girls (N=16). The median birth length Z-score for all was -3.8 (range -7.3– -1.0).
Conclusion: In most cases, growth failure was detected prenatally. Majority of the pregnancies were carried to full term but less than half were born by normal vaginal delivery. The median birth length was below normal. More research is needed to further examine the early findings and diagnostic processes in CHH.

C0128 RMRP-RELATED SPECTRUM: CLINICAL, RADIOLOGICAL AND MOLECULAR CHARACTERIZATION OF A PORTUGUESE COHORT.

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Introduction: Cartilage-hair-hypoplasia (CHH), first described by McKusick is part of a spectrum of RMRP-related disorders. This continuum of disproportionate short stature ranges from milder cases with metaphyseal dysplasia to severe spondyloepimetaphyseal abnormalities. Extraskeletal findings such as defective immunity, haematogical alterations, increased malignancy risk, gastrointestinal problems and sparse hair relate mainly to CHH.
Aims: Describe and correlate phenotype-genotype of RMRP-spectrum disorders for better-informed counselling and management in the Portuguese population.
Cohort & methodology: Clinical and molecular characterization of 13 CHH-spectrum cases observed in Portuguese hospitals, based on medical records retrospective analysis.
Results: We describe 7 male and 6 female patients, from 11 unrelated families, with a CHH-spectrum diagnosis, currently between 1 and 51 years-old. Recognition of disease ranged from prenatal (6/13) to adolescence (11-years-old), with evidence of short stature/bone dysplasia (12/13), mostly with normal neuromotor development (8/13). The majority of diagnosis were achieved after specific clinical suspicion, although reverse phenotyping was essential in two patients.

Before Medical Genetics evaluation, five patients had a missed diagnosis due to technical limitations – duplications in the promoter region missed by NGS or exome not covering RMRP. Subsequently, targeted Sanger-sequencing was mandatory for molecular confirmation.
All patients were compound heterozygous for 16 different variants, 13 known and three novel. Three variants were recurrent: n.-25_-4dup (2 families); n.196C>T (6 families); n.97_98dup (2 families).
The older patient had severe skeletal phenotype with -9.7 SD in height,nine patients had moderate phenotypes and three cases were mild. Suggestive radiological features such as metaphyseal-dysplasia (6/12), axial-skeletal abnormalities (6/12), bowed femora/tibiae (8/12) and hand-bone dysplasia (6/12) were evaluated.
Variable hypotrichosis was identified in 8/13 patients.
Impaired lymphocyte proliferation was present in 6/7, one with severe persistent immune thrombocytopenia and one with severe T-cell lymphopenia, complicated with auto-immune haemolytic anemia. The lather carries an unusual variant: n.*3T>C, previously associated with severe immunodeficiency. No malignancies were reported.
Nine patients had gastrointestinal dysfunction or failure to thrive, namely one with Hirschprung disease and one ulcerative colitis.
Conclusion: Our data are globally in accordance with the literature. This presentation focuses on detailed description of our RMRP-spectrum cohort, promoting awareness of its natural history and the importance of clinical suspicion for adequate testing.

C0072 EPSTEIN-BARR VIRUS POSITIVITY IN MALIGNANCY SAMPLES OF PATIENTS WITH CARTILAGE-HAIR HYPOPLASIA.

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Introduction: Cartilage-hair hypoplasia (CHH) is a rare metaphyseal chondrodysplasia, characterized by short stature, immunodeficiency, and increased risk of malignancies, particularly lymphomas. Lymphomas often occur at a relatively young age, and prognosis is poor compared to the general population. The pathogenesis of lymphomas in CHH is unknown.
Aims: This study investigated the role of various viruses in the pathogenesis of malignancies in patients with CHH.
Cohort & methodology: We collected malignancy tissue samples for 15 CHH patients (12 lymphomas and 3 others, including thyroid papillary adenocarcinoma, endometrioid adenocarcinoma and neuroendocrine carcinoma). To compare the findings in immunocompetent controls, we retrieved malignancy samples from the Finnish Biobank so that each patient had three controls who matched the patient's sex, age and the type and origin of the malignancy. We took one to five punches from the CHH patients' malignant tissue samples and one punch from every control's malignant tissue sample. All punches were examined for a total of 41 viruses with highly sensitive new generation molecular detection methods.
Results: The 15 CHH patients' median age at the time of malignancy was 32.6 years (range 6.4-69.5 years). Eleven of them deceased of the malignancy; in half of them survival was less than 3 months from diagnosis. We tested all malignancy samples by hybrid-capture sequencing targeting 41 DNA viruses. Altogether 13 different viruses were detected. The highest viral DNA prevalence in the CHH patients was of EBV and human herpesvirus 7 (HHV-7). EBV was detected in every CHH patient's sample in all but one punch, in contrast to EBV positivity in 64% of the control samples. HHV-7 was detected in 53% of the CHH patients' samples in contrast to 25% of the controls. For five CHH patients with detailed EBV serology data, EBV immunoglobulin G was detected on average over 10 years prior to malignancy diagnosis.
Conclusion: We detected EBV in all tested CHH malignancy samples. Our findings suggest a pivotal role for EBV as a driver of lymphomagenesis in CHH. Patients with CHH should be regularly screened for EBV and anti-EBV therapy should be strongly considered as a part of lymphoma therapy in CHH.

C0136 MULTIPLE OSTEOCHONDROMAS: CLINICAL AND MOLECULAR CHARACTERIZATION OF A PORTUGUESE COHORT.

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Introduction: Multiple Osteochondromas (MO) is a rare autossomal dominant condition characterized by benign tumours emerging from the perichondrium of bones. It is a potentially debilitating disease, often causing deformities, functional limitation and joint pain at multiple sites. The malignization risk to osteochondrosarcoma is low (~2%-5%) but increases with age. A timely diagnosis can enable early follow-up and management of complications, as well as adequate genetic counselling.
Aims: Clinical and molecular characterization of a Portuguese cohort of MO patients for better-informed management and counselling.
Cohort & methodology: Descriptive study of a cohort of patients diagnosed with MO observed at our centre (2015-2023) based on medical records retrospective analysis.
Results: A total of 116 cases were analysed, across 80 families, 61 (52.6%) females and 55 (47.4%) males, with a mean current age of 26.9 ± 15.5 years. In 65/80 index cases, EXT1/EXT2 sanger sequencing was performed and revealed a variant in 57 cases. On 3 of the 8 negative cases, a multigene NGS panel was performed and revealed CNVs in two cases: one EXT1 exonic deletion and one EXT2 multiple contiguous gene deletion. Additionally, this strategy revealed one family with PTPN11 metachondromatosis, excluded from this cohort. In total, we found 48 different variants in EXT1 (34 P/LP and 3 VUS) and EXT2 (14 P/LP), 17 of which are novel. In 7 cases the causative variants occurred de novo, being the mean age of first manifestation in this group of 3.7 ± 3.3 years.
Ninety-two MO cases had enough clinical data to be phenotyped, at the latest evaluation, according to the Rizzoli MO classification: 26 (28.3%) in class IA/IB, 39 (42.4%) in class IIA/IIB and 27 (29.3%) in class IIIA/IIIB. Bowing deformity of the forearms (42/92) and the lower extremities (49/92), and scoliosis (7/92) were reported. Malignization was confirmed in two unrelated patients (both at 30 yo).
Conclusion: Our results confirmed a high molecular diagnostic yield (59/65 index cases, 90.3%). Taken together, our data expands the existing knowledge on MO phenotype-genotype spectrum. We hope to contribute to a better understanding of the clinical aspects of the disease and to a more streamlined approach to MO management.

C0132 ACROMELIC DYSPLASIAS: A SERIES OF EIGHT PATIENTS AND A LONG FOLLOW-UP OF A BOY WITH ACROMELIC DYSPLASIA RELATED TO FBN2.

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Introduction: Acromelic skeletal dysplasias are a group of rare genetic conditions.
Aims: The main goal of this study was to identify the etiology of eight patients classified as having acromelic skeletal dysplasias.
Cohort & methodology: Using NGS methods, we studied four male and four female individuals whose ages ranged from newborn at one day of life to teenage.
Results: The diagnosis and gene related to each one were: Albright dysplasia – three patients (GNAS), Acromicric dysplasia (FBN1), Brachydactyly type A1 (IHH), Acrodysostosis (PRKAR1A), and Geleophysic – two patients. One of these two latter patients had the clinical-radiological diagnosis ruled out since genome sequencing revealed one pathogenic variant and one variant of uncertain significance in the B3GLCT gene, which made sense as a differential diagnosis. The Geleophysic dysplasia diagnosis of the second patient in this group was confirmed by a homozygous missense variant in the FBN2 gene. This patient was first evaluated soon after his birth and after ruling out a possible metabolic disorder because of his infiltrated appearance, he was classified as having Geleophysic dysplasia. His phenotype was characterized by brachydactyly, short length (-4 SD at 10 months of age), and skeletal changes (delay of ossification of the femoral heads, retarded carpal ossification, and pronounced shortening of phalanges mainly those of the 2nd and 5th fingers). This boy was followed up until the age of 13 and maintained his phenotypic appearance: mild facial dysmorphism, abnormal integument with a hardened consistency, mainly in the limbs that also presented brachydactyly of the hands and feet, and gait on tip-toe since 15 months old. His short length/height, previously low during his infancy, became average by 7 years old and remained until the last time he was evaluated at the age of 13. His height was probably rescued because this patient was also diagnosed with Klinefelter syndrome during his childhood.
Conclusion: In conclusion, the acromelic dysplasia related to GNAS was the most common phenotype, the so-called Peters-plus syndrome is reported as an interesting differential diagnosis to Geleophysic dysplasia, and lastly, we present for the first time a follow-up of a boy with acromelic dysplasia related to FBN2.

C0129 HELICAL COL1A1 VARIANT IN FAMILY WITH FEATURES OF ARTHROCHALASIA-TYPE EHLERS DANLOS SYNDROME.

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Introduction: COL1A1 encodes procollagen alpha1 chains of type I collagen. Mutations affecting the helical region of the alpha chains cause classic Osteogenesis Imperfecta (OI), and molecular defects in the N-propeptide cleavage site cause Arthrochalasia type Ehlers Danlos Syndrome (aEDS). We describe a familial variant of COL1A1 encoding part of the helical region of the alpha chain with a clinical phenotype strongly suggestive of aEDS.
Cohort & methodology: The probandis a 15-year-old male with a history of left-sided congenital hip dysplasia (CDH), joint laxity and hypermobility, skin elasticity, and kyphoscoliosis. Similarly, his younger sister had unilateral CDH, skin hyperextensibility, joint hypermobility and kyphoscoliosis. Both had a Beighton score of 6/9. There is a history of joint hypermobility in the father, paternal uncle and paternal grandmother.
A next generation sequencing Connective Tissues Diseases panel for the proband detected a heterozygous c.2032G>A (p.Glu678Lys) in COL1A1. Familial variant testing was positive in the sister and father.
Results: The described familial variant has been classified as uncertain significance. In-silico analysis predicted pathogenicity. Frequency datain gnomAD is reported as 0.00045%. This variant is within exon 31 impacting the helical region of the gene; this variant is listed in the ClinVar Database as likely pathogenic for OI type I. Most forms of aEDS are caused by heterozygous mutations that result in partialor complete loss of exon 6 in COL1A1 or COL1A2 impacting the N-terminal cleavage site, but not the helical domain. The proband and his sister present clinically with signs and symptoms ofaEDS. Minimal criterion for aEDS requires bilateral CDH whereas the siblings both present with unilateral aEDS. Their molecularly impacted father is also suspected of having clinical aEDS.
Conclusion: Diagnosis of aEDS should be considered in the absence of exon 6 deletions in COL1A1 or COL1A2 and in unilateral, and not exclusively bilateral, congenital hip dysplasia, when other features of aEDS arepresent. Identifying this variant with aEDS will assist with diagnostic clarification and enhance our understandingof the function of type 1 procollagen.

C0024 CHONDRODYSPLASIA PHENOCOPY AND SHORT STATURE IN CHILDREN AFTER EARLY HAEMATOPOIETIC STEM CELL TRANSPLANT FOR NON-ONCOLOGIC AND ONCOLOGIC DISORDERS.

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Introduction: Skeletal dysplasias (chrondrodysplasias) are individually rare genetic disorders of skeletal development that usually result in disproportionate short stature and more frequently now have an identified genetic cause. Paediatric haematopoietic stem cell transplant (HSCT) is associated with growth failure and some children with non-oncologic disorders (mainly hemophagocytic lymphohistiocytosis) have been described with a genetic-negative chondrodysplasia phenocopy after early HSCT.
Aims: We present a relatively large paediatric cohort with both non-oncologic and oncologic disorders after early HSCT with short stature and radiological findings of a chondrodysplasia.
Cohort & methodology: Total 14 children, 5/14 with an oncological diagnosis. Current age 8-15 years and all >5 years after their first HSCT, which was completed within the first 5 years of life and all had only chemotherapy conditioning except one required additional myeloablative total body irradiation. There was no evidence of chondrodysplasia prior to their primary disease diagnosis. The current height Z-score is either <-2.5 or <-2 SD below the mid-parental height.
Results: Findings include: abnormalities of the iliac crests (irregularity and/or laciness), vertebrae (mostly platyspondyly), metaphyses (mainly irregularity and striations), and epiphyses (dysplasia). In 13/14, at least two areas have a significant radiographic abnormality. Two patients have been established on growth hormone for growth hormone deficiency but shown an unusually poor response to treatment.
Conclusion: We present the largest case series of children with chondrodysplasia phenocopy and growth failure after early HSCT. This case series uniquely describes the chondrodysplasia in children with both oncologic and non-oncologic disorders. Although some primary disorders are associated with a skeletal phenotype, this chondrodysplasia phenocopy is not characteristic of these conditions, is acquired, and shows a similar pattern across all cases. Although the aetiology of a HSCT-associated chondrodysplasia phenocopy is unknown, better characterising this entity could help contribute to patient information prior to HSCT, understand risk factors for it's development, and predict response to other therapies, such as growth hormone. Our next steps include investigating the prevalence in our patient cohorts and measuring patient-reported outcome measures.

C0101 ARTIFICIAL INTELLIGENCE IN DIFFERENTIAL DIAGNOSIS, BONE AGE ASSESSMENT, AND MONITORING OF SKELETAL DYSPLASIAS.

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Introduction: Artificial intelligence (AI) algorithms are already in use in some clinical settings, however, there is still a lot of room for improvement, especially in the field of rare diseases and mainly due to the inherent training data scarcity in this field.
Aims: In this contribution, we first present Deeplasia, our open-source bone age (BA) assessment AI that we specifically validated on patients with different skeletal dysplasias (SDs). Next, we present our Bone2Gene project on developing an AI for recognizing and differentiating characteristic radiographic patterns in patients with different SDs.
Cohort & methodology: For Deeplasia, we trained several convolutional neural network models and chose three to build an accurate ensemble. We used the BA dataset from the Radiological Society of North America (RSNA), comprising 12,611 training, 1,425 validation, and 200 test hand and wrist X-ray images. To evaluate Deeplasia's effectiveness on dysplastic hands, we retrospectively gathered 568 X-rays from 189 patients with molecularly verified diagnoses of seven distinct genetic bone conditions, among them achondroplasia and hypochondroplasia. To evaluate the performance of Deeplasia for patient monitoring, we used a subset of the dysplastic cohort (149 images) and estimated the test–retest precision on longitudinal data. Next, for developing Bone2Gene, we added four more genetic conditions to the cohort. To cope with data scarcity, we employ a technique called transfer learning in which we fine-tune Deeplasia for the task of classification of different SDs with only slight changes to the architecture.
Results: The mean absolute error (MAE) of Deeplasia for the RSNA test set (with six references) and the dysplastic set (with two references) is 3.9 and 5.8 months, respectively. The test–retest precision of Deeplasia on longitudinal data is estimated to be below 2.7 months. For the classification task, our preliminary Bone2Gene classifiers achieve a mean accuracy of 57% (for 11 distinct classes).

Conclusion: We show that our open-source AI, Deeplasia, is capable of accurately determining the age and tracking the growth of both normal and dysplastic bones. Furthermore, the promising results from our preliminary classifiers indicate that Bone2Gene is on the right path to becoming an AI assistant for accelerating referrals and differential diagnosis of SDs.

Session 5: Novel treatments and repurposing of treatments of skeletal dysplasias

Moderators
Ravi Savarirayan & Sergio Sousa

C0017 VOSORITIDE INCREASES GROWTH IN CHILDREN WITH HYPOCHONDROPLASIA: PHASE 2 TRIAL RESULTS.

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Introduction: Hypochondroplasia is a rare skeletal dysplasia resulting in disproportionate short stature and is due to activating variants in FGFR3. Vosoritide, a C-type natriuretic peptide analog, was recently approved for increasing linear growth in children with achondroplasia. This is the first study to examine the safety and efficacy of vosoritide in children with hypochondroplasia.
Aims: To describe the change in growth velocity and hypochondroplasia specific height SDS after 1 year of therapy with vosoritide.
Cohort & methodology: This is a prospective, Phase II study of vosoritide in children with hypochondroplasia. Twenty-six pre-pubertal subjects with hypochondroplasia enrolled in the trial (23 with the Asn540Lys mutation). Two subjects dropped out during the observation period. Mean (SD) age at screening was 5.9+2.3 years. Fifty percent of subjects were female. Subjects were followed for a 6-month observation period to establish a baseline annualized growth velocity (AGV) and then received daily subcutaneous vosoritide (15 mcg/kg/day) for 12 months. Hypochondroplasia specific height SDS were calculated using data from recently published European hypochondroplasia growth curves.
Results: We previously reported that AGV increased by a mean of 1.81 cm/yr during the intervention versus observation period (95% confidence interval 1.16-2.46), p<0.0001. This change corresponds to an increase in

age and sex adjusted AGV Z-score of +2.26 SD. The mean baseline hypochondroplasia specific height SDS was -0.41+0.76 SD. It increased by a mean of 0.03 SD (95% CI -0.12-+0.19) during the 6-month observation period versus a mean increase of 0.41 SD (95% CI 0.32-0.50) during the 12-month intervention period for a mean difference of 0.38 SD (95% CI 0.20-0.55), p<0.0001.
There were no serious adverse events related to vosoritide treatment. Injection site reactions were common (83% of subjects) but mild. No subjects discontinued therapy due to an adverse event.
Conclusion: This is the first clinical trial of vosoritide for children with hypochondroplasia. We demonstrate similar efficacy of vosoritide in children with hypochondroplasia to what has been seen in children with achondroplasia. Vosoritide improved hypochondroplasia specific height SDS. There were no new safety signals.

This study was funded by an investigator-initiated grant from BioMarin.

C0022 VOSORITIDE IMPROVES GROWTH IN RASOPATHIES, ACAN AND NPR2 DEFICIENCY: PRELIMINARY DATA FROM A PHASE 2 TRIAL.

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Introduction: Vosoritide is a CNP analog that binds its receptor on chondrocytes, promoting growth by inhibiting the ERK1/2-MAPK pathway.
Aims: To assess the safety and efficacy of vosoritide in children with various genetic causes of short stature including Noonan syndrome, aggrecan (ACAN) deficiency, heterozygous NPR2 mutations, and NF1.
Cohort & methodology: Phase II study including prepubertal children with a genetic variant in one of the above categories and height ≤-2.25 SD. Subjects are followed for 6-month observation period to establish baseline annualized growth velocity (AGV) and then receive daily vosoritide (15 mcg/kg/day) for 12 months. The primary outcomes are change in AGV and height SD from baseline and rate of AEs.
Results: To date, 24 subjects have enrolled in the trial (9 ACAN, 7 Noonan, 7 NPR2, 1 NF1). Mean age is 7.0 years (range 3-11), with 7/24 subjects being female. Mean baseline height is -3.1 SD. 14 subjects have initiated on vosoritide, 10 have completed 6 months of therapy, and 8 have completed 12 months of therapy. For the 8 subjects who completed 12 months of therapy, mean AGV increased from a baseline of 3.7 cm/yr to 8.5 cm/yr at 12 months. Mean height SD changed from -3.6 to -2.9 during 1 year of treatment. Three subjects with NPR2 mutations had increases of 3.3, 4.8 and 9.3 cm/year; three with Noonan syndrome had increases of 3.0, 4.0 and 5.8 cm/year, and two with ACAN mutations had increases of 3.2 and 5.4 cm/year in their AGVs.
Vosoritide was well tolerated, and no subjects discontinued participation due to AEs. There were no serious AEs related to treatment. Four subjects developed scoliosis that was potentially related to treatment (3 Grade 1, 1 Grade 2). Two subjects developed worsening genu valgum requiring intervention.
Conclusion: Vosoritide treatment showed marked improvement in AGV and height SD in all patient categories. It was overall well tolerated. It is unclear if genu valgum and scoliosis AEs are related to treatment, associated rapid growth, or underlying risk for genetic condition.
This study was funded by an investigator-initiated grant from BioMarin.

C0021 NEW TREATMENTS FOR CHILDREN WITH ACHONDROPLASIA.

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Introduction: Achondropalsia is the most common heirtable form of dwarfism, caused by gain of function FGFR3 pathogenic variants. It is estimated to affect over 300,000 people worldwide. The treatment of this condition has been symptomatic until recently.
Aims: The Aim of this talk will be to summarize the ongoing clinical trials and data of the new disruptive therapies that are approved or in developmnent for the treatment of children with achondroplasia. These will include vosoritide, navepegritide, infigratinib, and SAR442501.
Cohort & methodology: The talk will also look at the challenges for future trials in children with achondroplasia and related FGFR3 skeletal dysplasia

C0133 TRANSCON CNP (NAVEPEGRITIDE) IMPROVES PHYSICAL FUNCTIONING AND WELL-BEING IN CHILDREN WITH ACHONDROPLASIA (ACH) IN THE ACCOMPLISH TRIAL.

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Introduction: Clinical manifestations of ACH are associated with significant, potentially life-threatening complications and reduced health-related quality-of-life (HRQoL). While ACH has historically been considered a growth disorder, manifestations beyond linear growth include reduced muscle strength and stamina and suggest that ACH also impacts muscular function. Further, there is significant unmet need for interventions that ameliorate complications and improve HRQoL. TransCon CNP is a prodrug of C-type natriuretic peptide (CNP) under investigation for the treatment of ACH.
Aims: A 1-year analysis from ACcomplisH, a phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial of once-weekly TransCon CNP versus placebo in children with ACH, is presented here.
Cohort & methodology: Prepubertal participants (2-10y) were randomized 3:1 to receive TransCon CNP across 4 dose-escalation cohorts, or placebo for 52 weeks, after which participants could receive TransCon CNP in an open-label extension. HRQoL assessments compared 52-week results from participants whose initial TransCon CNP dose was 100µg/kg/week with results from the pooled placebo group in the randomized period. P-values are nominal. Safety was reported for all participants over the entire study duration.
Results: 57 participants (mean age [SD], 5.9y [2.8]; 42% ≥5y; 42% female) were enrolled; 100% continued into the open-label extension. Significant

improvements were observed for Daily Living Functioning (p=0.047; n=16;13 [treated;placebo]) and Emotional Well-Being (p=0.045; n=13;9) domains of the Achondroplasia Child Experience Measure-Impact assessment, and the SF-10 Physical Summary among participants ≥5y (p=0.002; n=9;5). Growth across the full trial population (n=57) on TransCon CNP 100µg/kg/week for 52 weeks was consistent with results from this dose cohort during the randomized period. Overall, there were no safety signals; no treatment-related serious adverse events (AEs) were reported. Most treatment-emergent (TE)AEs were Grade 1-2; no TEAEs led to treatment modifications or death. No trends were observed in ACH-related AEs.

Conclusion: Participants who received TransCon CNP 100µg/kg/week demonstrated significant improvements in well-being and physical functioning at 52 weeks. Once-weekly TransCon CNP continues to offer clinical benefits with a favorable safety profile. These results support continued development of TransCon CNP for ACH and further elucidation of the mechanisms by which TransCon CNP can potentially improve outcomes beyond linear growth, including radiological endpoints, HRQoL, physical functioning, and body composition.

C0146 TYRA-300 DEMONSTRATES SIGNIFICANT INCREASES IN BONE LENGTH IN TWO MOUSE MODELS OF FGFR3-RELATED SKELETAL DYSPLASIA.

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Introduction: Achondroplasia (ACH) is the most common human skeletal dysplasia affecting ~1 in 25,000 births. Infants with ACH have an increased risk for death related to critical foramen magnum stenosis leading to cervicomedullary compression. A specific mutation in FGFR3, G380R, causes approximately 99% of achondroplasia. FGFR3 is expressed in growth plate chondrocytes where it functions to disturb endochondral bone formation. The G380R mutation, as well as other activating mutations, results in increased FGFR3 activity, which disrupts chondrogenesis in the growth plate, disturbing long bone elongation. Vosoritide, a C-natriuretic peptide analogue, acting exclusively on the MAP kinase pathway, was approved as a daily injection to increase annual growth velocity in children with open growth plates. While an important breakthrough, long-term effects on ACH-associated comorbidities are not yet known. Hypochondroplasia (HCH) is a milder condition characterized by rhizomelic short stature, most commonly caused by an FGFR3 N540K mutation. TYRA-300 is an oral, highly selective FGFR3 tyrosine kinase inhibitor currently undergoing a Phase 1 clinical trial, SURF301 (Study in Untreated and Resistant FGFR3+ Advanced Solid Tumors). To explore the effectiveness of TYRA-300 in FGFR3-related chondrodysplasias, TYRA-300 was evaluated in an $Fgfr3^{Y367C/+}$ mouse model which mimics the phenotype of ACH. TYRA-300 administered daily at a 1.2 mg/kg dose for 15 days in the $Fgfr3^{Y367C/+}$ mouse model increased body length by 17.9% compared to the vehicle ($p<0.0001$) and increased the length of the femur (+22.6%), tibia (+33.0%) and L4-L6 (+23.5%) ($p<0.0001$). mCT analyses showed an increase of the foramen magnum area (+15.08%) in TYRA-300 treated $Fgfr3^{Y367C/+}$ mice compared to vehicle treated mice ($p<0.0001$). Histological staining of the femurs revealed restoration of the hypertrophic zone and secondary ossification center within the epiphysis after TYRA-300 treatment. Collagen X staining also indicated that TYRA-300 improved the structure of the trabecular bone and increased chondrocyte differentiation. TYRA-300 was also evaluated in an $Fgfr3^{N534K/+}$ mouse model of HCH. Treatment with TYRA-300 also resulted in statistically significant increases in bone length in this model. These data demonstrated that inhibiting FGFR3 directly led to significantly increased bone lengths in these two independent FGFR3-driven preclinical models.

C0015 PRECLINICAL AND CLINICAL STUDY OF UMEDAPTANIB PEGOL (ANTI-FGF2 APTAMER) IN ACHONDROPLASIA.

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Introduction: Achondroplasia (ACH) is the most prevalent genetic form of dwarfism in humans, caused by activating mutations in FGFR3 tyrosine kinase. The clinical need for safe and effective inhibitor of FGFR3 is unmet, leaving ACH an incurable condition.
Aims: We evaluated umedaptanib pegol (anti-FGF2 aptamer) developed to neutralize the FGFR3 cognate ligand, FGF2, for its activity against FGFR3 in ACH.
Cohort & methodology: Preclinical: The effect of umedaptanib pegol on the abnormality induced by FGFR3 signaling was investigated in cultured chondrocytes, cartilage xenografts derived from ACH human iPS cells and ACH mouse model. Clinical: The phase 1 study was conducted to evaluate safety and pharmacokinetics (PK) of umedaptanib pegol in 24 healthy Japanese male volunteers (20-45 years of age) at a single (0.1-1.0 mg/kg) or two subcutaneous doses (0.1-0.6 mg/kg). The phase 2 study was preceded by an observational study in ACH patients (5-14 years old) and followed by the early phase 2 study at dosing of 0.3 or 0.6 mg/kg at an interval of 1 to 4 weeks.
Results: Preclinical: In cultured chondrocytes and cartilage xenografts derived from ACH human iPS cells, umedaptanib pegol rescued the abnormality induced by FGFR3 signaling. When delivered by subcutaneous injection, umedaptanib pegol restored defective skeletal growth in an ACH mouse model (Sci. Transl. Med., 13:eaba4226, 2021). Clinical: The PK after subcutaneous administration of umedaptanib pegol was generally linear at doses ranging from 0.1 to 1.0 mg/kg, and it was confirmed that both tmax and t2/1 were almost constant over this dose range. In the safety and tolerability evaluation, an acute anaphylactic reaction was observed in one subject at a single dose of 1.0 mg/kg of umedaptanib pegol, which was resolved quickly upon treatment with the drug and therapy. No other clinically significant abnormal findings were observed. In phase 2 study, up to now (March 2024), there appeared no safety concern in six patients who received more than 100 administrations in total.
Conclusion: We demonstrate a ligand-trap concept of targeting the cartilage FGFR3 in ACH mouse and cell models. The safety and tolerability of subcutaneous administration of umedaptanib pegol at doses ranging from 0.1 to 0.6 mg/kg up to twice with an interval of 1 or 2 weeks were not of particular concern in clinical trials.

C0076 SNAIL IN THE CONTROL OF BONE LENGTH: A NEW THERAPEUTIC TARGET FOR ACHONDROPLASIA.

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Introduction: Achondroplasia (ACH) stands out as the most frequent skeletal dysplasia in humans, resulting in disproportionate short stature. The skeletal manifestations encompass a spectrum of alterations of varying severity, significantly impacting the quality of life. This condition arises from activating mutations in the Fibroblast Growth Factor Receptor 3 gene (FGFR3), the main regulator of bone development and growth. With a prevalence of 1 case per 10.000-30.000 live births, although its inheritance pattern is autosomal dominant, 80% of cases are due to sporadic mutations.
Despite its classification as a rare disease, considerable efforts have been dedicated to developing effective treatments. The recent approval of Vosoritide (VOXZOGO; BioMarin International Limited) marks a milestone, as it inhibits the MAPK/ERK branch of the FGFR3 pathway. However, not all patients respond favourably to this treatment, and its instability and costliness presents a barrier to accessibility. Therefore, identifying additional targets to inhibit FGFR3 signalling holds broad importance for advancing ACH treatment strategies.
Our previous research has highlighted the role of Snail1, an epithelial-mesenchymal transcription factor, as a key transcriptional effector of FGFR3 in bone. Snail1 influences both branches of the pathway, regulating chondrocyte proliferation (STAT1) and differentiation (MAPK/ERK). Moreover, we demonstrated that inhibiting Snail1 attenuates the aberrant activity of the mutant FGFR3 in achondroplasic chondrocytes. We will show in vivo data confirming that Snail1 holds promise as a good therapeutic target for Achondroplasia.

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Session 6: Other topics

Moderators
Virginia Fano & Cristina Alves

C0039 PAIN REHABILITATION OF PATIENTS WITH A SKELETAL DYSPLASIA DIAGNOSIS – HOW TO TAKE CARE OF THEIR SPECIAL NEEDS AND AT THE SAME TIME USE EXISTING PROGRAMMES.

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Introduction: Adults with rare skeletal dysplasias can be in need of rehabilitation due to pain, fatigue, high surgical burden, and loss of function. However, there are few programmes specially designed for persons with rare disorders, and the programmesoffer rehabilitation based on standard of care (e.g. chronic pain, post-surgery, etc.). Due to the rarity of their condition, such patients rarely encounter others with the same diagnosis. Additionally, most healthcare workers at rehabilitation centres have limited knowledge about skeletal dysplasia diagnoses.
Aims: The aim of this study is to investigate the feasibility of integrating a group of patients with a skeletal dysplasia diagnosis and chronic pain in an existing enhanced pain rehabilitation program with additional resources from the National Resource Center for Rare Diagnoses (TRS).
Cohort & methodology: Two groups, each consisting of 8 patients with rare skeletal dysplasias, were included as subgroups of larger groups of pain patients and scheduled to follow an ordinary rehabilitation programme. TRS contributed with educating staff at the Rehabilitation Centre about the different diagnoses, and giving advice and guidance during the entire rehabilitation process. In addition to the ordinary

teaching programme, TRS had three lectures with the patient groups, focusing on topics especially relevant for people with skeletal dysplasia. Staff from TRS also joined 4 group therapy sessions. We evaluated this project both qualitatively,interviewing both patients and staff, and quantitatively.
Results: Preliminary data show that participants report a positive change on several variables and are quite satisfied with this form of collaboration. They especially appreciated the possibility of rehabilitation together with other patients with a similar diagnosis. Further data on the feasibility of the programme and compliance will be presented.
Conclusion: Preliminary results suggest that it is feasible and expedient to integrate a group of patients with a rare skeletal dysplasia diagnosis in ordinary rehabilitation programmes, and at the same time take care of the special needs of this group.

C0083 MINDFUL SELF-COMPASSION TO REDUCE PAIN INTERFERENCE AMONG ADULTS WITH OSTEOGENESIS IMPERFECTA: A PILOT STUDY.

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Introduction: Between 60-80% of adults with osteogenesis imperfecta (OI) experience chronic pain which can profoundly disrupt functionality and quality of life. Moreover, individuals with OI have significant pain interference compared to the general population. Currently available pain therapies often provide marginal efficacy, and may contribute to individuals seeking pain management through unsafe means.
Aims: Mindful self-compassion (MSC), rooted in self-kindness, common humanity, and mindfulness, has emerged as a promising intervention for coping with chronic pain among adults with chronic pain due to a variety of etiologies. The aim of the study is to assess the feasability of employing MSC to address pain in adults with OI.
Cohort & methodology: We conducted an 8-week pilot study to assess the feasibility of the MSC program among adults with OI and co-occurring chronic pain. Individuals attended the validated MSC course, which consisted of 8 virtual 2-hour session given by two trained MSC teachers. Participants completed a battery of validated questionnaires to assess pain and various aspects of wellbeing and physical function at baseline and post intervention. Participants wore the ActiGraph GT9X watch during the first and last week of the intervention to measure sleep duration and sleep efficiency.
Results: Seven adults with OI and co-occurring pain participated in the MSC program (2 males, 4 females, 1 gender fluid; 5 individuals with OI type I, 2 OI individuals with type IV). The program was feasible, as indicated by high attendance (86%) and high questionnaire completion rates (<2% unanswered questions). While our pilot study was not powered to show efficacy, we observed a decrease in pain interference on the PROMIS pain interference questionnaire (mean 55.9 ± standard deviation [SD] 5.5 at baseline vs 50.0 ± 7.3 at 8 weeks, Cohen's d=0.9, p value <0.05), and an increase in self-compassion on the self-compassion scale (median 3, range 2.6-3.9 at baseline vs 3.5, range 3-4.3 at 8 weeks, Cohen's d=0.85, p value <0.05). Using actigraphy to measure sleep in adults with OI was feasible, with sleep data being successfully collected and confirmed

against sleep diaries from all participants.
Conclusion: Implementation of MSC is feasible as therapeutic option to address chronic pain in OI

C0106 SKELETAL DYSPLASIA PATIENTS UNDERGOING CERVICAL SPINE FUSIONS HAVE SIMILAR RE-OPERATION RATES REGARDLESS OF POST-OPERATIVE BRACING AND FUSION TO THE OCCIPUT.

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Introduction: Skeletal dysplasia patients often have cervical stenosis and cranio-cervical instability. These patients may undergo cervical and occipital-cervical spinal decompressions and fusions to improve craniovertebral junction instability and mitigate neurologic symptoms. We hypothesize skeletal dysplasia patients with neurologic deficits can recover after improving cord instability, while instrumentation is reliable in these patients without high risk of fixation failure. We further hypothesize fusion to the occiput results in a lower reoperation rate, while post-operative bracing doesn't affect reoperation rate.
Aims: Our study evaluates the efficacy of occipital-cervical and cervical fusions in improving skeletal dysplasia patients' baseline neurologic deficits and whether fusing to the occiput and postoperative bracing influence reoperation rate.
Cohort & methodology: A retrospective review of skeletal dysplasia patients who underwent cervical or occipital-cervical decompression and fusion was performed. All patients required a 2-year minimum for long-term follow-up visit data. Outcomes included radiographic evidence of fusion, re-operation rate, and neurologic course as measured by Barthel index. Chi-squared tests compared outcomes between patients who underwent cervical vs. occipital-cervical fusion and patients who braced vs. did not brace post-operatively.
Results: 16 patients with a mean age of 27 years were included. Our patients had achondroplasia, chondrodysplasia punctata, spondyloepiphyseal dysplasia, osteogenesis imperfecta, Morquio Syndrome, and Hurler Syndrome. All patients showed adequate fusion at latest follow-up; none showed signs of fixation failure. Amongst patients with measurable Barthel indices, the average Barthel index was 54 pre-operatively, 55.5 post-operatively, and 52.7 at long-term follow-up. The overall re-operation rate was 45%. Types of post-operative bracing included C-collars and Halo bracing. Chi-squared tests revealed no statistically significant differences in re-operation rates between occipital-cervical and cervical fusion and bracing and non-bracing patients (p=0.76; 1.000).
Conclusion: Cervical and occipital-cervical decompressions and fusions may aid skeletal dysplasia patients in improving neurologic function relative to baseline but seem to prevent significant neurologic worsening more definitively. Instrumentation is reliable in these patients with no signs of fixation failure or pseudoarthrosis in our cohort. Fusion to the

occiput and post-operative bracing do not decrease rate of re-operation. Cervical stenosis and instability in these patients can be adequately addressed with internal fixation.

Session 7: Care and monitoring of skeletal dysplasia patients

Moderators
Melita Irving & Lucia Sentchordi

C0114 REAL-WORLD SAFETY AND EFFECTIVENESS OF VOSORITIDE TREATMENT IN ACHONDROPLASIA CHILDREN: PORTUGUESE EXPERIENCE.

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Introduction: Achondroplasia (ACH) is the most common cause of disproportionate short stature and is caused by constitutive activation of FGFR-3. Vosoritide is a CNP analogue that leverages the CNP pathway to counteract overactive FGFR-3 signaling and stimulate endochondral bone growth. In August 2021, the European Medicines Agency (EMA) approved Vosoritide (daily subcutaneous injection, 15 µg/kg) for patients aged ≥2 years with ACH and open growth plates. In Portugal, children are being treated under an early access program.
Aims: To characterize growth (OMS curves) and evaluate treatment compliance and adverse events of patients with ACH receiving Vosoritide in our center.
Cohort & methodology: In this work, we performed a retrospective cohort study from January 2022 to March 2024 of children treated with Vosoritide. Our team adapted the French monitoring protocol previously implemented.
Results: We report 26children (11F:15M) with mean age of treatment initiation of 7,3 years (2-14Y). There were antecedents of foramen magnum

decompression in seven cases and non-invasive ventilation in seven cases.
The mean annualized growth velocity (AGV) of the 23 children who completed 12M of treatment was 5.7 cm/year [1.2-8.8] with mean OMS z-score variation of +0,2 SD [-0.41-+0.82]. Of these, eight children completed 24 months of treatment:AGV was 5.8 cm/year [2.2-7.6] and z-score variation +0.3 SD [-0.12-+0.95]. From the patients with poorer response, two reached final height and stopped treatment. Besides injection site reactions, adverse events were reported in a reduced number of children: hypotension (n=1), vomit (n=1) and hypertrichosis (n=1). No serious adverse events were noticed.
Conclusion: Our data indicates that Vosoritide in real-world conditions has a safety profile in accordance with clinical trials outcomes. The data on the overall cohort points to a slightly smaller effect on height than reported and a wider variability in response. This may be related to the heterogeneity of the cohort, which included children with complications, sequela and different age groups. We are exploring more detailed evaluations by subgroups. Patients and families demonstrated good adherence. It is crucial that vosoritide treatment is integrated in a multidisciplinary thorough follow-up and that we collect data on real-world larger cohorts.

C0094 EARLY REAL-WORLD EXPERIENCE WITH VOSORITIDE TREATMENT IN ACHONDROPLASIA: A SINGLE-CENTER REPORT FROM TURKEY.

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Introduction: Vosoritide, a C-type natriuretic peptide analogue, has emerged as the first therapeutic agent approved to enhance growth velocity in individuals with achondroplasia (ACH).
Aims: To assess growth response to vosoritide in children with ACH under the care of a specialized MDT.
Cohort & methodology: A retrospective study was conducted at Acibadem University, Istanbul, focusing on children diagnosed with ACH who received treatment with once-daily subcutaneous doses of 15 µg/kg vosoritide. Children enrolled in the study underwent MDT visits every three months, during which QoL assessment, monitoring of medical complications, anthropometric measurements, and adverse event surveillance were conducted. All collected data were analyzed, and SDS were calculated using ChildMetrics based on Turkish growth standards.
Results: The cohort in our outpatient clinic comprised of 68 individuals (34 girls). Median age at presentation was 1.6 years. Off-label use permission was sought from the Ministry of Health for 42 patients [median age was 4 years (IQR 2.1-6.9, 6 months – 12.0 years]. Treatment initiation was granted for 22 patients [median age at onset of 5.0 years (IQR 2.9-9.1)]. 60% were aged between 2-4 years, 25% between 5-7 years, and 15% between 8-12 years. Twenty patients were prepubertal. The first vosoritide dose was on September 27th, 2022. As of March 2024, the median treatment duration is 10.9 months. Among patients who completed the 6-months (n=16), the initial and 6th month height SDS were -5.13±0.84 and -4.98±0.87, respectively (p=0.035). For those who completed the first year (n=7), initial and 1st-year height SDS were -5.10±1.00 and -4.87±1.00, respectively (p=0.043). BMI SDS, sitting height/height ratio, and arm span-height difference showed no statistically significant change. Notably, no vosoritide-related adverse events were observed in any of the patients.
Conclusion: We present the early real-world data from the first and yet largest achondroplasia cohort treated with vosoritide in Turkey. As with previous studies discuss early real-world experience, we believe data across diverse populations will improve clinical practice worldwide. Despite effectiveness in promoting growth among children with achondroplasia, uncertainties persist regarding its impact on final adult height and other co-morbidities.

C0055 UNDERSTANDING THE IMPACT OF ACHONDROPLASIA ON FUNCTIONING AND WELL-BEING: VALIDATION OF THE ACHONDROPLASIA CHILD EXPERIENCE MEASURE–IMPACT (ACEM–IMPACT).

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Introduction: Research on the impacts of achondroplasia on children's functioning and well-being is limited and findings are inconsistent, often due to generic measures used to assess these impacts.
Aims: The purpose of the study was to psychometrically validate the ACEM–Impact, a child achondroplasia-specific impact measure, developed according to FDA guidelines for observer-reported outcome measures.
Cohort & methodology: Parents of children with achondroplasia were assessed. First, data from a noninterventional, observational, web-based survey (N=200) were analyzed to determine factor structure, reliability, convergent and known groups validity. Analyses were then repeated using data from a phase 2, multicenter, double-blind, randomized, placebo-controlled trial (N=57). Based on these findings, the final ACEM–Impact was generated.
Results: Factor analysis resulted in a 25-item, 6-domain measure assessing Daily Living Functioning, Physical Functioning, School Functioning, Social Functioning, Social Well-being, and Emotional Well-being. Internal consistency reliabilities were satisfactory, with domain values ranging from 0.76-0.93 and 0.86 for the total score. Test-retest reliability for the total scores was adequate for both the observational and trial samples (total 0.76, 0.79 respectively) with domains ranging from 0.65-0.82. Correlations for a priori hypothesized convergent validity relationships for the total scores were also satisfactory (moderate: r = 0.30-0.49 to strong: r > 0.50) in both the observational and the clinical trial samples and for domains, adequate in either or both samples. All known groups a priori hypotheses for total and domains were found to be statistically significant ($P \leq 0.05$) with the exception of the school functioning domain, which was significant only in the observational sample. Of note, there was a statistically significant relationship with SF-10 scores for both the SF-10 Physical Summary score ($P < 0.0001$) and Psychosocial Summary score ($F = 19.92$, $P < 0.0001$) such that those with better quality of life had better total ACEM–Impact scores.
Conclusion: The study provides evidence to support the reliability and validity of the ACEM–Impact as a scientifically sound measure of the impact of achondroplasia on children's daily functioning and well-being. Understanding and assessing the impacts of achondroplasia, which may be improved with treatment, is critical in the clinical management of achondroplasia as new treatments are being developed.

C0027 BODY COMPOSITION BY BIOELECTRICAL IMPEDANCE ANALYSIS (BIA) IN ADULTS WITH ACHONDROPLASIA IN CLARITY (THE ACHONDROPLASIA NATURAL HISTORY STUDY).

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Introduction: Achondroplasia is the most common skeletal dysplasia (~1:20,000), with short limbs, macrocephaly, frontal bossing and foramen magnum constriction. Spinal stenosis, obstructive and central sleep apnea and genu valgus are complications potentially exacerbated by obesity. Body mass index (BMI, kg/m²) is linked to adiposity and health outcomes in average stature adults, but might not be appropriate for people with achondroplasia. We previously showed that BIA estimated body composition as well as dual X-ray absorptiometry.
Aims: In this study, anthropometry and BIA with conventional prediction equations were applied to free-living adults with achondroplasia to characterize body composition.
Cohort & methodology: Height, weight, and head, neck, waist, and hip circumferences were measured, and BIA performed (RJLQuantum4.0) at Little People of America meetings in 2023. Equations estimated fat free mass (FFM) and fat mass; percent body fat (%BF); BMI and fat mass index (FMI, kg/m²) were calculated.
Results: 52 individuals with achondroplasia enrolled. Of 44 adults (23F, 21M, respectively, throughout), mean±SD age was 46.8 ±18.0 and 48.0±16.3 years (P=0.81). Weight (54.3±3.4 and 57.4±2.5 kg); waist (83.8±3.6 and 87.6±3.3 cm) and hip (102.8±3.1 and 96.3±3.6 cm) circumferences; and BMI (37.0±2.2 and 33.1±1.4 kg/m2) were similar by sex (all P>0.05). Women were shorter (121.1±1.3 versus 131.6±1.1 cm, P<0.0001), with smaller head (59.2±0.6 versus 61.0±0.5 cm, P=0.01) and neck (35.0±1.0 versus 39.5±1.0 cm, P=0.004) circumferences and less FFM (31.9±1.2 versus 41.1±1.1 kg, P<0.0001), but more total fat (22.4±2.3 versus 16.3±1.6 kg, P=0.04), higher %BF (39.2±1.8 versus 27.1±1.8, P<0.0001), and higher FMI (15.2±1.6 versus 9.4±1.0 kg/m², P=0.003). %BF in achondroplasia was akin to that of average stature adults (39.6 % and 27.7 %), in whom FMI (11.7 and 8.1 kg/m²) and BMI (~28 kg/m², both F and M) were lower.
Conclusion: Among adults with achondroplasia, women had greater adiposity than men. %BF in this achondroplasia cohort was similar to typical average stature adults, but short stature exaggerated implied

adiposity using BMI or FMI. %BF calculated from BIA may represent adiposity well in adults with achondroplasia and could be correlated with health outcomes to establish weight goals in adults with achondroplasia, just as BMI is utilized in average stature adults.

C0137 THE PREVALENCE OF AUTISM AND NEURODEVELOPMENTAL DISORDERS IN A UK COHORT OF PATIENTS WITH ACHONDROPLASIA.

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Introduction: Achondroplasia is a genetic condition characterised by short limbed short stature and characteristic clinical and radiological features. It is the most common skeletal dysplasia arising in 1 in 20,000 to 30,000 live births. The developmental profile of these children is unique, owing to the anthropometric differences. These differences are mainly confined to gross motor aspects of development.
Hippocampal malrotation is a constant feature seen in achondroplasia and in the milder FGFR3-related condition hypochondroplasia. In hypochondroplasia, these temporal lobe change have been linked to learning disability, epilepsy and neurobehavioral disorders such as ADHD and ASD. In Achondroplasia however, such links are much less commonly described (Ismail et al, 2021), (Dy et al, 2019).
Aims: This study aims to determine the prevalence of ASD and neurodevelopmental disorders in children with Achondroplasia from UK reference centre cohort of over 200 children.
Cohort & methodology: All children seen within the Achondroplasia service at the Evelina Children's Hospital, London were included in the study. Records spanning 5 years (from 2019 to 2024 were reviewed retrospectively. Entries suggestive of neurobehavioural difficulties such as developmental delay, autism spectrum disorder, social communication difficulties and similar, were carefully examined and categorised.
Results: The results were analysed and compared to age matched UK general population data available in the literature.
Conclusion: Autism spectrum disorder is seen in a minority of children with achondroplasia in our cohort. The national and global prevalence of ASD is on the rise. This may be impacted by greater societal awareness and more access to neurodevelopmental assessments. This trend is also likely to be reflected in children with achondroplasia. Significant developmental delay is seen in a small proportion of our cohort. Further investigation into these cases is needed to determine whether this can be attributed to achondroplasia, or whether an additional diagnosis is likely.

2024 ISDS

C0145 LONG-TERM IMPACT OF PALOVAROTENE TREATMENT ON HETEROTOPIC OSSIFICATION VOLUME IN PATIENTS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA: DATA FROM THE PHASE III MOVE TRIAL.

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Introduction: Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare genetic disorder characterised by progressive heterotopic ossification (HO). The phase III MOVE trial (NCT03312634) evaluated palovarotene, a selective retinoic acid receptor-γ agonist, in FOP. Post hoc 18-month interim analyses showed palovarotene reduced new HO volume compared with patients untreated beyond standard of care in a natural history study (NHS; NCT02322255). Palovarotene was generally well tolerated with adverse events consistent with other systemic retinoids, but there was a high risk of premature physeal closure in paediatric patients.[1] Long-term (48?month) efficacy of palovarotene in patients who paused and restarted or stopped treatment in MOVE, due to a partial clinical hold in patients <14 years or dosing interruptions in patients ≥14 years, was evaluated.

Cohort & methodology: Mean annualised HO volume changes assessed by low-dose whole-body computed tomography (WBCT) were evaluated to trial completion. Analyses were performed for the MOVE intent-to-treat (ITT) period for: (i) all patients regardless of treatment status (compared with untreated patients from an FOP NHS), (ii) patients who paused and restarted treatment with data in pre-pause, interruption and post-restart periods (≥2 WBCT scans post-restart), and (iii) patients who paused and stopped treatment.

Results: In the ITT period, patients received palovarotene for a mean (standard deviation) of 25.4 (12.5) months and were off treatment for 13.1 (9.3) months. For all patients and for patients who paused and restarted treatment in the ITT period, HO volumes were lower when patients received palovarotene. When patients paused and stopped treatment (n=16), mean annualised new HO volume was 84.9% lower when patients received palovarotene (2.3×10^3 mm^3; mean follow-up: 12.6 months)versus when they did not (15.6×10^3 mm^3; mean follow-up: 15.7 months). When patients stopped treatment, annualised new HO did not exceed that in untreated patients from the NHS, suggesting no treatment rebound or withdrawal effect.

Conclusion: Long-term data from MOVE consistently showed lower annualised new HO volume when patients were treated with palovarotene versus when they were not. The results support previous post hoc findings on the use of palovarotene for reducing new HO. However, the risk-benefit profile of palovarotene should be reviewed on an individual basis.

2024 ISDS

C0067 PIK3CA RELATED OVERGROWTH SPECTRUM (PROS): PHENOTYPIC VARIABILITY IN 16 MOLECULARLY PROVEN PATIENTS AND RESPONSE TO SIROLIMUS.

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Introduction: Gain of function variants in PIK3CA causes a heterogenous spectrum of disease leading to segmental overgrowth or macrodactyly.
Aims: We describe an observational study from 2013-2024 detailing the phenotypic variability of segmental overgrowth in 16 mutation proven patients with PROS and the response to sirolimus.
Cohort & methodology: The male to female ratio was 3:1. Skin and subcutaneous tissue from the hypertrophied region were chosen for analysis in all patients except two, where brain and tumour tissue were used. The mosaic status in these patients varied from 2% to 27%.
Results: Macrodactyly was the most common presentation (12/16). Predominant involvement of lower limb was seen in 11/16 and upper limb only in 4/16.Significant hypertrophy of the cheeks was seen in 4/16 and hypertrophy of the gluteal region in 2/16.Syndactyly/polydactyly was evident in 5/16. His1047Arg in exon 21 was the recurrent mutation in 6/16 but there was no genotype phenotype correlation for any of the variants. In our cohort we had one patient each with Megalencephaly-Capillary Malformation (MCAP) and CLOVES. We also had an unusual presentation with C4 - C6 extradural lesion leading to cord compression with His1047Arg. Another unique presentation was a child with drug resistant epilepsy with left hemimegalencephaly with polymicrogyria and had undergone left hemispherotomy. Brain tissue was analysed and he had a variant in Glu542Lys. Only one patient had presented with macrocephaly consistent with MCAP. Capillary malformation was obvious in 6/16 and extensive nevus in 2/16.Three patients had seizure disorder. Cognitive impairment was evident only for 2 patients, (hemimegalencephaly and MCAP).
Nine patients are receiving Sirolimus due to the unavailability of Alpelizib in India. Plasma sirolimus levels were monitored and dose was adjusted according to a target serum levels of 2-4 ng/ml. Serial monitoring of the hypertrophied segment was performed by manual measurements for all. The longest duration of treatment period was 9 years.
Conclusion: No serious adverse effects were observed for the cohort who were treated with sirolimus. No significant overgrowth was observed after initiation of the treatment but there was no regression of prior overgrowth.

Keywords: PIK3CA, macrodactyly, segmental overgrowth, somatic mosaicism, sirolimus

C0113 GENOME SEQUENCING IN A COHORT OF 31 FETUSES WITH GENETIC SKELETAL DISORDERS.

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Introduction: Approximately 200 genetic skeletal disorders can present prenatally, detectable through abnormalities on ultrasound during pregnancy. Severe forms are typically identified by the end of the second trimester, while milder phenotypes are recognized in the third trimester. Diagnosing skeletal dysplasia prenatally presents many challenges due to the large number of disorders and limited phenotypic information ultrasound can provide.
Aims: This study, conducted at Karolinska University Hospital from 2015 to 2022, evaluates the efficacy of genome sequencing of 31 fetuses (14 females and 17 males from 31 unrelated families) with skeletal abnormalities detected on prenatal ultrasound and confirmed by radiographs at birth or after termination of pregnancy.
Results: DNA was isolated from amniocentesis, chorion villus biopsy during pregnancy, or fetal tissue post-termination, with gestational age between 12 to 29 weeks. Genome sequencing and gene panel analysis of 31 fetuses identified pathogenic or likely pathogenic variants in 21 cases, achieving a diagnostic yield of 68%. Additionally, five variants of uncertain significance were identified in five fetuses, which were strongly suspected as causative based on radiographic features and found in genes associated with the clinical condition. Overall, we detected 35 variants in 27 fetuses, 24 of those variants were previously unreported. Further trio analysis on the five fetuses with unsolved molecular diagnosis resolved one additional case. Four fetuses presenting with osteogenesis imperfecta, spondylocostal dysostosis, and severe metaphyseal osteosclerosis remain molecularly unresolved.
Conclusion: Our findings confirm that broad skeletal dysplasia panel testing can effectively diagnose fetal skeletal dysplasias in this cohort. The presence of phenotypic data is essential to assure diagnostic accuracy. Despite the high detection rate, unresolved cases still pose challenges in genetic counseling and current testing technologies.

Session 8: Genetic testing of Skeletal dysplasias

Moderators
Valerie Cormier-Daire & Karen Heath

C0044 10 YEARS' EXPERIENCE IN DIAGNOSING SKELETAL DYSPLASIAS BY NEXT-GENERATION SEQUENCING IN SPANISH AND PORTUGUESE PATIENTS.

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Introduction: Skeletal dysplasias (SDs) are a growing group of clinically and genetically heterogeneous disorders of cartilage and bone.
Aims and methods: We assessed the diagnostic yield of a customized Next-generation sequencing (NGS) panel (SkeletalSeq, Roche Nimblegen, V3-15) by a retrospective review of the SD patients referred during the period 2014-2024. Positive results included variants classified as

pathogenic, likely pathogenic or strong VUS related to the phenotype. Cases where only one variant for an autosomal recessive disorder, but which was strongly related to the patient´s phenotype, were also classified as positive.
Results: The cohort consisted of 2649 patients, 526 with short stature and minor skeletal anomalies (SS). A positive diagnostic result was obtained in 1252 (47%) cases, including 33 with CNVs and 5 with mosaic variants. A positive diagnosis was more likely identified in SD cases 1123/2123 (52.9%) rather than SS, 129/526 (24.5%). Diagnostic yield was also higher among fetal samples, 62/102 (60.7%). Interestingly, when we take only into account patients clinically and radiologically assessed by a multidisciplinary team, the diagnostic yield was significantly higher: 63.6% SD (283/445) and 81% fetal samples (17/21) compared to 35% SS (19/54). To reclassify VUS as pathogenic variants, several functional studies were performed: splicing assays (transcriptome, minigenes), luciferase-reporter assays or RNA expression studies in different tissues. Some of the identified variants were found in genes with very few previously reported pathogenic variants; eg. ALX3, BPNT2, GNPNAT1, IQCE, RAB33B, RIPPLY2, SGMS2, and ZSWIM6.
Conclusions: 1) In our experience, an updated customized NGS panel is still a good economic approach for the first-tier genetic diagnosis of SDs. The inclusion of regulatory regions, disease-causing non-coding exons, and deeper read depths offer advantages over the more commonly used WES virtual panels. CNV analysis is important to include and special attention to possible mosaicism in cases with a clinically well-defined SD with one or few candidate genes and prior negative results. 2) When possible, it is also important to complete the study of VUS by rapid functional studies using patient´s tissues or in vitro assays. 3) Patient evaluation by a multidisciplinary team results in a considerably higher detection rate.

C0048 SYSTEMATIC WES REANALYSIS AND RAPID FUNCTIONAL STUDIES IN A SKELETAL DYSPLASIA COHORT YIELD NEW DIAGNOSES.

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Introduction: Exome analysis (WES) is a pivotal tool for genetic diagnosis of skeletal dysplasias (SD). Despite its utility, the continual discovery of novel causal genes highlights the necessity for periodic re-evaluation of unresolved cases.
Aims: To combine WES reanalysis and rapid functional studies to enhance the diagnostic yield in a cohort of 53 SDs without diagnoses.
Cohort & methodology: Exome analysis (singletons/duos/trios) was performed using VarSeq (Golden Helix). Further genomic studies were also performed when necessary (SNP-arrays, breakpoint PCRs). Functional and/or transcriptomic studies were conducted using patient serum, lymphocyte RNA or in vitro minigene assays.
Results: A probable molecular etiology was elucidated in 16/53 cases (31%). Of these, 4 had variants in genes identified posterior to the initial analysis (MBTPS1, COLEC10, RPL13, EMILIN1) and 12 had newly identified or characterized variants in SD-associated genes. These included: 1) The identification of an intronic MYH3 variant, NM_002470.4:c.348+39A>G in a girl with multiple pterigium and vertebral synostosis in whom only one MYH3 variant had been previously identified. Although in silico predictions were negative, the variant resulted in aberrant splicing, thus confirming Spondyocarpotarsal synostosis syndrome with contractures and pterygia, MYH3-related. 2) We detected a splice site variant, NM_003791.4:c.2353+3A>G in MBTPS1, and a whole gene deletion in a boy with a spondyloepimetaphyseal dysplasia (SEMD). Functional studies confirmed the diagnosis of SEMD Kondo-Fu type. 3) In a child with severe pre- and postnatal bone fractures, we identified a homozygous pathogenic variant in EMILIN1 due to chromosome 2 uniparental isodisomy. 4) Loeys-Dietz syndrome was diagnosed in a patient with microcephaly and scoliosis and his similarly affected mother, who both had a missense variant in the last base of TGFB3 exon 5 which altered splicing. 5) We detected and delimited a hemizygous intragenic PLS3 duplication in a patient with bone fragility.

Conclusion: We advocate for routine WES reanalysis every 1-2 years to maximize diagnostic yield in unresolved cases. Secondly, rapid functional assays need to be incorporated into routine genetic diagnosis, so that variants of unknown significance can be reclassified as pathogenic and the patient's diagnosis can be confirmed.

C0011 RAPID ANALYSIS OF GENOMIC DATA TRANSFORMS MANAGEMENT OF INFANTS WITH SKELETAL DYSPLASIA.

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Introduction: Following the 100 000 Genomes Project in England the systematic introduction of whole genome sequencing (WGS) into healthcare via a national genomic test directory has enabled diagnosis for rare genetic disorders including many types of skeletal dysplasia. Rapid WGS for acutely unwell infants has had particular utility in influencing their clinical management and frequently, long-term outcome.

Aims: To improve and transform clinical care for infants with skeletal dysplasia and skeletal malformation syndromes by rapid genomic diagnosis.

Cohort & methodology: We reviewed referrals for rapid WGS between October 2022 and February 2024, in a single national provider laboratory, for infants who were acutely unwell and in whom the clinical presentation suggested a skeletal dysplasia or related condition. We determined the number and range of positive diagnoses made via comparison to a 422 relevant gene panel, identifying cases where WGS had a major clinical impact.

Results: Since the introduction of rapid WGS, 1577 genomes have been analysed, either as trios, duos or single cases. Of these, a positive diagnosis of skeletal dysplasia was found in 104 cases overall (~6.6%), 38 of these were new born infants in a neonatal intensive care unit, others were in paediatric intensive care or high-dependency wards. Results were communicated to referring clinical teams within a median of 9 days of sample receipt (range 4–27 days). For many patients the diagnosis marked a key change in management or treatment, examples include dysplasias arising through metabolic dysfunction, suspected ciliopathies, complex malformation syndromes and very rare disorders with limited published data. In some instances, infants presenting with predominant skeletal findings, such as multiple fractures, were found to have a primary neuromuscular or other disorder and this changed the direction of clinical care.

Conclusion: We conclude, illustrating with example cases, that rapid WGS provided through a national programme via a laboratory focusing on this service builds significant expertise within the clinical-laboratory interface, provides consistent and equitable access to rapid WGS for a large population and enables rapid and accurate diagnosis for enhanced patient management.

C0064 REVIEW OF 400 GENOME ANALYSIS FOR PATIENTS WITH OSTEOCHONDRODYSPLASIA IN THE NATIONAL FRENCH SEQOIA LABORATORY.

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Introduction: In 2018, a government-led genomic program was introduced in France, resulting in the creation of two national laboratories, namely SeqOIA and Auragen. Since then, SeqOIA laboratory has provided genome sequencing for 400 osteochondrodysplasia patients with either a negative targeted panel sequencing or in first line for atypical phenotype.
Aims: We present the results from this cohort.
Results: A diagnosis was reached in 124 patients (31%), 42 cases (10%) carried a variant of unknown significance, while 234 genomes were negative (59%).
Regarding the 124 positive genomes, 92 genes were involved, with a maximum of 5 patients carrying variants in the same gene (COL2A1, FGFR3, RPL13). 8 patients carried structural variants : 3 inversions, 3 large deletions, 1 large duplication and 1 translocation involving NSD1 gene . We also identified 5 deep intronic variants and 3 uniparental disomies. 4 double diagnoses were also made. Those findings highlight the benefit of the WGS approach.
Variants of uncertain significance, located in 38 different genes, encompass intronic variants, variants in genes not yet involved in human pathology, and variants of unknown significance currently studied at the functional level.
Conclusion: We conclude that whole genome sequencing has revolutionized the molecular diagnosis of osteochondrodysplasias, improving significantly the diagnostic yield. This advancement is particularly noteworthy as it enables diagnoses that were not accessible through panel or exome sequencing coupled with an array CGH.

C0124 MOLECULAR EVALUATION OF PATIENTS WITH SKELETAL DYSPLASIA AND DYSOSTOSIS THROUGH WHOLE GENOME SEQUENCING: A COHORT FROM BRAZILIAN RARE GENOMES PROJECT.

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Introduction: Osteochondrodysplasias (OCD) and dysostosis are a group of skeletal diseases with genetic heterogeneity. Next Generation sequencing advent has facilitated molecular diagnosis in this group of patients. The Rare Genomes Project (RGP) is a Brazilian project supported by the Ministry of Health aiming to shorten diagnostic odyssey of patients with rare diseases, giving them a faster diagnosis, using WGS as a tool. Currently, about 8,124 samples from patients with rare diseases were sequenced, including probands with OCD/dysostosis.
Aims: This presentation aims to report the preliminary molecular data from the cohort of patients with OCD/dysostosis.
Cohort & methodology: Patients' samples who were referred to RGP with clinical hypothesis of OCD or dysostosis were sequenced. PCR-free whole-genome sequencing (WGS) was performed on Illumina Novaseq 6000 equipment, and bioinformatic processing was performed using Dragen and in-house developed tools.
Results: 175 patients (89 males – 50.9%) with clinical hypothesis of OCD or dysostosis had their genome sequenced and the analysis completed. Median age was 9 years old (0-74 years). Most of the studied patients came from Southeast (51.4%), followed by Northeast region (43.4%). Molecular diagnosis was elucidated in 103 cases (58.9%), the result was negative in 41 (23.4%) and inconclusive in 31 patients (17.7%). Osteogenesis imperfecta (OI) contributed to 46.6% of the diagnosis (48/103). 16 out of 48 cases of OI were autosomal recessive (33.3%), while 32 autosomal dominant (66.7%); multiple exostosis contributed with 3.9% of the diagnosis (4/103), followed by campomelic, cleidocranial, COL2A1, FGFR3 dysplasia, spondylocostal dysostosis, fibrodysplasia ossificans progressive, GNAS-related dysplasia, each one contributing to 2.9% (3/103) of the molecular diagnosis. COL1A2 (17.5%), COL1A1 (11.6%) and FKBP10 (5.8%) genes were enriched in positive cases. All, but one variant (IFITM5: c.-14C>T), reported in positive cases were located in coding or splicing site regions (mainly canonical). One patient had a single EXT1 exon deletion which maybe could not be identified through other molecular techniques.
Conclusion: Preliminary results show a high diagnostic rate, expand diagnostic possibilities and knowledge about this group of skeletal diseases.

C0075 PRENATAL EXOME SEQUENCING IN CONSTITUTIONAL BONE DISEASES: A SERIES OF 47 CASES.

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Introduction: During pregnancy, ultrasound examinations reveal fetal developmental abnormalities in 3 to 5% of pregnancies, with constitutional bone diseases (CBD) accounting for 0.5% of these cases. In France, interdisciplinary bodies known as CPDPN are tasked with establishing the prognosis of particularly serious anomalies. In the context of bone diseases, the focus lies on assessing functional severity , as the neurodevelopmental prognosis for the unborn child is,most of the time, favorable. When severe skeletal features are detected early in the first trimester,the prognosis is usually severe, corresponding to lethal CBD . When skeletal features are non specific and identified later during pregnancy, genetic studies may help to make a the diagnose a CBD prior to the scheduled bone scan at 28 weeks of gestation. These genetic studies systematically include chromosomal microarray analysis (CMA), and since 2020, our center has been offering prenatal exome sequencing (PES) as well.
Aims: The aim of our study is to assess the benefits of PES in CBD
Cohort & methodology: From 2020 to March 2024, we conducted 47 prenatal exome sequencing (PES) analyses on cases with ultrasound evidence of bone anomalies and a negative CMA analysis.
Results: A molecular diagnosis was reached in 43% of cases (20/27). Pathogenic variants were identified in the following genes: DYNC2H1 (n=2),

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C0010 BIALLELIC LOSS OF FUNCTION VARIANTS IN FUZ RESULT IN AN OROFACIODIGITAL SYNDROME.

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Introduction: The FUZ (Fuzzy Planar Cell Polarity Protein) is essential for primary ciliogenesis. As a component of the CPLANE complex (ciliogenesis and planar polarity effector), it is involved in intraflagellar vesicular trafficking within primary cilia and plays a critical role in cell signalling such as Wnt and hedgehog signalling pathway. Only two affected individuals with skeletal dysplasia with the variants in ***FUZ***, c.98_111+9del and c.851G>T have been reported till date. The phenotypes of the affected individuals comprised a long, narrow chest, moderately short ribs, short long bones, and polydactyly of all four limbs, ventricular septal defect, hypoplastic kidneys, midline facial cleft, thickened nuchal fold and dilated third ventricle.
Aims: To describe two additional families with variants in FUZ gene and describe the FUZ-related orofaciodigital syndrome.
Cohort & methodology: Here, we describe two patients from two unrelated non-consanguineous Indian families, each with multiple affected fetuses. Exome sequencing was performed in the probands, followed by segregation analysis in their parents by Sanger sequencing.

Results: Common features among affected individuals from both families were digital anomalies (polydactyly, syndactyly), orofacial clefting, short ribs and cardiac defects. Proband 1, a nine-year-old girl, displayed distinctive facial features (prominent forehead, low set ears and broad nasal bridge), broad thumbs, clinodactyly, and polysyndactyly in feet, along with a partial atrioventricular canal defect. Proband 2, at 19 weeks of gestation was noted to have cleft lip, polydactyly (seven digits in both hands and feet), bilateral duplicated halluces and atrioventricular septal defect. These clinical findings recapitulate orofaciodigital syndrome. We observed a novel homozygous missense variant, c.601G>A p.(Glu201Lys) in proband 1. Proband 2 had compound heterozygous variants: a maternal in-frame deletion c.625_636del, p.(Val209_Leu212del) and a paternal missense variant c.601G>A, p.(Glu201Lys). In-silico analysis tools predicted these variants to be disease causing, resulting in loss of function of the FUZ protein.
Conclusion: Our report provides further evidence to implicate biallelic loss of function variants in ***FUZ*** in an autosomal recessive skeletal dysplasia resembling orofaciodigital syndrome.

C0023 EUROPEAN ACHONDROPLASIA FORUM PRACTICAL CONSIDERATIONS FOR FOLLOWING ADULTS WITH ACHONDROPLASIA - A PATIENT HELD CHECKLIST.

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Introduction: Achondroplasia is a lifelong condition requiring lifelong management. However, many people are lost to follow-up after the transition from paediatric to adult care, and there is no standardised approach for management in adults.
Often, people with achondroplasia are relatively healthy at the point of transition from paediatric to adult care; they may therefore feel no need to continue accessing regular medical care as a young adult. Achondroplasia does not necessarily require regular, routine check-ups in adulthood if people are feeling well.
Cohort & methodology: The European Achondroplasia Forum (EAF) has developed a patient-held checklist to support adults with achondroplasia in managing their health. Patient-held tools have been shown to increase adherence to guideline-based care, facilitate communication, and assist in the enhancement of handover and patient-centred practices for people with chronic conditions. The EAF checklist will support a systematic and structured way of monitoring on an opt-in basis, without stigma or unnecessary medical burden. It is intended to guide consultations and discussions, and to support and empower people to manage their own health.

Results: The checklist highlights key symptoms of spinal stenosis and obstructive sleep apnoea, the most frequent and potentially severe medical complications in adults with achondroplasia, and acts as a framework to support individuals and their primary care provider in completing routine review. General advice on issues such as blood pressure, pain, hearing, weight, adaptive aids, and psychosocial aspects are also included. The checklist provides key symptoms to be aware of, in addition to action points so that people can approach their primary care provider and be directed to the appropriate specialist, if needed.
Conclusion: The EAF propose that the checklist be delivered to young people with achondroplasia during the transition from paediatric to adult care. It will be important to communicate the benefits of proactive management of any symptoms that may arise, so that individuals are confident about working with their primary care provider for their ongoing health and wellbeing into adulthood

C0026 A NOVEL GENETIC MECHANISM (FOR SCHWARTZ-JAMPEL SYNDROME, SJS) TO SOLVE A DIFFICULT CASE; SIGNAL PEPTIDE VARIANTS – THE 'POSTAGE ADDRESS' OF GENE INSTRUCTIONS.

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Introduction: Background: Caucasian neonate with severe short-limb short-stature, contractures and multiple anomalies. Born in pandemic, video-robot consultations. R14 WES negative.
Aims: Methods: Radiology reviewed (Japan) suggested perlecanopathy. Data transferred to Oxford via RUDY for reanalysis.
Results: Homozygous VUS (c.41T>G, *p.L14R), HSPG2* (exon 1, signal peptide). Significant drop in signal peptide score (0.95à0.42). Originally filtered out (R14) as; low coverage, parental genotype unsupportive (0/0 maternal, 0/4 paternal reads). Manual IGV inspection identified variant; 6/6 proband, 0/1 mother, 1/6 father. Variant in ROH, not in gnomAD. Clinical correlation of contractures, stiffness and EMG myotonia increased diagnostic confidence. Sanger sequencing confirmed proband homozygosity, parental heterozygosity. Functional studies (Immunocytochemistry, confocal microscopy) on fibroblasts from skin biopsy (proband and mother) cf. healthy controls; reduced deposition of perlecan/ fibronectin in proband, suggesting ECM disruption. Western blot/ subcellular protein-localization experiments ongoing, before variant re-classification.
Conclusion: SJS diagnosis confirmed. Several lessons possibly useful to solve similar negative WES / WGS cases.
Radiographic re-phenotyping / strong clinical suspicion / expertise unlocked *HSPG2* re-analysis.
This required networking / expert collaboration from Sweden / Japan.
Pathways for data re-analysis (e.g. RUDY) via research are key.
Signal peptide variants are uncommon but important mechanisms potentially resulting in non-classical phenotypes (in this SJS case; initial absence of facial myotonia, presence of wormion bones).
Important to explore low coverage variant in autozygous regions where relevant.
Remote consultation are challenging. Molecular analysis confusing as multiple ROHs suggested consanguinity (though consanguinity not elicited in genetics video-consult but confirmed via primary clinicians

in retrospect). Family questioned diagnosis as proband's dysmorphism / stiffness incongruent to reported patients. If seen physically, easier to correlate diagnostic suspicion. Face-to-face consultations are better for building rapport, trust and examination, thus may alleviate such challenges.
Special ingredients for solving such cases include expert collaboration and perseverance.

C0033 EXAMINING THE EFFECT OF VOSORITIDE TREATMENT ON BONE STRENGTH IN CHILDREN WITH ACHONDROPLASIA.

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Introduction: Achondroplasia, the most common form of dwarfism, is an autosomal dominant disorder affecting endochrondral bone formation.
Aims: The objective of this study was to determine whether vosoritide (Voxzogo), an FDA-approved drug meant to increase endochondral bone linear growth, affects both length and development of bone strength in children with achondroplasia using measurements of the second metacarpal.
Cohort & methodology: This study included 130 deidentified AP hand/wrist radiographs from 30 children with achondroplasia (13M, 17F; ages 5.75-11.06 years). Proprietary hand films were collected at five time points: screening (pre-treatment), week 104 (at rollover into the phase II extension study), week 156, week 208 and week 260 on treatment. Measurements included second metacarpal length and midshaft width, cortical thickness, robustness (total area/length), and cortical area (correlated with bone strength). Measurements were compared to 378 radiographs from 114 controls (61M, 53F; ages 6-16 years) via non-parametric Kruskal-Wallis tests ($p<0.05$).
Results: Children with achondroplasia at week 208 and week 260 of treatment demonstrated longer metacarpals with increased cortical area compared to baseline; those at week 260 also displayed increased cortical thickness (all $p<0.05$). There was no significant difference in metacarpal robustness compared to screening across the treatment timepoints. Furthermore, no differences were seen between males and females with achondroplasia at any time point. Compared to the controls, children with achondroplasia had higher robustness and lower RCA throughout treatment ($p<0.001$).
Conclusion: We observed that 2-3 years of vosoritide treatment was associated with significant increases in bone length compared to baseline, as well as increases in metacarpal cortical area, which is correlated with strength. This preliminary clinical trial suggests this bone lengthening treatment did not adversely affect bone strength in children with achondroplasia. The lack of a significant difference in robustness after treatment indicated that periosteal expansion continued outward at a pace which maintains robustness, allowing the bone to remain strong as it lengthened. Future work comparing treated and untreated children with achondroplasia at each timepoint is necessary to understand the long-term impact treatment has on the development of bone strength. Overall, this work may have important clinical implications in terms of treatment choices for children with achondroplasia.

C0045 NEGATIVE NAIL PATELLA SYNDROME, WHEN TO RECONSIDER AN ESTABLISHED DIAGNOSIS.

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Introduction: We present a 51 year old Caucasian male with proportionate short stature, childhood-onset patella dislocations, small patellae, dysplastic nails, underbite, unilateral ptosis. Nail changes, asthma and small patellae also noted in his daughter (aged 17). He was initially diagnosed with nail patella syndrome (NPS), several years previously.
Aims: Methods: Proband and daughter referred to Clinical Genetics for further investigation of possible skeletal dysplasia. Clinical evaluation, photography, radiology, and genetic testing.
Results: LMX1B sequencing negative for nail patella syndrome (negative testing in 15% of patients with NPS). Important negatives for NPS: Radiograph hip (father) negative for posterior iliac horns (seen in 80% NPS), no triangular lunulae, renal investigations unremarkable. Findings suggestive of an alternative diagnosis of ischiocoxopodopatellar syndrome (ICPPS) included: presence of infra-acetabular axe-cut notches on hip x-ray, small patellae, pes planus and short 4th-5th rays. Heterozygous TBX4 (c.1010del p(Leu337Arg fs*42) NM transcript 018488.3. found in both proband and daughter, indicative of ICPPS.
Conclusion: Ischiocoxopodopatellar syndrome (ICPPS; also known as small-patella-syndrome) was confirmed. ICPPS is rare condition (incidence < 1 in a million). This case highlighted important distinctions between ICPPS and NPS:
Specific radiological signs in ICPPS (infra-acetabular axe-cut notches) vs NPS (posterior iliac horns)
Whilst dysplastic nail changes were observed in the proband and to a lesser extent his daughter, these were not consistent with the expected findings in NPS of triangular lunulae, nail ridging, pitting, splitting and discolouration with more severe symptoms in the nails of the first three digits. (Careful clinical examination to ensure that clinical signs are not misattributed.)
This case also showed the importance of correct diagnosis due to potential sequelae and comorbidities. For example, renal involvement in NPS vs pulmonary hypertension in ICPPS. Evaluation for relevant complications is currently in progress.

C0050 SPINAL SURGERIES IN PATIENTS WITH B3GALT6-RELATED DISORDERS: A CASE SERIES OF FOUR PATIENTS.

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Introduction: *B3GALT6*-related disorders are extremely rare. Severe and early-onset spinal deformities are hallmarks and usually require surgical correction. Syndromic scoliosis surgeries are accompanied by a significantly higher rate of perioperative complications. Little surgical experience has been reported in patients with *B3GALT6*-related disorders.
Aims: To report our experience and recommended management options for patients with *B3GALT6*-related disorders toreduce complications improve clinical outcomes.
Cohort & methodology: Patients molecularly diagnosed with *B3GALT6*-related disorders and received spinal surgeries were included in the study and the medical records were retrospectively reviewed.
Results: We report surgical experience in 4 patients with *B3GALT6*-related disorders. Patient 1 was a 4-year-old male presenting with severe kyphoscoliosis and segmentation defect. He received a T12 posterior spinal osteotomy, a T10-L3 interbody fusion, and a dual growing rod instrumentation applied from T3 to L3. However, a L3-L4 facet dislocation was observed at the 18-month follow-up. Genetic testing revealed biallelic pathogenic variants in *B3GALT6*. Joint hypermobility is one of the clinical hallmarks and might lead to the adding-on phenomenon. Therefore, a revision surgery was performed, during which the level of the lowest instrumented vertebra was extended from L3 to L4. The early post-operative and follow-up outcomes after subsequent distractions were satisfactory. The surgical plans for patients 2 and 3 were therefore modified before surgery and no post-operative complication was observed. Patient 4 underwent preoperative halo-pelvic traction to minimize complications, followed by posterior spinal fusion. The surgical outcome was satisfactory.
Conclusion: Surgical plan should be modified considering joint hypermobility in patients with *B3GALT6*-related disorders. Preoperative halo-pelvic traction may also be safe and effective in this group of patients.

C0056 UNDERSTANDING OBSERVER-REPORTED SIGNS OF ACHONDROPLASIA: VALIDATION OF THE ACHONDROPLASIA CHILD EXPERIENCE MEASURE–OBSERVABLE SIGNS MEASURE (ACEM–OSM).

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Introduction: Parents living with a child with achondroplasia are better able to identify signs of achondroplasia than those who see the child less frequently. The ACEM–OSM is a parental, observer-reported outcome measure developed according to FDA guidelines to assess observed signs of achondroplasia.
Aims: The psychometric validation results for the ACEM–OSM are presented.
Cohort & methodology: Parents of children with achondroplasia were assessed.First, data from a noninterventional, observational, web-based survey (N=200) were analyzed to determine factor structure, reliability, convergent and known groups validity. Analyses were then repeated using data from a phase 2, multicenter, double-blind, randomized, placebo-controlled trial (N=57). Based on these findings, the final ACEM–OSM was generated.
Results: Factor analysis found a satisfactory comparative fix index (0.99) for an 8-item, single factor structure yielding a total score. Internal consistency reliability was satisfactory (0.88). Test-retest reliability was adequate for both samples (0.73, observational; 0.88, trial). To support the convergent validity, it was hypothesized that the ACEM–OSM score would correlate moderately to strongly with the Parent Global Impression of Severity (PGIS)-Child Symptom ratings and the PROMIS Global Health total scores. This hypothesis was supported by both the observational and trial data. Specifically, the ACEM-OSM correlated moderately with the PROMIS Global Health total scores (r= -0.45, r= -0.48) and strongly with the PGIS-Child Symptom ratings (r=0.62, r=0.70) for observational and trial data, respectively. Additionally, all a priori hypothesized known groups were found to be statistically significant. Children of parents who reported child health as “excellent” or “good” had better mean ACEM–OSM scores compared with parents who provided a “fair” rating (*P*=0.01). Parents of children who reported better scores for child quality of life (QoL; as measured by the SF-10) had better mean ACEM–OSM scores than parents who reported worse QoL (*P*<0.001). These findings were confirmed in the trial sample.
Conclusion: The ACEM–OSM is a rigorously developed and validated measure which can be used to more accurately assess and target treatments to improve the condition. Identifying the daily signs of achondroplasia can be helpful to both clinicians and researchers in better understanding and addressing its health consequences.

C0058 ACHONDROPLASIA AND SUBDURAL BLEEDING: AN UNDER-RECOGNISED CLINICAL FINDING AND AN ERRONEOUS SUSPICION OF NAI.

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Introduction: We report eight cases of subdural haematoma (SDH) in infants with achondroplasia, in the UK and Denmark, a thus far under-reported and under-recognised complication of achondroplasia.
Aims: We aim to raise awareness of SDH as a recognised association with achondroplasia.
Cohort & methodology: We conducted a retrospective study of all patients under our care, and identified eight infants with achondroplasia and finding of SDH on imaging.
Results: The patients underwent cranial imaging due to examination finding of increasing head circumference or as part of routine achondroplasia follow up to investigate for foramen magnum stenosis. Imaging showed subdural fluid/haematoma in all patients. Some patients were consequently examined or investigated for Non-Accidental Injury according to regular clinical procedures. Ultimately, no patients showed further evidence of NAI. All patients remained asymptomatic of the SDH and were managed conservatively. They all continue to develop age appropriately for patients with achondroplasia.
Conclusion: As presented, SDH can occur in achondroplasia, and the diagnosis should be kept in mind when managing infants with SDH in order to ensure prompt and precise diagnosis, and to avoid unnecessary examinations or investigation for NAI.

C0066 THE ACHONDROPLASIA ROADMAP.

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Introduction: The Achondroplasia Roadmap is a tool that provides a holistic approach to explain the challenges and complexities of achondroplasia from the pre-natal phase through young adulthood.
Aims: There is an unmet need for comprehensive information available for parents, pediatricians, allied healthcare professionals and others about achondroplasia at different phases of childhood. Further, parents lack resources to support them in navigating the emotional and social challenges their children face in growing into their teen. In addition to improving parents' knowledge about the condition, the Roadmap will be an essential resource in talking about achondroplasia with teachers, peers and others who are part of their social and education networks. It will also be a resource to raise awareness and understanding about the challenges faced by families and children with achondroplasia within medical communities.
Cohort & methodology: International perspectives from Patient Associations, individuals with achondroplasia and parents of children with the condition were collected from 11 Achondroplasia patient association leaders. Based on guided discussions, major life milestones and accompanying medical, emotional and social issues that families and children may face were developed into the Roadmap. Patient organization representatives co-created and revised the content.
Results: The Roadmap is a unique, comprehensive resource on achondroplasia primarily for parents that provides information at different childhood life stages. The aim is to help them know what they may expect, find solutions and guide and support their child in living a happy and full life. The Roadmap highlights important topics such as genetic counseling, medical issues, navigating the social environment and promoting empowerment and increasing independence, presenting these and other issues at each key phase of the journey: pre-natal, birth-2 years of age, 3-6 years, 7-12 years and 13-18 years.
Conclusion: The project is unique in that it is based on a person-centered approach, has engaged the international achondroplasia community to provide insights from diverse cultural and socio-economic backgrounds and leverages direct experience and perspectives from those living with achondroplasia and parents. The Roadmap was developed by the International Council of Achondroplasia Patient Association Leaders, an ad hoc body representing 11 countries, with support from BioMarin.

C0069 SPLIT HAND-FOOT MALFORMATION: CHALLENGES IN THE DIAGNOSIS AND GENETIC COUNSELING.

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Introduction: Split hand-foot malformation (SHFM) is a congenital limb malformation affecting primarily the central rays of the hands and/or feet, with variable expressivity, incomplete penetrance and syndromic forms. It is genetically heterogeneous, including point mutations and structural variants in different loci, including biallelic variants in *MAP3K20*. This month, 5 individuals were reported in the literature with heterozygous variants in this gene, supporting a dominant-negative mechanism. We report 6 probands with variable phenotypes of SHFM, one of them also presenting a *de novo*, heterozygous, recurrent variant in *MAP3K20*.
Aims: To describe the clinical and molecular aspects of a small cohort of individuals with SHFM.
Cohort & methodology: Six individuals with SHFM were clinically evaluated in a Tertiary Center in São Paulo, Brazil: 4 of them presented additional, non-skeletal findings, including one individual clinically diagnosed as AEC syndrome and another one with split foot, hand syndactyly and ectodermal findings and 2 with pure skeletal phenotypes, one a familial case with long bone deficiency. Molecular testing was performed in all cases including genomic array and/or exome/whole-genome sequencing (ES/WGS)
Results: Structural variants (deletion 7q21, *de novo* duplication in 10q24 and familial duplication in 17p13 in two cases, with variable expressivity and incomplete penetrance), or point mutations (p.Tyr202Cys, in the DNA-binding of *TP63* in the case of the individual with AEC syndrome, and a single *de novo* variant p.Asn279del in *MAP3K20* in a proband with additional ectodermal findings).
Conclusion: Our results highlight that although several loci have been associated with SHFM, the genetic basis and mechanism of pathogenicity of this group is still not fully understood, as demonstrated by variable expressivity/incomplete penetrance in the familial cases with duplication including *BHLHA9*, as well as the unusual location of the variant in the DNA binding domain of *TP63* in an individual with AEC syndrome. The presence of a single variant in *MAP3K20* in our case gives further support for an autosomal dominant pattern of inheritance, possibly by a dominant-negative effect, as recently reported. Interestingly, the phenotype includes, among other findings, ectodermal involvement, which could be a hint for the underlying molecular etiology. FAPESP 2013/08028-1; CNPq: 303375/2019-1

C0084 3M SYNDROME: FROM PHENOTYPE TO GENOTYPE.

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Introduction: Three M (3M) syndrome is an autosomal recessive disease characterized by short stature, facial dysmorphism and skeletal anomalies. Deleterious changes in the *CUL7*, *OBSL1* and *CCDC8* genesestablish the diagnosis.
Aims: We describe the clinical evolution of a 12-years-old Italian boy who showed significant growth retardation and characteristic facies. Functional study of a *CUL7* variant that presumably affect splicing supports our clinical diagnosis.
Cohort & methodology: We conducted direct sequencing analysis of selected genes and then NGS panel for skeletal dysplasias.Transcript analysis using RNA extracted from fresh blood samples was performed by RT-PCR.
Results: At 6 month our patient showed a phenotype strongly suspicious for 3M syndrome.A subsequent evaluation at 2 years confirmed the same hypothesis. Direct sequencing of *CUL7, OBSL1* and *CCDC8* genes was carried out: the analysis identified a paternal, heterozygous c.2063+5G>C in *CUL7* and a maternal, heterozygous variant c.487_489delAAG in *OBSL1,* both classified as VUS. The parents decided not to continue the investigations, however they returned after 10 years in relation to poor growth. A NGS panel for skeletal dysplasias was then performed: a maternal likely pathogenic variant c.4391A>C (p.His1464Pro) in the *CUL7* gene was identified, along with the previously reported c.2063+5G>C *CUL7* variant. Transcript analysis showed that the paternal *CUL7* variant is responsible of exon 8 skipping, that altered the open reading frame.
Conclusion: Our report highlights that patient phenotyping can quicken the diagnostic process: functional analysis demonstrated an effect on splicing, which, together with the characteristic clinical and radiological features, supports the pathogenicity of the c.2063+5G>C variant in *CUL7*.

C0086 NOCICEPTION AND PAIN IN OSTEOGENESIS IMPERFECTA: APPROACH FROM PHYSIOTHERAPY.

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Introduction: Nociception in Osteogenesis Imperfecta (OI) comes from a mixture of low bone mineral density, lack of mobility, lack of strength, joint hypermobility, fatigue, poor alignment of the bone load axis, degeneration, body deformities and probably some consequences. unfortunate fractures and surgery. Pain, as a subjective, multifactorial and personal sensation, requires a personal assessment and multidisciplinary approach. Not all patients with OI are affected by these clinical problems in the same way, intensity, duration, time of life, etc. Improving these clinical characteristics means reducing painful sensations.
Aims: Explain how and why physical therapy can improve these conditions and modulate pain.
Cohort & methodology: Explanation of the nociceptive phenomenon in OI and its possibility of treatment through some particular clinical cases where the pain is caused by: low BMD, lack of mobility, lack of strength, joint hypermobility, fatigue, poor alignment of the load axis of the bones, early degeneration, deformities and some unfortunate consequences of fractures or surgeries. Physiotherapy and adapted physical activity is a program for each case, evaluating its impact.
Results: Different research points favorably to the benefits of physical exercise in these different clinical situations, which will result in a long-term benefit for pain. We contrast it with the different clinical and evaluated cases.
Conclusion: Scheduled exercise and physiotherapy adapted to each person with OI should be one of the main tools to improve pain and quality of life.

C0088 A SECOND PATIENT OF CAMPTODACTYLY, TALL STATURE, AND HEARING LOSS SYNDROME WITH A NOVEL HOMOZYGOUS FGFR3 VARIANT.

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Introduction: Camptodactyly, tall stature, and hearing loss syndrome (CATSHLS, #134934) is an ultra-rare disorder caused by loss-of-function (LoF) variants in FGFR3. Only three families are known to date. Monoallelic LoF variants have been reported in two families, while biallelic inheritance is present in only one family from Egypt.
Aims: This report aims to contribute to our understanding of an ultra-rare genetic syndrome by sharing data on a patient presenting with novel a genomic variant.
Cohort & methodology: We present the first child of consanguineous healthy parents, born at term with a birth weight of 2800gr (-1.3SDS). Birth length and head circumference (HC) were not noted. At birth, pes valgus and flexion contractures of elbows were present. Hip dysplasia was first diagnosed when he began to walk at 19 months. At 3 years old, he was referred for genetic evaluation. In physical examination, growth parameters were as follows HC: 47,5cm (-1.6SDS), weight: 14kg (-034SDS), height:102cm (1.4SDS). Pectus excavatum, flexion contractures of elbow and wrist, fusiform fingers, proximally placed thumbs, genu valgum, pes planovalgus, and prominent heels were noted. He had a global developmental delay, mainly affecting speech. The hearing test was normal. Radiologic images revealed mild metaphyseal widening and bilateral coxa valga.
Results: Solo WGS revealed a novel homozygous FGFR3, c.1261del, (p.Leu421Serfs*13) variant. Reverse phenotyping of the patient showed that his clinical findings were consistent with CATSHLS. This supports the previous evidence regarding biallelic LoF FGFR3-related phenotype.
Conclusion: We discuss the molecular and clinical spectrum of the syndrome and present the second case of ultra-rare, autosomal recessive CATSHLS.

C0090 CAREGIVER PERSPECTIVES ON VOSORITIDE TREATMENT: MEANINGFUL HRQOL IMPROVEMENTS IN CHILDREN WITH ACHONDROPLASIA.

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Introduction: Achondroplasia, caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*), leads to short stature and varying multi-system complications that may affect health?related quality of life (HRQoL). Vosoritide increases growth rates by inhibiting FGFR3 signalling and is the first approved pharmacological treatment for children with achondroplasia.
Aims: This qualitative analysis summarizes caregiver perspectives on their family and children's experiences with achondroplasia, perspectives on meaningful aspects of health to treat with pharmacological therapy, and the impact of vosoritide on their child's daily life.
Cohort & methodology: Written testimonials were collected from caregivers of children (N=12) who were enrolled in vosoritide clinical trials in the United States, the United Kingdom, Australia, and Japan to support discussions with regulators and other key stakeholders. Caregivers were asked to provide a brief written narrative characterizing the impact of achondroplasia on their children's lives and any changes observed in their children while on vosoritide. The statements were thematically analyzed with Atlas.ti using a codebook based on an achondroplasia conceptual model (Aldhouse et al. 2022).
Results: Psychosocial impacts, functional/physical limitations, and increased medical needs and complications were highlighted as key impacts of achondroplasia on daily living. Caregivers reported a range of signs, symptoms, and HRQoL impacts (across physical, emotional, and social functioning domains) as meaningfully improving after vosoritide treatment. Noticeable improvements reported were height increase (n=7), straighter limbs (n=3), and a straighter spine and longer fingers (n=2), with no reported worsening of any signs or symptoms. Key improvements in physical functioning were improved motor skills (e.g., higher reach, walking/running, balance, and cycling; n=10) and self-care (n=5). Psychosocial functioning improvements included improved confidence (n=6) and social interactions (n=5). Six caregivers mentioned added treatment burden (i.e., challenges associated with daily injections) but acknowledged the benefits outweighed this inconvenience.

Conclusion: This work provides complementary evidence supporting emerging findings from clinical trials, qualitatively elucidating the benefits vosoritide yields beyond growth and ways this treatment may improve multiple aspects of daily life for those living with achondroplasia. On-going analysis of the HRQoL data from the clinical trials aim to provide further evidence of the impact of vosoritide over time.

C0093 GIRL WITH CUTANEOUS SKELETAL HYPOPHOSPHATEMIA SYNDROME TREATED WITH BUROSUMAB: 2 YEARS FOLLOW UP.

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Introduction: Cutaneous skeletal hypophosphatemia syndrome (CSHS) is a mosaic RASopathy caused by postzygotic activating mutations in HRAS, NRAS or KRAS. It is characterised by the presence of congenital epidermal, melanocytic, or sebaceous nevi, elevated circulating FGF23 levels that causes renal phosphate wasting and rickets, skeletal hypomineralization and focal bone lesions ipsilateral to nevi.
Aims: We report a 12 yo, girl, third child of healthy non consanguineous parents, from Argentina with CSHS.
Cohort & methodology: At 15 days old, she presented with an extensive epidermal nevus. She developed leg length discrepancy at the age of 2 yo. On x-ray showed extended skeletal involvement, poorly defined cortical-medullary junctions and lytic lesion on the side of the skin lesion. All the metaphyses showed rickets. On biochemical evaluation, phosphatemia was persistently low 2.1 mg/dl (NV: 3-6) with hyperphosphaturia and elevated alkaline phosphatase (ALP) 661 IU/L (NV < 300).
Sanger sequencing of the main hot spots of HRAS, NRAS and KRAS was performed. A previously reported somatic variant, c.37G>C (p.Gly13Arg) in HRAS was detected from DNA isolated from the affected skin tissue. This variant was not present in DNA from peripheral blood or unaffected tissue.
Results: She received conventional treatment for hypophosphatemic rickets with oral phosphate salts and calcitriol with favorable metabolic control until she was 6 yo. At that time she developed a central precocious puberty and evolved with a severe clinic compromise with asthenia, chronic pain, weakness, reduced functional capacity and compromise of independent walking. Due to clinical, radiological and biochemical worsening with decrease in phosphatemia (1.4 mg/dl) and increase in ALP (2117 IU/L) despite the good compliance to conventional treatment, she started treatment with Burosumab at 11 yo. After 3 months of this treatment, she reported improvement in her physical abilities.
The phosphatemia and tubular phosphate reabsorption increased gradually with upward dose titration of Burosumab until 2 mg/kg/dosis. However she developed hypercalciuria: 6-12 mg/kg/day (NV<=4) , with calcemia: 9.6-10.8 mg/dl (NV 8.9-10.5) and parathormone: 26-53 pg/ml (NV: 12-95)
Conclusion: We report a girl with CSHS confirmed by somatic HRAS mutation and the complications associated. She started treatment with Burosumab with good clinical response after 21 months of treatment.

C0097 FATAL PULMONARY HYPERTENSION IN AN INFANT WITH SEVERE OSTEOGENESIS IMPERFECTA.

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Introduction: Osteogenesis imperfecta (OI), most commonly caused by pathogenic variants in *COL1A1* and *COL1A2*, results in a wide range of severity. Type 1 collagen is an important structural component of bronchi, alveoli, and blood vessels. OI type II results in either stillbirth or death in the immediate perinatal period, most often from pulmonary insufficiency. Animal models have shown pulmonary hypoplasia independent of chest wall size. In human adults, OI results in decreased spirometry based on wingspan. Pulmonary hypertension (PH) has not previously been reported in OI.
Results: Case: Mother was referred at 25 4/7 weeks with suspected life limiting skeletal dysplasia of her fetus. Evaluation confirmed the diagnosis and genetic testing revealed a recurrent pathogenic variant in *COL1A1* (c.1777G>A, p.Gly593Ser) consistent with OI. The published phenotypes consistent with this variant are variable, but generally severe. Patient was born at 36 5/7 weeks and required non-invasive respiratory support for 48 hours, weaning to room air by DOL 5. Skeletal survey showed fractures in all long bones and poor bone mineralization, but no pulmonary hypoplasia. He was diagnosed with severe OI, intermediate between Types II and III. He had three subsequent admissions for hypoxemia secondary to possible microaspiration, ultimately requiring continuous oxygen at 3 months of age. Echocardiogram at 3 months of age showed normal anatomy and mild elevation in pulmonary artery pressure (1/3 systemic pressure). Ultimately, he was admitted at 5 months with severe hypoxemic respiratory failure necessitating mechanical ventilation and diagnosed with suprasystemic PH. Parents elected to withdraw support and the child expired.
Conclusion: Discussion: PH was unsuspected as it has not been previously reported in OI. This patient had an adequate size thoracic cage but developed suprasystemic PH after the perinatal period. It is hypothesized that PH in OI results from impaired growth and defective lung tissue from abnormal type 1 collagen. We observed that rapidly developing PH may portend early mortality in OI. Clinicians should be aware and look for this potential complication in patients with OI. PH in OI is a potential area for investigation and intervention.

C0102 INTRON RETENTION; AN EMERGING MOLECULAR MECHANISM WHICH UNDERLIES RARE SKELETAL DYSPLASIA CONDITIONS AND IS A POTENTIAL FUTURE THERAPEUTIC TARGET.

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Introduction: Skeletal dysplasia conditions are a group of rare, genetic diseases, characterised by skeletal abnormalities and are often seen alongside a constellation of extra-skeletal pathologies. They arise from variants in 552 genes (Unger et al., 2023), that encode multiple proteins involved in skeletal homeostasis (Krakow and Rimoin 2010). Despite much progress being made, there are still many of these conditions, without defined underlying molecular mechanisms.
Intron retention occurs when there is persistence of an unspliced intron within mature mRNA (Grabski et al., 2021). Increasingly, it seems that intron retention may play a pivotal role in many diseases.
Intron retention is not currently a well-recognised molecular mechanism that can underpin skeletal dysplasia.
Aims: To describe the potential role of intron retention in patients with a skeletal dysplasia, without a molecular diagnosis, using standard genomic methods.
Cohort & methodology: Cases with no molecular diagnosis from the UK 100,000 Genomes Project were re-analysed by multidisciplinary team collaboration including clinicians, bioinformaticians and radiologists, as part of the Musculoskeletal Genomics England Clinical Interpretation Partnership (GECIP). A literature search, using the PubMed database, using the terms “intron retention” and “skeletal dysplasia” was also performed.
Results: One exemplar case is of a male proband, with pectus excavatum, winged scapulae, short stature, kyphoscoliosis and dysmorphic facial features. On re-analysis, the proband was found to have a novel NM_003791.4:c.2572+5G>A variant in MBTPS1in trans with c.1789_1790delinsG, p.(Asn597Valfs*9). On further analysis of RNAseq data, increased levels of intron 19 retention were observed. Variants in MBTPS1 are known to be associated with Spondyloepiphyseal dysplasia, Kondo-Fu type.

Conclusion: Here, evidence is presented to show that intron retention represents a novel mechanism, which can underlie skeletal dysplasia. The discovery of novel pathogenic molecular mechanisms in patients with skeletal dysplasia could enable targeted therapies to be developed in the future.

C0107 PRENATAL GENETIC DIAGNOSIS THROUGH EXOME TRIO SEQUENCING IN FOETUSES WITH A SUSPECTED SKELETAL DYSPLASIA.

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Introduction: The usefulness of whole exome sequencing (WES) in the context of prenatal diagnosis has been evaluated in several series, estimating an additional diagnostic yield of approximately 10-30% in fetuses who previously had a non-diagnostic karyotype and chromosomal microarray, depending on ultrasound findings. Among the different ultrasound abnormalities, current evidence suggests that WES has one of the highest diagnostic yields (up to 50%) in fetuses with suspected skeletal dysplasia.
Aims: To evaluate the diagnostic yield of WES in fetuses with suspected skeletal dysplasia
Cohort & methodology: In the period 2019-2023, 40 prenatal WES studies were performed in pregnancies with ultrasound abnormalities suggestive of skeletal dysplasia, following genetic counselling and informed consent. Exome sequencing was performed on fetal DNA samples and parental DNA. Only variants classified as pathogenic or likely pathogenic according to the ACMG criteria were reported.
Results: Of these 40 fetuses, pathogenic or probable pathogenic variants were identified in 13/40 (35%) of the cases; 5 of the cases were associated with different variants in FGFR3, 2 cases were associated with variants in COL2A1, including one case of a single exon deletion, and the remaining 6 were single cases affecting the genes TMEM216, NALCN, ACTA1, ABL1, EVC2 and B3GLCT. Of these 6, 4 are genes not included in the current nosology of skeletal dysplasias. In addition, pathogenic or probable pathogenic variants unrelated to the ultrasound phenotype were identified in 3 cases.
Conclusion: Exome trio sequencing proves valuable for prenatal diagnosis, although its application in the prenatal setting is hampered by the limited clinical phenotype and the lack of comprehensive gene databases linked to prenatal ultrasound phenotypes. Our data support the potential of this approach, while highlighting the complexity of interpreting the results in the prenatal setting and the need for careful and interdisciplinary evaluation of cases.

2024 ISDS

C0109 ATELOSTEOGENESIS TYPE I: ULTRASOUND, PHENOTYPIC, RADIOLOGICAL AND MOLECULAR FEATURES.

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Introduction: AOI and AOIII are characterized by severe short-limbed dwarfism, distally tapered humeri and femora, dislocated hips, knees, and elbows, clubfeet and occasionally complete lack of ossification of single hand bones. Differential diagnosis between the 2 conditions may be difficult due to the large phenotypic overlap between the 2 forms, which may be part of a common phenotypic spectrum. AOI is lethal in the perinatal period. In individuals with AOIII, survival beyond the neonatal period is possible with intensive and invasive respiratory support. Both are caused by heterozygous mutations in the *FLNB* gene (603381), which encodes filamin B, on chromosome 3p14.
Aims: We describe the ultrasound, phenotypic, radiological and molecular features of a fetus with AOI.
Cohort & methodology: We conducted WES analysis of selected genes related to the clinical indication (*SLC26A2, GPC6, COL2A1 and FLNB*) on fetal DNA.
Results: A 26-year-old pregnant woman was referred to the geneticist after an abnormal second-trimester gestational ultra sonography, showing fetal dysmorphisms.Prenatal findings at 19+6 weeks were: Long bones <3° p, bilateral clubfoot, severe micrognathia. Amniocentesis was offered to the couple and was performed at 20+1 weeks of gestation. Karyotype analysis and array-CGH analysis of amniotic fluid revealed a normal male karyotype. The couple decided to voluntarily terminate the pregnancy at the 21st week. Physical examination of the fetus revealed: hypertelorism, prominent eyes, depressed nasal root, malar hypoplasia, severe micrognathia, low set ears, spatulated thumb, rhizomelia, bilateral clubfoot. Babygram X-ray showed short and distally tapered humeri and femurs, hypoplasic ribs, pelvic hypoplasia, shortened tibia. WES analysis of selected genes related to the clinical indication (*SLC26A2, GPC6, COL2A1 and FLNB*) on fetal DNA demonstrated the following heterozygous de novo variant of the gene *FLNB*: (NM_001457.4):c.[502G>A];[502=] p.[(Gly168Ser)];[Gly168=], classified, according to ACMG criteria, as pathogenic (class 5). This variant is compatible with AOI (MIM#108720) and AOIII (MIM#108721), conditions with autosomal dominant transmission.
Conclusion: Our case underlines the importance of multidisciplinary prenatal ultrasound, phenotypic, anatomic-pathological, radiological evaluation which allows to suspect this condition, to be confirmed with the molecular test and underlines the phenotypic overlap between AOI and AOIII which represent a single phenotypic spectrum.

C0112 THE CURRENT LANDSCAPE IN PHARMACOLOGICAL TREATMENTS FOR SKELETAL DYSPLASIA.

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Introduction: Until recently, treatment options for skeletal dysplasia were predominantly surgical, such as limb lengthening, or relied on nonspecific strategies, such as recombinant human growth hormone (rhGH). However, these approaches have limited efficacy and/or a high risk of complications. Advancements in the understanding of the molecular mechanisms behind skeletal dysplasia have paved the way for the development of novel treatments targeting the specific disrupted signaling pathway associated with each condition. Vosoritide, the first drug to receive worldwide approval, marked a significant breakthrough in this regard, catalyzing the emergence of a growing repertoire of precision treatments either approved or currently under investigation.
Aims: We aim to review the latest advancements in the pharmacological management of skeletal dysplasia, offering an update on the key developments from this rapidly evolving and complex field.
Cohort & methodology: A comprehensive and concise review will be conducted, analyzing data from the most relevant studies on novel drugs for skeletal dysplasia published in recent years.
Results: Historically, over 40 distinct molecules have been investigated in clinical trials, with numerous others currently undergoing preclinical evaluation. Among these, six have received approval for use across various forms of skeletal dysplasias (elosulfase alfa for Morquio A, vosoritide for achondroplasia, interferon gamma-1b for osteopetrosis, burosumab for X-linked hypophosphatemia, asfotase for hypophosphatasia, and palovarotene for fibrodysplasia ossificans progressiva), while some others have been used off-label in many centers. Profound knowledge of bone physiology has been behind attempts to use molecules initially developed for other disorders to modulate signaling pathways in bone development, employing a strategy known as drug repurposing. Furthermore, advancements in gene therapy and in the technology for tailored development of novel molecules hold great potential; however, they are hindered by substantial cost burdens.
Conclusion: By addressing both challenges and new perspectives, we hope to inform clinicians about the current landscape in therapeutics for skeletal dysplasia, unifying the community under the goal of improving patient care through precision medicine.

C0116 SCHWARTZ-JAMPEL SYNDROME WITH PRENATAL PRESENTATION: A CASE REPORT WITH ADDITIONAL FINDINGS AND REVIEW OF THE LITERATURE.

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Introduction: *HSPG2* codes perlecan and is linked to two autosomal recessive skeletal dysplasias: Schwartz-Jampel Syndrome (SJS) and the lethal Silverman-Handmaker dyssegmental dysplasia (SHDD). Biallelic LoF variants cause SHDD and less deleterious variants cause SJS. One might infer that SJS and SHDD are part of the same spectrum, however there is a wide gap in phenotypical manifestations between both conditions, possibly attributed to frequent termination of pregnancy and both conditions being particularly rare.
Results: Case Report. A nonconsanguineous healthy couple was referred to Medical Genetics due to 2nd trimester ultrasound showing short long bones suggestive of skeletal dysplasia (femoral z-score of -7 at 32 weeks) in a male fetus. Invasive prenatal diagnosis for anticipatory care disclosed two pathogenic *HSPG2* variants: NM_005529.6 c.5788C>T p.(Gln1930*) and c.9326del p.(His3109Profs*16) in compound heterozygosity. Breech presentation warranted a C-section at 40 weeks. Vital signs were normal at birth. Length was below P3 and the rhizomesomelic shortening of the limbs confirmed. Skeletal survey showed abnormal vertebral ossification, bowing of the long bones, metaphyseal irregularity and flaring, and bilateral postaxial foot polydactyly. The newborn's genotype and phenotype were consistent with a severe form of SJS. Multisystem investigations were unremarkable. Mild hypertonia was observed from the age of 12 months.
Conclusion: Discussion. Both variants c.5788C>T and c.9326delwere previously described in the literature, the first in a SHDD diagnosed prenatally and the second postnatally in siblings with SJS. Stum et al (2016) showed that the c.9326del variant precipitated alternative splicing that allowed residual function and was non-lethal in homozygosity. Predicting a prognosis for our patient's genotype was challenging in the prenatal setting, since this *HSPG2* genotype had not been reported before and the presentation more severe than expected for SJS. Additionally, to our knowledge, this is the first report of polydactyly in SJS.

C0122 SPONDYLOPERIPHERAL DYSPLASIA CAUSED BY A NON-CODING 3-PRIME-UTR VARIANT IN THE COL2A1 GENE MOLECULARLY CHARACTERIZED USING PRIME EDITING.

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Introduction: Spondyloperipheral dysplasia is characterized by short stature, short extremities and brachydactyly caused by pathogenic variants in ***COL2A1***. Structural perturbations that interrupt the assembly of the protein lead to COL2A1-related dominant negative effects.
Aims: We describe an adult male who presented at birth with disproportionate short stature, narrow thorax, platyspondyly, short hands and feet, and scoliosis. Genome sequencing identified a ***de novo*** single variant in the 3' untranslated region (UTR) of ***COL2A1*** (NM_001844.5:c.*161A>G). We hypothesized that the variant generates a cryptic splice site, leading to the generation of pathogenic alternative C-terminal isoforms.
Cohort & methodology: We utilized prime editing to model the variant in the HAP1MLH-/- human cell line and characterize splicing outcomes. Homozygous and heterozygous mutant cell lines were established, and RT-PCR was used to identify alternative COL2A1 isoforms involving exon 52 to the 3'UTR proximal to the variant described.
Results: Isolation and sequencing of alternative RT-PCR COL2A1 isoforms indicated the formation of novel isoforms with altered exon 52-54 splicing at moderate frequency. The predominant isoform generates a stop-loss variant, producing 40 de-novo amino acids at the conserved c-terminus and likely acts in a dominant negative manner to cause disease.
Conclusion: To date, only a limited number of 3' UTR changes associated with disease have been reported. We present a patient that remained molecularly undiagnosed until detailed analysis of the non-coding regions of the gene was completed. Moreover, we demonstrate how prime editing can be a rapid and efficient tool to model and characterize variants of unknown significance for meaningful interpretation.

C0126 PERINATAL LETHAL FORM OF IFITM5-RELATED OSTEOGENESIS IMPERFECTA: CASE REPORT.

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Introduction: The ***IFITM5*** gene is associated with variable forms of osteogenesis imperfecta (OI), estimated to be responsible for about 5% of non-lethal forms. Variants in the 5-UTR of the ***IFITM5*** gene have been associated with OI-type V, with variable severity but clinically distinguishable by the presence of hypertrophic calluses and ossification of the interosseous membrane, among other characteristics. Subsequently, recurrent pathogenic variants have been described in exon 1, in cases of more severe form of prenatal onset and progressive evolution.
Aims: We present a perinatal lethal case associated with the c.119C>T (p.Ser40Leu) variant in the ***IFITM5*** gene. To our knowledge no cases of lethal presentation have been reported.
Cohort & methodology: Case Report.
Results: This is the third pregnancy of a healthy non-consanguineous couple and two healthy children.At 13 weeks, an abnormal position and shortening of the lower extremities is detected. Subsequent examinations demonstrate deformity of the skull bone against transducer pressure, flattened spine, all long bones incurved below p3 with fracture features and misalignment of the legs. Genetic testing by amniocentesis is offered and the possibility of lethal skeletal dysplasia, probable lethal form of osteogenesis imperfecta type, is explained. The couple decides to continue with their pregnancy. Karyotype was 46,XX and DNA sample was obtained for subsequent osteochondrodysplasia panel. At 26 weeks, the mother had symptoms of preterm labor, premature rupture of membranes, and a female was born by emergency cesarean section (Apgar score 2-1, weight 1149 g (p90: +1.3z), size 28 cm (p0.2; -2.9z)). The child dies within a few hours of life. Postnatal radiological study was compatible with lethal form of osteogenesis imperfecta. NGS panel shows c.119C>T (p.Ser40Leu) variant in the ***IFITM5*** gene.
Conclusion: This recurrent exonic variant (p.Ser40Leu) has been described with early severe phenotypes, but this is the first time to our knowledge that it has been reported with lethal perinatal outcome. This report confirms the high phenotypic variability observed in IFITM5-related OI, support a genotype–phenotype correlation for severe phenotypes different to OI-V, and illustrates that the ***IFITM5*** gene should be considered in the study of lethal phenotypes of osteogenesis imperfecta.

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C0134 AUTOSOMAL RECESSIVE ACROMESOMELIC DYSPLASIA MAROTEAUX TYPE ASSOCIATED WITH A LARGE INTRAGENIC DUPLICATION IN NPR2.

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Introduction: Acromesomelic dysplasia Maroteaux type (AMDM) is a rare autosomal recessive skeletal dysplasia characterised by severe disproportionate short stature. Typical radiological findings include significantly short and broad metacarpals, metatarsals, and phalanges along with cone-shaped epiphyses and oval-shaped vertebral bodies. Patients with AMDM usually have normal birth length and weight but have a sharp decline in skeletal growth thereafter. By the age of two years, abnormal growth plates and short, misshapen bones in the extremities and spine suggest a skeletal dysplasia. Loss of function pathogenic variants in *NPR2* cause AMDM. Nonsense, frameshift, splice-site, and missense variants have all been described in AMDM.
We report a 9-year-old female from a consanguineous family of Pakistani descent with prenatal onset short stature (Birth length 43 cm, weight 2672 g) and clinical and radiologic findings of AMDM. Molecular confirmation of the diagnosis was made through a combination of clinical exome, research genome and targeted copy number variant analysis to identify an 11kb intragenic duplication in NPR2.
Cohort & methodology: Clinical whole exome sequencing (WES) at GeneDx was performed using an Illumina platform. Research-based whole genome sequencing (WGS) was performed at the Hospital for Sick Children as part of the SickKids Genome clinic via a customized pipeline. GeneDx copy number analysis for known copy number variant(s) (CNVs) was performed using targeted microarray, multiplex ligation-dependent probe amplification (MLPA), and/or quantitative PCR (qPCR) with adequate coverage for the region(s)of interest.
Results: A homozygous duplication that involves exons 3-20 of the NPR2 gene (NM_003995.3) and a portion of the SPAG8 gene was identified. The coordinates of the duplication are Build37:Chr9:35,797,714-35,808,979. This ~11kb duplication interrupts the NPR2 gene leading a loss of function allele. Both parents are confirmed carriers.
Conclusion: AMDM is caused by homozygous or compound heterozygous loss of function variants in the NPR2 gene. We report a 9-year-old female confirmed to have AMDM due to a large homozygous duplication in *NPR2* whose diagnostic odyssey highlights the clinical utility of next generation sequencing as important genetic diagnostic tool for skeletal dysplasias. Research WGS identified a duplication that eluded WES, microarray, and single gene sequencing of NPR2. To our knowledge, this is the first report of a large homozygous intragenic duplication in NRP2 causing AMDM.

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C0138 CHARACTERIZATION OF PATIENTS WITH OSTEOGENESIS IMPERFECTA FROM A CHILEAN TERTIARY CARE CENTER: A RETROSPECTIVE DATABASE ANALYSIS.

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Introduction: Osteogenesis imperfecta (OI) comprises a spectrum of generalized connective tissue disorders characterized by hereditary, phenotypic, and genetic heterogeneity, predominantly affecting metabolic bone balance. Approximately 85-90% of cases result from pathogenic variants in the *COL1A1* and *COL1A2* genes. OI is characterized by increased susceptibility to fractures, vertebral compressions, bone deformities, and growth deficiency.
Aims: The aim of this study is characterization of chilean patients with OI
Cohort & methodology: We conducted a retrospective analysis of clinical, radiological, and molecular fidings of 65 patientes with OI treated at the Red de Salud UC-CHRISTUS in Chile. The database was established based on radiological suspicion of OI, supplemented with indicative clinical features, and molecular confirmation when available.
Results: In our cohort 44.1% were female and 55.3% male. The majority of patients were classified as OI type I (52.3%), followed by type III (18.4%) and IV (27.6%).
Regarding clinical characterization, 72.3% exhibited blu sclera, 26.1% dentinogenesis imperfecta, 32.3% short stature, 66.6% pathological spinal curvature, and 26.1% chest anomalies. Only 53.8% of them iniated biphosphonates trearment.
In terms of radiological findings, only 16.1% underwent a complete radiological survey. Most patientes (95.2%) exhibited a variable degree of osteopenia, and 88.4% presented with wormian bones. Congenital fractures were reported in only 23.4% of cases, with a higher incidence among those with OI type III (46.6%). Regarding the number of fractures, 38% had 1-4 fractures, 34.9% har 5-10 fractures, and 22.2% had more than 10 fractures, with 65% reporting vertebral crush fractures and 89.2% with limb fractures. Among patients who underwent bone densitometry, 52.5% showed at least one affected site.
Only 16.9% of patientes han genetic evaluation. Among those with molecular studies (11 patientes), 63.6% had variants in *COL1A1* and 36.3% in *COL1A2*.
Conclusion: Our retrospective analysis allows the characterization of OI patientes in a tertiary care center in Chile, providing insights into the clinical, radiological, and molecular aspects of the disease. The predominance of OI type I and the absence of OI type II align with previous reports, along with the perinatal mortality associated with the latter.
A notable limitation of our study is the relatively low proportion of patientes who underwent genetic testing.

C0141 FULL SKELETON RADIOGRAPHIC STUDY: DESCRIPTION OF THE EXPERIENCE IN A SKELETAL DYSPLASIA REFERENCE CENTER OVER THE PAST 10 YEARS.

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Introduction: Full skeleton X-ray (FSX) is an important diagnostic tool used to evaluate bone structure and skeletal development. Its primary indications include the suspicion of diffuse bone anomalies, growth delays, metabolic diseases, and skeletal dysplasias (SD).
Aims: Objective: This study aims to share the experience from the past decade of FSX at a specialized SD center.
Cohort & methodology: Materials and Methods: We conducted a retrospective analysis of all FSX performed from May 2013 to May 2023 at our Center. Patients were evaluated using a standardized FSX protocol, with reports generated by an expert pediatric radiologist. Patients underwent evaluation through a standardized FSX protocol, which was reviewed by an expert pediatric radiologist.
Results: A total of 286 cases were reviewed, 48% were females and 52% males. Of them, 2.4% were newborns, 18.8% infants, 22.4% toddlers, 15.7% preschoolers, 31% childhood, 8.3% young teens and 0.7% teenagers. The most common referral clinical diagnosis were SD (66%, 28% with a specific SD suspected) and short stature (24%). Of the total FSX, 53 (19.5%) were consistent with some form of SD. Among these, SD was already suspected in 62% of cases, 11% were referred for short stature, and the remainder for different reasons. For patients with a clinical suspicion of a specific SD, 59% showed radiological findings consistent with the suspicion. The most frequently observed conditions were dyschondrosteosis of Leri-Weill (8), hypochondroplasia (5), metaphyseal chondrodysplasia (4), achondroplasia (3), multiple exostosis (3), and osteogenesis imperfecta (3). Among children referred for short stature, only 10% were diagnosed with SD.
Conclusion: FSX is a valuable diagnostic tool for identifying SD and should be implemented using a standardized protocol. Integrating clinical history with FSX findings is essential, as shown in this study, where the diagnostic yield increased from 19% for all diagnoses to 59% for cases with a clinical suspicion of SD. Conversely, only 10% of children referred for short stature were found to have SD.

C0143 MOLECULAR FINDINGS IN VERY RARE SKELETAL DYSPLASIAS.

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Introduction: Around 6000 rare diseases are described, including skeleatl dysplasias (SD).
Aims: We describe three cases of utra rare diseases under surveillance in the SD clinics of Garrahan Hospital, Argentina, a center of reference.
Results: Case 1. 13-year-old girl, only daughter of a non-consanguineous couple, who has a history of aortic coarctation and bicuspid valve. Since she was 8 months old, she has had painful peripheral joint retractions that progress in severity and extension, causing chronic arthropathy and motor disability. She associates growth retardation, tumors on the soles and carpotarsal osteolysis. Clinical exome reports the presence of 2 variants in MMP2: c.302G>A and c.1006+5G>A classified as probably pathogenic and of uncertain significance according to ACMG criteria, which could affect a splicing site. Ongoing family segregation studies would allow the reclassification of this variant. MMP2 is associated with autosomal recessive Multicentric Osteolysis, Nodulosis, Arthropathy; MONA (OMIM 259600).
Case 2. 16-year-old adolescent, 3rd child of a healthy couple, presented with spine compromise, dens hipoplasia and spinal cord narrowness. He associates severe short stature (-9.9 sDE), acromyria, microcephaly with intellectual disability, bilateral cerulean cataract, dilation of aortic sinuses and facial dysmorphisms. Exome study detects a pathogenic variant in COG4: c.1546G/A, allowing the diagnosis of Saul Wilson Syndrome (MIM 618150).
Case 3. 7-year-old boy, 5th child of a healthy non-consanguineous couple, with early diagnosis of bilateral hyperplastic posterior primary vitreous with subsequent tractional retinal detachment. At 18 months of age a femoral fracture and subsequent platyspondyly indicated the need of antiresorptive treatment. Ocular pathology genes panel detects the pathogenic homozygous variant in LRP5: c.2555C>T, associated with Osteoporosis Pseudoglioma syndrome (MIM 259770), being both parents carriers of the condition.
Conclusion: As extremely rare entities, families have to deal with an increased burden due to the general lack of knowledge about them. Difficulties in communication, coordinating care and accessing aid are described. Being a reference center for Skeletal Dysplasias and the possibility of performing a precision diagnosis, has allowed us to offer appropriate treatment and follow-up.

Poster session 2

C0013 "NATURAL HISTORY OF THE SPINE IN ACHONDROPLASIA AND ITS MANAGEMENT STRATEGY".

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Introduction: Children with achondroplasia usually develop thoracolumbar kyphosis during the first months of life, a bulge of the spinal column because of general muscular hypotonia and macrocephaly. However, in most children this deformity will correct spontaneously as the spinal muscles strengthen and increase in strength during development. This development is altered by a delay in motor and language development milestones. This delay is conditioned by the generalized hypotonia that children present, which, together with the weight of the head, causes this hyperflexion of the spine, thus favoring the wedging of the first and second lumbar vertebrae. When left untreated, it can lead to permanent or progressive thoracolumbar kyphosis.When children begin autonomous walking, thoracolumbar kyphosis tends to disappear and, generally, lumbar lordosis appears. At advanced age, neurological deficits such as lower limb paresthesias, claudication, clones, and bladder or bowel dysfunction may become more common, and lower lumbar stenosis may appear.
Aims: Study the evolution of the spine in Achondroplasia from birth to adult life.
Develop a strategy for clinical assessment of the spine in patients with achondroplasia.
Carry out a therapeutic action protocol according to the results obtained.

Cohort & methodology: We want to study the evolution of the spine in Achondroplasia from birth to adult life. To do this, patients will be recruited from the Alpe Achondroplasia Foundation database and will be included according to the research inclusion criteria.Inclusion criteria will be:- Patients with a genetic diagnosis of achondroplasia.- Children and adults.Exclusion criteria will be:- Patients who refuse to participate in the evaluation.In the clinical methodology of the research, several assessments will be carried out:Assessment of the spine with measurements and tests that best suit Achondroplasia.Quality of life scale, adjusted to the condition of Achondroplasia.Complementary tests, such lateral x-rays it. Other data will be collected during therapies such as Physiotherapy, Aquatic Therapy...We want to develop, with all the information collected, a management strategy and create a protocol for the evolution and management of the spine in Achondroplasia.
Results: The results and conclusions are still being studied.

C0025 TRAMETINIB EFFECTS ON SKELETAL INVOLVEMENT IN TWO CHILDREN AFFECTED BY OCULOECTODERMAL SYNDROME CAUSED BY KRAS MOSAIC MUTATIONS.

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Introduction: Oculoectodermal syndrome (OES) is caused by somatic mosaic mutations in the *KRAS* proto-oncogene. Clinical phenotype is characterized by multiple congenital abnormalities including ocular, dermatological, cardiovascular, and neurological involvement. Skeletal lesions typically appear during the first 5 years of life and include non-ossifying fibromas of long bones causing recurrent fractures, and giant cell granulomas of the jaw. Currently no treatment is available for this condition.
Trametinib, an inhibitor of the MEK protein of the RAS pathway routinely used in oncology, has shown significant efficacy in patients with other RASopathies, particularly on lymphatic and arteriovenous malformations, cardiac involvement, and dermatological lesions.
Aims: We report the effects of trametinib on non-ossifying fibromas of long bones in two OES patients.
Cohort & methodology: Two OES children, aged respectively 6 and 8 years old, presented with multiple non-ossifying fibromas of long bones causing recurrent fractures, leading to major functional impairment.
Mosaic *KRAS* variants c.38G>A (p.Gly13Asp) and c.436G>A (p.Ala146Thr) were found respectively in 25% of alleles of DNA extracted from fresh skin biopsies from the two patients, thus confirming the diagnosis of OES.
To assess the impact of these mutations on *KRAS* function and the possible effects of trametinib, we conducted transient overexpressions

of KRAS in HEK293 cells.
We subsequently initiated trametinib treatment at a dose of 0.02 mg/kg/day in the two patients.
Results: In vitro studies confirmed that the two observed *KRAS* mutations induce hyperphosphorylation of the Erk1/2 protein, which is significantly reduced by trametinib.
In vivo, we observed a significant clinical and radiological improvement after 12 months of treatment, with no recurrence of fractures, restored ambulation, significant remineralization of bone lesions.
Mild side effects were observed, including acne-like lesions, delayed wound healing, and xerosis, improved by topical treatments. Biologically, a moderate elevation of CPK without clinical impact was noted.
Conclusion: Trametinib was well-tolerated and significantly improved bone lesions in these two children with severe OES. A therapeutic trial is needed to further confirm these positive results, in a larger patient cohort.

C0030 GH TREATMENT IN A SPANISH COHORT OF 53 CHILDREN WITH SHOX/SHOX ENHANCER ALTERATIONS.

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Introduction: Alterations of *SHOX* or its enhancers are the most frequent monogenic cause of short stature and since 2008, patients may be treated with growth hormone, financed by the Spanish Public Health System.
Aims: National retrospective multicentre review of rhGH treatment in a large Spanish cohort of children with molecularly confirmed SHOX deficiency. Demographics, efficacy and responsiveness predictors were evaluated.
Cohort & methodology: SGA, ethnicity, SHOX defect, familial history, growth parameters (weight, height, BMI), Tanner stage, sitting height, arm span, Madelung deformity and SHOX radiological signs, bone age (Greulich Pyle), IGF1, IGFBP3(SDS), HOMA index were collected. Data points included pre-GH treatment, 1,2 years after initiation, and at the last visit.
Results: Total of 53 patients (28M/25F), 22% SGA. Final height achieved in 14 (26.4%). 85% prepubertal (7.8±2.86 y). 32 had ***SHOX*** intragenic defects (60%), 21 enhancer defects (40%). Ethnicity: 65% Caucasians, 35% Gypsy (95% with p.Ala170Pro).
Disproportion was evidenced only in 42% by arm span/height ratio<0.965 (13/31) and 47% by sitting height/height ratio >0.555 (11/23). At least one radiological sign was present in 43.4% of cohort: 24.5% radial radiolucency, 24.5% radial triangularization, 17% radial bowing, 13% metacarpal shortening, 11% pyramidalization of the carpal row and 3% ulna dislocation. Disproportionate cases began rhGH treatment at earlier ages. Mid-parental height was -1.78DS±0.87. Height SD improved with rhGH treatment: basal -2.84SD, first-year (-2.17SD), second-year (-1.76SD) and at the last visit (-1.6SD) (Δ +1.24SD±0.81). 68% of patients were P≥3 at last consult. Patients at final height: Δ +0.98SD±0.75 (p=0.023). Predictors of good response included: enhancer defects (p=0.04), initial chronological age (r=0.37, p=0.03), and better improvement in height and somatomedin levels in the first year (r=0.6 and 0.55 respectively, p=0.001). RhGH dose (basal visit): 0.041±0.0043mg/

kg/day (0.029-0.048). Duration: 3.96±2.49 years (0.83-11.81). Bone age accelerated. Lack of adherence in 5 patients (9%). AGnRH was added in 3 patients.

Conclusion:

rhGH treatment improved basal height: Δ+1.24DS±0.81; patients achieved adult height: Δ+0.98DS±0.75.

Predictors of good response were improvement in height and somatomedin levels in the first year of treatment, chronological age at the beginning and having an enhancer defect.

C0036 STARTING A MULTIDISCIPLINARY DYSPLASIA CLINIC DURING A PANDEMIC: LESSONS, FAILURES AND PLENTY OF COFFEE.

Catherine Gooch[1]

[1]*1 Childrens PLace*

Introduction: Starting a new multidisciplinary clinic is always a large task, but the journey to starting a Skeletal Dysplasia Clinc at St Louis Children's Hospital was complicated by the COVID-19 Pandemic, a local bone research center closing leading to staff changes, and by my own maternity leaves. I learned much throught my journey to start the clinic and this gave me much greater insight into my instuitution (Washington University in St Louis School of Medicine) and academic medicine.

Aims: My aim was to build a multidisciplinary skeletal dysplasia clinic that would provide a medical home for our pediatric patients with complex genetic skeletal conditions, including metabolic bone disease.

I would like to discuss what I learned about how to start a new clinic, emphasizing the following things:

Division/Department Leadership

Faculty Members

Support Staff

Physical Space

Creating Opportunities

Results: Our clinic was started in November of 2021 and we have seen dozens of patients with many diagnoses. Our multidisciplinary staff includes 3 Genetics MDs, 1 Genetics NP, 2 Nurse Coordinators, 2 Physical Medicine and Rehabilitation Providers, 1 General Orthopedic Surgeon, 1 Spinal Orthopedic Surgeon, 1 Neurosurgeon. We also have trainees from Genetics, Pediatrics and Endocrine rotate in our clinic as well as medical students and genetic counseling students. We are wrapping up our first clinic research project. We have an Infusion Center above our clinic where patients can get bone-specific medication infusions before clinc. Our Nurse Coordinators can also arrange same-day appointments for patients with providers who are not Dysplasia Clinic team members such as Audiology and Ophthalmology.

Conclusion: With the correct support and hospital infastructure, starting a multidisciplinary Skeletal Dysplasia Clinic was do-able and very rewarding, although not without its challenges. Starting the clinic was delayed due to the COVID19 Pandemic and my personal absences. While there are still multiple problems we regularly encounter, the clinic staff and I feel that starting our clinic provides a centralized medical home for patients and that they benefit from an unchanging care team of specialized providers. I would love to brainstorm with other insutitions about further improvements.

C0046 CATEL-MANZKE SYNDROME CAUSED BY COMPOUND HETEROZYGOSITY IN TGDS.

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Introduction: We present a neonate with hyperphalangy and radial deviation of the index fingers, micrognathia and cleft palate with critical airway narrowing, and large joint hypermobility with dislocations. Initial skeletal dysplasia panel was nondiagnostic. Reanalysis for *TGDS* revealed a pathogenic variant commonly seen in Catel-Manzke syndrome, along with a second previously unreported variant.
Cohort & methodology: Case Report: Fetal ultrasound at 36 5/7 weeks EGA demonstrated shortened long bones, severe micrognathia, and a cleft palate. The baby was delivered by Caesarean section at 36 1/7 weeks.
Results: Radiographs demonstrated mildly shortened long bones, Pierre-Robin sequence with severe micrognathia, and a shallow left acetabulum with cranial dislocation of the left femoral head. The hands demonstrated a small supernumerary delta-shaped digit interposed between the head of the second metacarpal and the epiphysis of the second proximal phalanx, resulting in radial deviation. During hip sonography, the knees were clinically hyperflexible, with spontaneous anteroposterior dislocation and reduction.
Based on the results of the skeletal survey, an entity in the group of skeletal dysplasias associated with joint dislocations was suspected. An extensive skeletal dysplasia panel was initially nondiagnostic. However, dedicated reanalysis for *TGDS* revealed two mutations, the first being c.298G>A, p.(Ala100Ser), a pathogenic variant previously reported in 8/11 patients with Catel-Manzke syndrome. The second was c.86+3A>C (intronic), a previously unreported variant. This was felt to be consistent with compound heterozygosity in TGDS resulting in Catel-Manzke syndrome.
Discussion: Catel-Manzke syndrome is quite rare, with only 11 patients previously reported with confirmatory exome sequencing. All had mutations in *TGDS*. While the first pathogenic variant seen in our patient has been reported in 8/11 patients, the intronic variant appears to be novel.
Conclusion: Catel-Manzke syndrome is due to homozygous or compound heterozygous mutations in *TGDS*. The combination of characteristic facial and hand features with joint hypermobility and dislocations should suggest this diagnosis.

C0054 PRENATAL DIAGNOSIS OF ATYPICAL HOLT-ORAM SYNDROME CAUSED BY A NOVEL INHERITED INTRAGENIC TBX5 DUPLICATION: A RARE MECHANISM WITH VARIABLE EXPRESSIVITY.

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Introduction: Holt-Oram syndrome (HOS) is a rare autosomal dominant heart-hand-syndrome characterized limb defects and congenital heart defects, caused by variants in *TBX5,* a transcription factor involved in cardiac and limb development. Most reported pathogenic variants are single nucleotide variants.
Aims: We report a case of an intragenic duplication in TBX5 associated with fetal ultrasound findings consistent with Holt-Oram syndrome in a family ascertained prenatally.
Cohort & methodology: The mother of the proband was seen at 22 weeks' gestation following a detailed fetal ultrasound showing left syndactyly of the first and second digits and clinodactyly of the fifth digit. The parents were non-consanguineous of Asian (mother) and Spanish (father) descent. The father had a history of ventricular septal defect and a congenital deformity of the anterior chest wall (Currarino-Silverman Syndrome). Nuchal translucency was 1.6 mm (at 12 weeks gestation) and prenatal cell-free DNA screening showed low risk for aneuploidies. Fetal echocardiogram identified no abnormalities. Microarray (CytoSNP-850K platform) and follow-up sequencing were undertaken via amniocentesis.
Results: Testing identified a heterozygous partial gene duplication including exons 2 through 7 of TBX5. The variant was paternally inherited and de novo in the proband's father. The baby was born at term. Postnatal physical examination was notable for absent pectoralis muscles bilaterally. The right the thumb was digitalized, proximally inserted and with narrow first interdigital space. The left thumb was rudimentary with syndactyly with the second finger. Examination of the father also revealed absent pectoralis muscles, pectus carinatum but no thumb abnormalities.
Conclusion: To our best knowledge, this is the first reported case of Holt-Oram syndrome caused by an intragenic duplication of exons 2 through 7 in *TBX5.* Importantly, this represents only the third published case of atypical HOS caused by an intragenic *TBX5* duplication (PMIDs: 22333898;

33930582). The proband has asymmetric upper limb abnormalities, without a congenital heart defect. However, cardiac manifestations are only present in 75% of cases. Notably, the father has a septal defect, and an unusual chest wall deformity without limb anomalies. This case reinforces the variable expressivity of *TBX5* variants and raises the possibility that other individuals with similar chest wall deformities may also have *TBX5* duplications.

C0057 DEEP PHENOTYPING OF THE SPINAL FEATURES IN EDS: A STUDY OF 20 PATIENTS AND REVIEW OF THE LITERATURE.

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Introduction: Ehlers-Danlos syndromes (EDS) represent a diverse group of heritable connective tissue disorders characterized by clinical and genetic heterogeneity. With 14 recognized subtypes and associations with 20 genes, EDS manifests in various features including joint hypermobility, skin hyperextensibility, and tissue fragility. Spinal deformities are prevalent among EDS patients, attributed to generalized ligamentous laxity and hypotonia. Despite the commonality of spinal issues, detailed characterization of spinal features in EDS remains underexplored. This study aims to address this gap by conducting a deep phenotyping analysis of the spinal features in EDS patients.
Aims: The primary aim of this study is to delineate the spinal manifestations in EDS patients through a detailed phenotypic analysis. We seek to identify specific radiographic patterns, assess the spectrum of spinal deformities, and evaluate the outcomes of surgical interventions.
Cohort & methodology: This retrospective study reviewed medical records of EDS patients at Peking Union Medical College Hospital (PUMCH) who underwent genetic testing as part of the Deciphering Disorders Involving Scoliosis and COmorbidities (DISCO) study. Inclusion criteria were molecularly confirmed EDS diagnoses. Radiographic analyses encompassed whole spine X-rays, three-dimensional CT reconstructions, and MRI scans of the cervical, thoracic, and lumbar spine. Surgical interventions and postoperative outcomes were also assessed.
Results: The study cohort comprised 20 EDS patients (12 males, 8 females) aged between 5 months and 36 years. Genetic variants were identified in 7 genes across 6 EDS subtypes. Radiographically, scoliosis and kyphosocliosis were predominant, with thoracic and thoracolumbar regions most affected. Vertebral body anomalies such as platyspondyly and wedging were noted. Early-onset and severe kyphoscoliosis were observed in specific EDS subtypes. Surgical correction was performed in 12 patients, with post-operative complications higher than in the general population.
Conclusion: This cohort study provides a comprehensive analysis of spinal features in Chinese EDS patients, revealing significant variability in spinal phenotypes and a high rate of post-operative complications. Early diagnosis and tailored management strategies are crucial for optimal patient outcomes. While the study's findings are foundational, a larger cohort is necessary for broader generalizability and statistical significance. The study contributes to the understanding of EDS-related spinal deformities and the complex interplay between connective tissue disorders and spinal abnormalities.

C0063 FIDELITY OF MOUSE MODELS OF HUMAN GENETIC SKELETAL DISORDERS.

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Introduction: The 2019 genetic skeletal disorders nosology update (G Mortier et al., ***Am J Mol Genet A. 2019; 179:2393-2419***) includes 441 genes for which mutations result in rare human skeletal disorders. A literature search (R Brommage and C Ohlsson, ***Front Endocrinol. 2020; 10:934***) identified mouse skeletal phenotypes mimicking the human skeletal disorders in 249 of the 260 genes (96%) for which comparisons are possible.
Aims: Mouse models included spontaneous and ENU-induced mutants, global and conditional gene disruptions, and transgenic mice with gene over-expression or specific base-pair substitutions.
Cohort & methodology: These 441 gene code for enzymes (33%), scaffolding proteins (18%), signal transduction proteins (16%), transcription factors (14%), cilia proteins (8%), extracellular matrix proteins (5%) and membrane transporters (4%). Skeletal disorders include aggrecanopathies, channelopathies, ciliopathies, cohensionopathies, laminopathies, linkeropathies, lysosomal storage diseases, protein-folding and RNA splicing defects, and ribosomopathies.
Results: The 2023 nosology update (S Unger et al., ***Am J Med Genet A. 2023; 191:1164-1209***) includes 552 genes. The number of nosology genes has increaed from 65 in 2001, 140 in 2006, 226 in 2010, 318 in 2015, 441 in 2019 to 552 in 2023, for an average of 22 genes identified per year.
Conclusion: Suggestions for a possible future mouse model review are welcome.
The author has contributed data to published skeletal phenotypes for ***Amer1***, ***Ednra***, ***Fam20c***, ***Lrp5***, ***Lrrk1***, ***Porcn***, ***Sfrp4*** and ***Sost*** mutant mice. ***Wnt16*** KO mice have low cortical bone thickness, and this phenotype was described prior to identification of the human ***WNT16*** GWAS bone mass and osteoporotic fracture risk signal.

C0068 CASES OF SURVIVORSHIP; RECOMMENDATIONS FOR PRENATAL GENETIC COUNSELING WITH DOUBLE SKELETAL DYSPLASIAS.

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Introduction: Double heterozygosity refers to an individual with two non-allelic dominant genetic conditions. Historically, double heterozygosity across various skeletal dysplasias has often been described as severely life-limiting or lethal. There is a paucity of published case reports of individuals with double heterozygosity for achondroplasia (OMIM: 100800) and a collagen-II-opathy (OMIM: 120140). Of the live births reported, all died in infancy from respiratory complications. Double-dominant achondroplasia, also known as homozygous achondroplasia, refers to an individual who has inherited an ***FGFR3*** variant (c.1138G>A) from each parent, and has similarly long been considered uniformly lethal in the neonatal period or shortly thereafter.
Aims: With advancements in medical technology, there is significant value in updating the medical literature by presenting cases of long-term survivorship to guide future prenatal counseling.
Cohort & methodology: We present two unrelated children with both molecularly confirmed achondroplasia and a collagen-II-opathy, ages 2 and 7 years old, as well as a 9-month-old infant with homozygous achondroplasia.
Conclusion: Parents with autosomal dominant skeletal dysplasias are often counseled on the likely lethal nature of double heterozygosity and double dominance. With access to life-sustaining interventions, all three individuals presented here have outlived previously defined expectations. Given an ever-developing variety of medical and surgical therapies available, and advancements in skeletal dysplasia care, we recommend that prenatal counseling include the challenges of prognostication, the option of life-sustaining interventions, and the value of care from providers with experience in rare dysplasia diagnoses.

C0071 ANTENATAL DIAGNOSIS OF CARTILAGE-HAIR HYPOPLASIA BY RAPID FETAL WHOLE EXOME SEQUENCING - IMPLICATIONS FOR NEONATAL MANAGEMENT.

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Introduction: Rapid fetal whole exome sequencing (WES) is available in England for pregnancies with fetal anomalies considered likely to have an underlying genetic cause, where a genetic diagnosis may assist management in the pregnancy. Indications include pregnancies with a suspected skeletal dysplasia.
Aims: We report the antenatal and postnatal findings in the first pregnancy of an unrelated couple where short long bones (<1st centile) and bowing of the femurs was detected via antenatal ultrasound scan. Head circumference and abdominal circumference were both close to the 50th centile and a skeletal dysplasia was suspected. Rapid WES was offered and the results showed the fetus was homozygous for a pathogenic variant in RMRP gene, consistent with a diagnosis of Cartilage-Hair Hypoplasia (Metaphyseal Chondrodysplasia, McKusick type). We discuss the impact of this antenatal diagnosis during the pregnancy and for neonatal management.
Cohort & methodology: This is a single clinical case report detailing how the antenatal diagnosis raised parental questions about the potential spectrum of phenotypic features in their child. We will discuss the postnatal care plan established following liaison with appropriate paediatric specialists.
Results: A clinical and radiological description of the proband including skeletal, gastrointestinal and immunological features will be presented. We will review the proband's progress, currently 10 months old.
Conclusion: The antenatal diagnosis of Cartilage-Hair Hypoplasia enabled parents to be aware of the full potential phenotypic spectrum, thus contributing to informed decision-making in the pregnancy, however raising challenges for counselling as some aspects could not be predicted. Information regarding the possibility of associated features such as gastrointestinal and immunological features in addition to the skeletal features was shared with the paediatric team, facilitating the prompt neonatal diagnosis of Hirschprung disease.

C0085 MOLECULAR AND CLINICAL CHARACTERIZATION OF A LARGE COHORT OF PATIENTS WITH ELLIS-VAN CREVELD SYNDROME AND A FAMILY WITH WEYERS ACROFACIAL DYSOSTOSIS.

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Introduction: Ellis-van Creveld syndrome (EvC) is a rare skeletal dysplasia primarily caused by mutations in ***EVC*** or ***EVC2***. Patients with EvC normally present with acromesomelic limb shortening, postaxial polydactyly, nail-teeth dysplasia and congenital heart defects. Weyers acrofacial dysostosis (WAD) is an ultra-rare dominant disorder caused by heterozygous truncating mutations localized at the C-terminal region of EVC2 and represents a milder form of EvC.

Aims: This work aims to expand the mutational spectrum and improve the clinical understanding of the EvC/EvC-like phenotype.
Cohort & methodology: Clinical and molecular data were obtained from 46 individuals from 43 unrelated families with a preliminary diagnosis of EvC and three WAD-affected individuals from one family. In addition, to confirm the deleterious effect of specific variants of uncertain significance, functional assays were performed in patient-derived primary fibroblasts and other cellular models.
Results: Molecular analysis in these patients identified 41 of the 43 EvC families with pathogenic mutations in either *EVC* or *EVC2*. The remaining two EvC families harbored a homozygous splicing variant in *WDR35* and a heterozygous *de novo* frameshift variant in *GLI3*, respectively. In the case of the WAD family, a novel C-terminal truncation variant in *EVC2* was detected in all three affected individuals.
Conclusion: This study contributes to a better understanding of the EvC clinical spectrum, as it represents the largest cohort of living patients to date. It also provides comprehensive insights into the *EVC/EVC2* mutational landscape; and expands the list of genes associated with EvC-like phenotypes to include *GLI3*.

C0087 DESCRIPTIVE STUDIO OF OSTEOGENESIS IMPERFECTA IN SPAIN

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Introduction: Osteogenesis Imperfecta is a genetic pathology that affects the formation of an essential molecule in the musculoskeletal system, collagen type I. The quantitative and qualitative deficiency of this molecule has direct clinical consequences in people affected by the pathology. Physiotherapy is a key profession for the management of these patients, so knowing their physical characteristics and their evolution depending on age is essential.
Aims: Determine the clinical characteristics of people with OI according to variables such as genetic confirmation, mutated gene, number of fractures and their location, main soft tissue injuries, presence or absence of scoliosis and the type of treatment received (surgery, physiotherapy and technical aids)
Cohort & methodology: A total of 90 participants were divided into 4 age cohorts: children (2-9 years), youth (10-18 years), young adults (19-40 years) and adults (41-65 years). For each cohort, the aforementioned variables were collected and statistical analysis was performed.
Results: The groups differed with respect to the number of fractures. There were statistically significant differences between the groups ($p<0.050$) regarding femur fracture, dorsal and lumbar crushes, ankle sprain, use of an electric wheelchair and the need for technical aids. Other injuries that had some relevance were dislocations. The receipt of physiotherapy had statistical significance, with its application being greater in the younger age groups.
Conclusion: The number of fractures and soft tissue injuries are more common in older age groups. The most common fracture is the femur, followed by dorsal and lumbar crushes. Ankle sprain is the most common type of injury. Dislocation of the patella and the head of the radius are relevant. Scoliosis, the main deformity, appears in a large percentage of cases. Physiotherapy treatment is present in the people with OI analyzed, mainly children and young people, the oldest affected are the ones who receive it the least.

C0089 EXPANDING THE PHENOTYPIC AND GENETIC SPECTRUM OF STEEL SYNDROME: NOVEL COL27A1 VARIANTS IN THREE PATIENTS FROM TURKEY.

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Introduction: Steel syndrome (STLS, #615155) is a rare autosomal recessive osteochondrodysplasia, characterized by congenital bilateral hip dislocation, carpal coalition, short stature, and distinctive facial features. The disorder is linked to pathogenic variants in the COL27A1 gene, encoding collagen type XXVII alpha 1. Although initially described in Puerto Rican children, subsequent reports have identified cases worldwide, suggesting a broader genetic and phenotypic spectrum.
Aims: Here, we present three patients from two consanguineous Turkish families, highlighting novel COL27A1 gene mutations and further delineating the clinical manifestations of STLS.
Cohort & methodology: The first case is a child presenting with congenital knee dislocation, bilateral hip dislocation, levoscoliosis, rhizomelia, and facial dysmorphic features. He had mild-to-moderate expressive language delay and a waddling gait.
The second family comprises two siblings of consanguineous parents. The first sibling exhibits a narrow chest with mild pectus excavatum, genu valgum, clinodactyly, carpal synostosis, hearing loss, and distinctive facial features. His brother shares similar facial dysmorphisms, partial syndactyly of the 2nd and 3rd toes, clinodactyly, and umbilical skin defects, but without hearing impairment.
Results: Initial chromosomal array, and whole exome sequencing (WES) of the first case resulted negative. However, a focused reanalysis of WES data revealed a homozygous deletion of approximately 116 kb on chromosome 9q32 (Seq[GRCh37] 9q32 (chr9:116956684_117072975)). This deletion encompasses the 6th to the 61st (last) exon of the COL27A1 gene, leading to a truncated protein, thus a loss-of-function phenotype.
WES analysis of the second family identified a novel, homozygous splice-site variant, c.2935-2A>C, in COL27A1 in both siblings.
Conclusion: These patients underscore the genetic heterogeneity and clinical variability of STLS. The identified homozygous 116 kb deletion and the novel splice-site mutation contribute to the expanding the spectrum of genetic alterations associated with STLS.

C0092 NOVEL VARIANT IN THE GNAS GENE IN A CHILD WITH OVERLAPPING FEATURES OF PROGRESSIVE OSSEOUS HETEROPLASIA (POH).

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Introduction: Progressive osseous heteroplasia (POH) is a rare genetic condition associated with progressive ectopic ossification involving the subcutaneous and deep connective tissue. Most often, paternally inherited inactivating pathogenic variants in the *GNAS* gene causes POH. In this report, we describe a 9-year-old female with symptoms and radiographs consistent with POH with a novel GNAS variant.
Cohort & methodology: The patient was first noted to have soft tissue ossification at right second finger distal phalanx, and over medial left knee at age 1. Since then, she developed additional soft tissue ossifications in the left knee, foot, hands and fingers; some of which have increased in size. Bone/calcium metabolism labs like thyroid profile, Vitamin D, calcium and phosphorus were normal except for mildly elevated parathyroid hormone (PTH). Of note, she also has a prior medical history of ADHD, small size and speech delay for which genetic workup including chromosome analysis and microarray were non diagnostic. The microarray did identify two copy number variants involving small duplications of 3p14.3 and 6p22.3, 1.1kb and 473 mb respectively, which were reported as variants of uncertain significance.
Results: Targeted *GNAS* gene sequencing was recommended due to the history of soft tissue ossification. Testing identified a novel variant, NM_000516.5 (GNAS): c.662T>G (p.Met221Arg). This variant has not been previously reported in individuals with POH or in population databases. *In silico* models predict the variant to be deleterious to protein function. However, a different amino acid substitution at the same position, c.662T>C (p.Met221Thr) has been reported in a patient with pseudohypoparathyroidism inherited from a mother with pseudo pseudohypoparathyroidism.
Conclusion: This case describes a novel variant in the GNAS gene in an individual with overlapping symptoms of POH thereby suspected to be causative for POH for this individual .This report adds to our current understanding of POH variants and alludes to the clinical spectrum of GNAS variants.

C0096 EXPLORING GAIT DIVERSITY IN ADULTS WITH ACHONDROPLASIA USING WEARABLE MOTION SENSORS.

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Introduction: Achondroplasia (ACH) is characterised by short disproportionate stature, spinal deformities, and reduced functionality (1). Walking is a common activity of daily living (2), and gait variability can be used as a marker of mobility and function (3). Wearable gait tracking and analysis can be used for walking monitoring, diagnosis, and treatments (4), yet there is a lack of studies in gait in adults with ACH (AwACH) through wearable sensors.
Aims: This study aimed to identify gait diversity among AwACH through a 9-axis inertial measurement unit wearable motion sensor (Movesense).
Cohort & methodology: Twelve adults with ACH (7 women (W),5 men (M), (35.8±13.7years), 7 with natural growth (N) and 5 with limb lengthening (LL) history (height=141±6.83cm), underwent anthropometric measures and waist to hip ratio (W/H) and height to foot length ratio (H/F) calculated. All performed the 6-minutes walking test (6MWT) with Movesense placed in the right shoe. The International Physical Activity (PA) Questionnaire was applied, and participants grouped in PA levels (PAL): inactive (L1, n=6) and moderately active (L2, n=6). Gait-related parameters were calculated: Stride interval (SI), Coefficient of variation (CV%) and Sample Entropy (SaEn). Descriptive analysis, t-student test and Pearson correlations were conducted.
Results: Women presented higher means in SI (2.65 vs 2.39), CV (23.41 vs 16.88) and SaEn (1.21 vs 0.87), versus Men ($p<0.05$, 95%CI). W_LL showed higher means in SI (2.69 vs 2.63), CV (25.10 vs 21.80) and SaEn (1.41 vs 1.05) vs W_N. Significant differences in SI were observed between genders (2.74, $p=0.02$) and PAL (2.33, $p=0.04$). Between LL and N, there were significant differences in height (5.32, $p<0.001$), H/F (2.69, $p=0.02$) and 6MWT (2.62, $p=0.03$). Correlations ($p<0.01$) between W/H and SI ($r=0.67$) and CV ($r=0.72$) were found.
Conclusion: Wearable motion sensors may be a useful tool for capturing gait diversity among AwACH. Interesting trends in gait parameters were observed between genders, PAL, and N vs LL. The correlations found between gait parameters and waist-to-hip ratio hint at a potential influence of body proportions on gait in this population. Larger studies are needed to explore the clinical implications of gait variability in AwACH and the potential of wearable technology for personalized interventions mobility optimization.

C0100 RUNX2-RELATED METAPHYSEAL DYSPLASIA WITH MAXILLARY HYPOPLASIA: A RARE SKELETAL DISORDER RESEMBLING SFRP4-RELATED PYLE DISEASE.

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Introduction: Metaphyseal dysplasia with maxillary hypoplasia with(out) brachydactyly (MDMHB – OMIM# 156510) is an ultra-rare disorder that has been reported in only four families to date. MDMHB is characterised by dental anomalies, midfacial hypoplasia, widening of the clavicles, metaphyseal flaring and cortical thinning of the long bones. It may be associated with brachydactyly, osteoporosis and short stature. Heterozygous intragenic duplications within ***RUNX2*** have been identified in all cases, and they comprise either exons 3 to 5 or exons 3 to 6 and therefore duplicate the glutamine-alanine and an intact Runt (DNA-binding) domains of RUNX2, explaining their gain-of-function effect.
Aims: To expand the knowledge on the genotypic and phenotypic spectrum of RUNX2-related metaphyseal dysplasia with maxillary hypoplasia
Cohort & methodology: Phenotypic assessment of the proband consisted of a clinical evaluation and radiographic examination. Genetic analyses included whole exome sequencing, Multiplex Ligation-dependent Probe Amplification, cDNA analysis and direct sequencing of the exon junctions.
Results: We report on a fifth MDMHB family with one affected individual. Clinical and radiographic examination revealed midface hypoplasia, dental anomalies, enlarged clavicles, genua valga and metaphyseal flaring and thin cortices with an osteoporotic skeletal appearance. The proband showed a striking phenotypic resemblance to ***SFRP4***-related Pyle disease. Exome sequencing identified a ***de novo*** heterozygous tandem duplication within ***RUNX2***, encompassing exons 3 to 7. This duplication is larger than the ones previously reported since it extends into the C-terminal activation domain of RUNX2.
Conclusion: We describe a new case of ***RUNX2***-related MDMHB and highlight the phenotypic resemblance of MDMHB with Pyle disease. We identified a unique ***de novo*** heterozygous intragenic tandem duplication of exons 3 to 7 of ***RUNX2*** as the disease-causing variant in the proband. This study extends our knowledge of the genotypic and phenotypic characteristics of MDMHB and ***RUNX2***-related bone disorders.

C0104 UNDIAGNOSED DESPITE TRIO WGS: A PATIENT WITH SPONDYLOEPIMETAPHYSEAL DYSPLASIA, LOWER EXTREMITY NEUROPATHY AND ARTERIAL TORTUOSITY.

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Introduction: Spondyloepimetaphyseal dysplasia represents a group of disorders associated with abnormalities in the spine, as well as the epiphysis and metaphysis of long bones. These disorders are highly variable in presentation and severity and include phenotypes associated with variants in genes such as COL2A1 and TRPV4.
Aims: To report a patient with a complex clinical presentation including spondyloepimetaphyseal dysplasia, lower extremity neuropathy and arterial tortuosity.
Cohort & methodology: Case report.
Results: We describe the case of an 8-year-old male born to non-consanguineous unaffected parents of Chinese descent who presented with craniofacial dysmorphism,findings suggestive of spondyloepimetaphyseal dysplasia andaortic elongation with thoracic vessel tortuosity from birth. Gait abnormalities with non-progressive lower limb weakness and hyperreflexia were noted since age 3. Recently, he has been noted to have a small phallus and dystrophic nail changes, which are under investigation. He has had normal cognitive and motor development, and his family history is unremarkable. Brain and spine MRI, blood CK andmucopolysaccharide testing were normal. Electromyography testing showed chronic neurogenic pattern.Genetic testing has included normal karyotype, microarray and skeletal dysplasia panel testing. Trio Whole Exome Sequencing revealed a maternally inherited VUS in KIF22 (c.1091G>C p.R364T) not associated with his phenotype. Trio Whole Genome Sequencing revealed a de novo intronic variant in KIF21B c.265-6A>G. RNA sequencing analysis of this variantin fibroblasts did not show any evidence of a disruption in splicing.
Conclusion: This report highlights a complex case of spondyloepimetaphyseal dysplasia without a molecular diagnosis despite extensive clinical and research-based testing. The association with arterial tortuosity suggests a hereditary connective tissue disorder. Recently, pathogenic variants in KIF21B have been associated with neurodevelopmental disorders, which is not consistent with the phenotype of our patient. We plan on performing long-read whole genome sequencing next in order to look for structural or regulatory region variants not assessable by previous genetic testing modalities.

C0108 T1-T12 AND T1-S1 LENGTH AT MATURITY IN SKELETAL DYSPLASIA PATIENTS.

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Introduction: Growing spine surgery is often done to help skeletally immature patients achieve a healthy T1-T12 length. Decisions regarding growth friendly instrumentation vs. fusion often rely on assumptions about the effects of T1-T12 height. We hypothesize that skeletal dysplasia patients will have different T1-T12 and T1-S1 lengths than typically developing persons at skeletal maturity, who normally measure in values of roughly 27 and 45 cm for T1-T12 and T1-S1, respectively, as per Dimeglio in his manuscript entitled “The growing spine: how spinal deformities influence normal spine and thoracic cage growth.” Despite this, these differences will not have a profound effect on their overall health implications.
Aims: The aim of this project is to assess the dimensions associated with adequate health in skeletally mature skeletal dysplasia patients.
Cohort & methodology: A retrospective review of skeletal dysplasia patients seen at one institution from 2018-2023 was performed. T1-T12 and T1-S1 lengths were measured in all patients who achieved skeletal maturity as per radiographic parameters (i.e., Risser 5) and had an underlying diagnosis of skeletal dysplasia. Patients were excluded from our analysis if they had spinal deformity or surgery for spinal deformity (i.e., scoliosis >30 degrees). Patients’ skeletal lengths were measured utilizing the Pediatric Spine Study Group (PSSG) standard radiographic method (superior endplate of T1 to superior endplate of L1; superior endplate of T1 to superior endplate of S2).
Results: 54 patients ultimately met our inclusion criteria and had radiographs available for measurement. The average age of the patient at time of X-Ray was 43 years of age. 35 patients had diagnoses of achondroplasia; 16 had diagnoses of osteogenesis imperfecta; 3 had diagnoses of spondyloepiphyseal dysplasia congenita (SEDc). Our average T1-T12 was 26.7 cm, while our average T1-S1 was 44.1 cm. 4 patients had pneumonia and 1 had heart failure within 1 year of having had their X-Rays.
Conclusion: Despite having shorter T1-T12 and T1-S1 lengths than ‘standard’ values at skeletal maturity, there was no appreciable increase in overall health-related complications for our cohort of skeletal dysplasia patients. In this population of patients, shorter T1-T12 and T1-S1 lengths should not necessarily cause elevated concern for an increased risk of health complications.

C0110 DESIGN AND OBJECTIVES OF THE ACORN STUDY: A NON-INTERVENTIONAL STUDY EVALUATING LONG-TERM SAFETY IN ACHONDROPLASIA CHILDREN TREATED WITH VOSORITIDE.

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Introduction: Achondroplasia is a rare skeletal dysplasia leading to impaired endochondral bone growth and multiple medical complications. Vosoritide (C-type natriuretic peptide analog) is indicated for treatment of genetically confirmed achondroplasia (≥4 months until epiphyseal closure).
Aims: We describe the first treatment-based registry, created to monitor long-term safety of vosoritide in real-world use.
Cohort & methodology: Acorn is a multicenter, non-interventional, post-authorization, Category 3 safety study requested by the Europe Medicines Agency. The study aims to recruit approximately 380 participants into 2 cohorts: (1) incident users aged ≥ 4 months to ≤ 8 years old, defined as those who either recently started, or plan to start treatment with vosoritide, and (2) prevalent users who initiated treatment as part of the French expanded access program or vosoritide open-label clinical trials. The primary objective is to evaluate long-term safety including bone-related adverse events (eg. joint and spinal cord disorders, fractures and slipped capital femoral epiphyses) and immunogenicity. Secondary objectives include evaluating the long-term impact of treatment on disease-related outcomes, including achondroplasia-related complications and surgeries and changes in anthropometric measures. The study period is 10 years from the date of first patient enrolled. In addition, participants who complete (reach final adult height) or discontinue treatment during the study, will be followed up 2 years later. Almost all vosoritide treated children aged ≥ 4 months to ≤ 8 years will be eligible for the study, leading to a more representative population of participants than in clinical trials. Data collected will reflect standard clinical practice and real-life management.
Results: The EMA-approved protocol is registered on the EU post-authorization study register (EUPAS47514). In total, 8-10 countries (~30 sites) are involved. Recruitment started in April 2023; 25 participants from 9 sites are enrolled (16 in cohort 1 and 9 in cohort 2) and data will be shared on the number, location and demographics of participants.
Conclusion: Vosoritide is the first approved medicinal treatment for children with achondroplasia. Acorn will collect important long-term, real-world data across Europe, and will provide important insights into the impact of long-term treatment on safety, effectiveness, and the use of vosoritide in context of other interventions.

C0118 TOWARDS CREATION AND CHARACTERIZATION OF COL2A1-SEDC AND BGN-SEMD IPSC-DERIVED CHONDROCYTE MODELS.

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Introduction: Endoplasmic reticulum (ER) stress, followed by excessive apoptosis, attributed to aberrant protein folding is increasingly emerging as a converging pathomechanism in chondrodysplasias, including type 2 collagenopathies. Induced pluripotent stem cell (iPSC)-derived chondrocytes exhibit known chondrodysplasia mechanisms and are thus highly suitable to investigate the pathological role of ER stress.
Aims: We aim to develop a human disease model to investigate whether ER stress also contributes to spondyloepiphyseal dysplasia congenita, *COL2A1*-related (*COL2A1*-SEDC) and spondyloepimetaphyseal dysplasia, *BGN*-related (*BGN*-SEMD).
Cohort & methodology: Peripheral blood mononuclear cells of two *COL2A1*-SEDC (p.Gly408Asp; p.Gly1107Arg) and fibroblasts two *BGN*-SEMD (p.Gly259Val) patients were reprogrammed into iPSCs using Sendai vectors delivering the four key reprogramming factors (OCT3/4, SOX2, KLF4 and c-MYC). For each patient iPSC line, an isogenic control was made with CRISPR/Cas9. To assess performance of the iPSC-chondrocyte differentiation protocol, we next created control pellets with mesenchymal cell (MC)-like cells as an intermediate.
Results: Pluripotency of the iPSCs was confirmed using immunocytochemistry for OCT4, SOX2, NANOG, TRA-1-60 and TRA-1-81 and by demonstrating the iPSCs' ability to differentiate into the three germ layers by means of directed differentiation and RT-qPCR. Genomic integrity was confirmed using the HumanCytoSNP-12 BeadChip. Flow cytometry analysis verified that >95% of the resulting MC-like cells were positive for the mesenchymal stem cell markers CD105, CD90, CD73 and CD44, while <2% expressed hematopoietic markers. The MC-like cells' ability to differentiate into osteoblasts and chondroblasts was demonstrated using Alizarin Red and Alcian Blue staining, respectively. Validation of growth plate cartilage-specific gene expression, i.e. *COL2A1*, *ACAN*, *SOX9*, *COMP*, *BGN*, *MATN3*, *COL10A1*, *MMP13* and *RUNX2,* and collagen type II deposition in the iPSC-chondrocyte pellets was obtained by RT-qPCR and immunostaining.
Conclusion: In conclusion, we have established *COL2A1*-SEDC and *BGN*-SEMD iPSC lines and successfully implemented the iPSC-chondrocyte differentiation protocol in our lab as a first step in establishing chondrodysplasia disease models to study ER stress.

C0123 DIAGNOSIS AND MULTIDISCIPLINARY MANAGEMENT OF TRICHORHINOPHALANGEAL SYNDROME TYPE I: CLINICAL AND MOLECULAR DESCRIPTION OF A FAMILIAL CASE.

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Introduction: Trichorhinophalangeal Syndrome Type I (TRPS1) is a rare autosomal dominant disorder caused by variants in *TPRS1* gene, clinically characterized by skeletal findings, ectodermal features and distinctive dysmorphic traits.
Aims: We present the case of a family affected by TPRS1, explaining how we reached the diagnosis and the subsequent multidisciplinary management. We also make a comparison with the only other described in the literature case of TPRS1 caused by the same sequence variant.
Cohort & methodology: In 2018, we visited a 33 years-old woman and her 14 months-old daughter with similar phenotypes, characterized by short stature and dysmorphic features such as a pear-shaped nose, dental anomalies, narrow palate, thin upper lip, sparse medial eyebrows and large prominent ears.
We suspected TRPS1 and performed Next Generation Sequencing of the *TPRS1* gene in the mother.
Results: We identified the heterozygous pathogenetic truncating variant c.769C>T p.(Arg257*).
We investigated the variant by Sanger sequencing in her unaffected parents, which resulted negative, confirming the ***de novo*** onset of the disease, and in her daughter, who carried the variant as expected.
Once the diagnosis was established, whole-body radiography was performed and revealed ulnar deviation of the fingers and thoracolumbar scoliosis in the mother; lower limb discrepancy, bilateral valgus flat feet, severely delayed bone age and thoracolumbar scoliosis in the daughter.
We planned multidisciplinary management for the daughter (now 7 years old), including endocrinology, orthopedics, physiotherapy, ENT and dental follow-up. The endocrinologists are considering GH treatment.
We also provided genetic counselling, explaining the possibility of prenatal and preimplantation genetic testing (PGT-M) before pregnancy.
Conclusion: The c.769C>T p.(Arg257*) variant has already been described in a 9-year-old Japanese female with de novo TRPS1 who presented with similar dysmorphic features and, in contrast to our patients, sparse scalp hair, brittle and thin fingernails, flexion contractures of the fifth fingers bilaterally, and brachydactyly of the great toes bilaterally. Scoliosis was not evident on clinical examination, but the parents refused imaging studies. No further information on management is available.
This report adds to the clinical and molecular knowledge of TRPS1, highlighting the intra- and inter-familial phenotypic variability in patients carrying the same variant and the importance of genetic counselling and multidisciplinary management in diseases responsible for skeletal dysplasias.

C0130 TYPE II COLLAGENOPATHIES: PHENOTYPIC VARIABILITY.

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Introduction: *COL2A1* gene variants are associated with type II collagenopathies with different clinical phenotypes, Vitreoretinopathy with Phalangeal Epiphyseal Dysplasia (VPED), Multiple Epiphyseal Dysplasia with Myopia and Conductive Deafness (EDMMD), Stickler Syndrome (SS) type I , Spondyloepiphyseal Dysplasia congenita (SEDc), Kegg Disease, Kniest Dysplasia, Czech Dysplasia, Avascular necrosis (AVN) of the femoral head and Legg-Calve-Perthes Disease (LCPD) among others.
Aims:
Studying the variability of genes associated with Skeletal Dysplasia
Clinically describing patients and their family members
Follow-up and genetic counseling
Cohort & methodology:
Detect Femur Length in the Third Trimester of pregnancy in all pregnant women at the Maternal and Child Hospital of Malaga.
Follow-up of newborn height.
NGS Panel of patients suspected for Skeletal Dysplasia
Bioinformatic analysis
Results: 28-week-fetal-male presented Short Femur Length (FL) below the 10 th percentile. No *FGFR3* variants were detected. His mother had surgery for right hip Dysplasia. At 5 days of life, his height was below the third percentile. At three years old, he presented osteoporosis, valgus femurs with Enlermeyer flask bone deformity. At the age of six, his phenotype was mild SEDc. Radial Head Subluxation (RHS) was revealed in X-ray. Right elbow presented last degrees of flexion due to pain. Patient also showed hypermobility of the wrists and phalanges.
Described heterozygous variant in the *COL2A1* gene, classified as probably pathogenic c.1420G>A (p.Gly474Ser) was detected. This Missense variant affects a highly conserved amino acid and is found in the coding sequence of the collagen triple helix domain. Deleterious effect was estimated.
Conclusion: Interfamilial and Intrafamilial variability is described in the clinical expression of type II collagenopathies. A clear genotype-phenotype correlation in *COL2A1* gene is not yet known. It is recommended, in non-severe patients, to evaluate the musculoskeletal and skeletal malformations and carry out ophthalmological and hearing tests annually.

C0135 VAN DEN ENDE-GUPTA SYNDROME: A CLINICAL CASE WITH NOVEL VARIANTS IN COL9A2 AND SCARF2 GENES.

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Introduction: Van den Ende-Gupta syndrome (VDEGS) is a rare autosomal recessive disorder distinguished by distinctive facial and skeletal features, typically resulting from biallelic pathogenic variants in Scavenger Receptor Class F member 2 (*SCARF2)* gene. Affected individuals exhibit normal intelligence and present with blepharophimosis, malar hypoplasia, nasal and ear anomalies, arachnodactyly and camptodactyly. VDEGS includes skeletal anomalies such as hooked clavicles, dislocated radio head, craniosynostosis and radioulnar subluxation.
Variants in the collagen type IX alpha 2 chain (*COL9A2)* gene are associated with dominant multiple epiphyseal dysplasia 2 (MED2). It is characterized by early onset pain and joint stiffness, a early degenerative joint disease and fatigue.
Aims: Early detection of arthrogryposis
Identifying disease-specific variants and establishing genotype-phenotype correlations
Characterizing new variants
Cohort & methodology: Joint mobility studies
X-rays of upper and lower limbs
Skull X-ray
Molecular biology tests, targeted NGS exome
Bioinformatic analysis and prediction of protein functionality
Results: Clinical case. 2-month-old female with suspected arthrogryposis showed sharp face, long fingers, tendency to mount, difficulty in extension. Bilateral congenital elbow malformation, congenital bilateral radial head dislocation, bilateral proximal ulnar curvature and bilateral short radius were detected.
Exome NGS detected VUS heterozygous variants, one in *COL9A2* gene and two in the *SCARF2* gene. In *SCARF2* gene the variants were c.854G>A, p.Arg285Gln and c.1073G>C, p.Arg358Pro. Both were found in trans configuration. Both were missense and splicing type, they have not been described yet in the scientific bibliography. Bioinformatics algorithms estimate that these changes were not tolerated.
The variant in *COL9A2* was c.2055delC, p.Ile686fs. It is not reported in the scientific bibliography.
Conclusion: Genetic diagnosis in Skeletal Dysplasia is essential for establishing an accurate differential diagnosis to succeed in clinical approaches.

C0140 CLINICAL SPECTRUM OF PTH1R GENE VARIANTS: A CASE REPORT OF VARIABLE PHENOTYPIC PRESENTATION.

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Introduction: The *PTH1R* gene encodes the parathyroid hormone receptor on chromosome 3p21-p22.1. It is expressed in various tissues and is associated with different clinical conditions such as Blomstrand Chondrodysplasia (BOCD, OMIM:215045) and Eiken dysplasia (OMIM:600002), both inherited in an autosomal recessive. It is also associated with Jansen chondrodysplasia (OMIM:156400) and Primary Failure of Tooth Eruption (PFE) (OMIM:125350), both inherited in an autosomal dominant.
Results: Case report: We report a male evaluated at 8 years and 5 months referred for short normal stature, brachydactyly, and micropenis. He is the second child of a non-consanguineous couple. The pregnancy was uneventful, and he was born via spontaneous delivery at 39 weeks, with a birth length of 49 cm (p42, z-0.17). He evolved with high myopia, language delay, slow learning, and difficulty in fine motor skills, with no evident dental problems. Biochemical and hormonal testing was normal. On physical examination, his weight was 31.8 kg, height was 120.7 cm (-1.01SD), and BMI was 21.8 (+2.1SD). He exhibited midfacial hypoplasia, brachydactyly, brachymetatarsia/metatarsia, and micropenis. X-ray showed bilateral shortening and widening of all metacarpals of both hands and metatarsal of both feet. The panoramic dental X-rays was normal. NGS short stature panel showed a de novo heterozygous variant of uncertain significance *PTH1R*:c.1393G>A(p.Glu465Lys).
Conclusion: Discussion: The variant identified in our patient, categorized as a variant of uncertain significance, lacks presence in population databases. Computational analysis suggests its potential disruption, confirmed as de novo. Reported in a Chinese family, it displays variable clinical expressions even among relatives. Located in cytoplasmic domain, four amino acids after transmembrane region and near the protein G binding site, exhibiting evolutionary conservation. Previous studies indicate diverse effects of reported variants on receptor function, including gain or loss. Currently, there are no studies that allow us to establish the impact of this variant on receptor function. Notably, other variants in this gene and in the parathyroid hormone receptor ligand (PTHLH) correspond to a phenotypic spectrum that presents with brachydactyly, with or without dental eruption failure, and with or without facial dysmorphias. This new variant could be involved in a variable phenotype associated with the PTH pathway.

C0142 CLINICAL AND MOLECULAR FEATURES OF A PORTUGUESE COHORT OF OSTEOGENESIS IMPERFECTA TYPE V.

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Introduction: Osteogenesis Imperfecta (OI) type V is a very rare moderate-to-severe form of OI clinically distinguishable by the presence of radial head dislocation, hyperplastic callus (HC), and calcification of the forearm interosseous membrane (CFIM). OI type V results from pathogenic variants in the *IFITM5* gene. The c.-14C>T variant is responsible for most cases.
Cohort & methodology: We retrospectively evaluated clinical, radiological, and molecular data from 9 Portuguese OI type V patients, including two related patients.
Results: The mean age of our cohort is 36 years and 6 patients are famales. Prenatal ultrasound abnormalities were found in 3 cases. One case resulted in pregnancy termination due to suspected lethal bone dysplasia. Molecular diagnosis was established through next-generation sequencing panel testing in 8 patients and targeted sequencing of *IFITM5* in the remaining patient. Eight patients harbored the heterozygous c.-14C>T variant and the remaining case (a fetus) the c.119C>T variant. Short stature and early-onset and recurrent fractures were universally observed, with a moderate-to-severe disease course. The first fracture occurred within the first 2 years of life in 8 patients; among those over 25 years of age (n=4), 3 had the last documented fracture in the second decade of life. Fractures involved more frequently the limbs. Lower limb joint dislocations were noted in 2 patients. Dentinogenesis imperfecta was reported in the 2 related patients, who also presented restrictive pulmonary disease.
Radiologically, all patients displayed increased radiolucency of the bones and HC and/or CFIM. In addition, 2 patients had Wormian bones. Laboratory findings include elevation of alkaline phosphatase in 2 patients and persistent hypophosphatemia in one patient.
Conclusion: In accordance with the literature, our study enforces the association of the c.119C>T variant with a more severe form of OI type V and that this type of OI can be suspected based on the radiological findings. Notably, we report prenatal findings in a significant number of cases and variable postnatal phenotypic presentations. Our cohort reinforces that this type of OI courses with precocious clinical onset with a moderate-to-severe course that stabilizes with age.

C0144 PHENOTYPIC SPECTRUM OF RMRP-RELATED DISORDERS: A CASE REPORT WITH MODERATE PHENOTYPE ASSOCIATED WITH A RARE VARIANT.

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Introduction: The RMRP gene transcribes an RNA strand that is a component of the mitochondrial RNase MRP complex, contributing to ribosome assembly and cell cycle progression. It is associated with autosomal recessive cartilage-hair hypoplasia-Anauxetic Dysplasia (CHH-AD). The phenotype is highly variable, characterized by metaphyseal chondrodysplasia, sparse hair, ectodermal dysplasia, varying degrees of immunodeficiency, hematological abnormalities, and an increased predisposition to cancer.
Aims: To describe the molecular findings in a case with CHH-AD
Results: Case report. We report a 12-year-old boy, born to young, healthy, and non-consanguineous parents, with parents and brothers of normal height.
He was born at term, with normal birth weight and length (1.89 SD and -0.4 SD). Since 5-months-old he has been presented with slowed growth rate velocity, bicuspid aortic valve, recurrent respiratory infections, CD4 deficiency, and hemolytic uremic syndrome. At the physical exam, his height was -3.0 SD, showed a flat face, widely spaced teeth, short neck, wide thorax, prominent abdomen, mild scoliosis, and mild lower limb asymmetry, slender fingers, short distal phalanges, broad and short thumbs and first toes, and thin hair. The full X-ray survey showed typical changes for CHH-AD
By NGS sequencing two variants were identified in trans in the RMRP gene, a pathogenic variant, n.147G>A, and a likely pathogenic variant, n.90C>A
Conclusion: In this case, two variants in trans in the exon 1 in the RMRP gene were found, including one (n.90C>A) that has been classified as of unknown significance or likely pathogenic. Given the position in the gene and a previously reported similar variant (n.90C>G), we infer that this variant is likely to impact the transcript's function, diminishing its ability to bind with other proteins and form the mitochondrial RNase MRP complex. Additionally, the case's phenotype is consistent with a moderate RMRP-associated spectrum.

Body weight (kg)	Dose	Vosoritide 0.4 mg solvent (water for injections): 0.5 mL concentration: 0.8 mg/mL		Vosoritide 0.56 mg solvent (water for injections): 0.7 mL concentration: 0.8 mg/mL		Vosoritide 1.2 mg solvent (water for injections): 0.6 mL concentration: 2 mg/mL	
		Daily injection volume					
		mL	Units	mL	Units	mL	Units
4	0.12 mg	0.15 mL	15 U				
5	0.16 mg	0.20 mL	20 U				
6-7	0.20 mg	0.25 mL	25 U				
8-11	0.24 mg	0.30 mL	30 U				
12-16	0.28 mg			0.35 mL	35 U		
17-21	0.32 mg			0.40 mL	40 U		
22-32	0.40 mg			0.50 mL	50 U		
33-43	0.50 mg					0.25 mL	25 U
44-59	0.60 mg					0.30 mL	30 U
60-89	0.70 mg					0.35 mL	35 U
≥ 90	0.80 mg					0.40 mL	40 U

Duration of treatment: Treatment with this medicinal product should be stopped upon confirmation of no further growth potential, indicated by a growth velocity of <1.5 cm/year and closure of epiphyses. *Missed dose:* If a dose of vosoritide is missed, it can be administered within 12 hours. If more than12 hours have passed since the original dosing schedule, the missed dose should NOT be administered. Patients/caregivers should be advised to continue with the next scheduled dose the following day. *Growth monitoring:* Patients should be monitored and assessed regularly every 3-6 months to check body weight, growth and physical development. Dose should be adjusted according to the patient's body weight (see Table). *Patients with renal or hepatic impairment:* The safety and efficacy of vosoritidein patients with renal or hepatic impairment has not been evaluated. *Paediatric population:* Thesafety and efficacy of VOXZOGO® in children aged less than 4 months is limited,no recommendation on a posology can be made. **Administration:** VOXZOGO® is for subcutaneous single use only. This medicinal product must be administered within 3 hours of reconstitution. Prior to injecting, a healthcare professional should: train caregivers on the preparation and subcutaneous injection of this medicinal product; train caregivers and patients to recognise signs and symptoms of decreased blood pressure; inform caregivers and patients what to do in the event of symptomatic decreases in blood pressure. Patients and caregivers should be instructed to rotate sites for subcutaneous injections. Recommended injection sites on the body include the front middle of the thighs, the lower part of the abdomen except for 5 cm directly around the navel, top of the buttocksor the back of the upper arms. The same injection area should not be used on two consecutivedays. VOXZOGO® should not be injected into sites that are red, swollen, or tender. Patients should bewell hydrated at the time of injection. It is recommended patients eat a light snack and drink an adequate amount of fluid (e.g., water, milk, juice, etc.) about 30 minutes before injecting. This is to reduce the signsand symptoms of potential decreases in blood pressure (dizziness, fatigue and/or nausea) occurring. If possible, this medicinal product should be injected at approximately the same time each day.

Contraindications: Hypersensitivity to the active substance(s) or to any of the excipients. **Warnings and precautions:** *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded. *Blood pressure effects:* Patients with significant cardiac or vascular disease and patients on anti-hypertensive medicinal products were excluded from participation in premarketing clinical trials. To reduce the risk of a potential decrease in blood pressure and associated symptoms (dizziness, fatigue and/or nausea),patients should be well hydrated at the time of injection. *Sodium:* This medicinal product contains less than 1 mmol sodium (23 mg) per unit volume, essentially 'sodium-free'. **Interaction with other medicinal products:** In vitro cytochrome P450 (CYP) inhibition and induction studies and in vitro transporter inhibition studies have been performed. Results suggested that vosoritide is unlikely to cause CYP- or transporter-mediated drug-drug interactions in humans when the medicinal product is administered concomitantly with other medicinal products. No other interaction studies have been performed. Because it is a recombinant human protein, vosoritide is an unlikely candidate for drug-drug interactions. **Fertility, pregnancy and lactation:** *Pregnancy:* There are no or limited amount of data from the use of vosoritide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of vosoritide during pregnancy. *Breast-feeding:* Available pharmacodynamic/toxicological data in animals have shown excretion of vosoritide in milk. A risk to newborns/infants cannot be excluded. Vosoritide should not be used during breast-feeding. Fertility: No impairment of male or female fertility has been observed in nonclinical studies. **Effects on ability to drive and use machines:** VOXZOGO® has moderate influence on the ability to drive, cycle and use machines. Vosoritide may cause transient decreases in blood pressure that are usually mild but syncope, pre-syncope, and dizziness, as well as other signs and symptoms of decreased blood pressure have been reported as adverse reactions with VOXZOGO®. The patient's response to treatment should be considered and if appropriate, advised not to drive, cycle or use machines for at least 60 minutes after injection. **Overdose:** In clinical trials, doses of vosoritide were explored up to 30 µg/kg/day. Two patients received up to 3

System organ class	Very common	Common	Uncommon
Nervous system disorders		Syncope	
		Pre-syncope	
		Dizziness	
Vascular disorders	Hypotension[a]		
Gastrointestinal disorders	Vomiting	Nausea	
Skin and subcutaneous disorders			Hypertrichosis
General disorders and administration site conditions	Injection site reaction[b]	Fatigue	
Investigations	Increased alkaline phosphatase		

[a] Hypotension includes both asymptomatic and symptomatic adverse reactions.

[b] Injection site reactions include the preferred terms; injection site erythema, injection site reaction, injection site swelling, injection site urticaria, injection site pain, injection site bruising, injection site pruritus, injection site haemorrhage, injection site discolouration, and injection site induration.

times the recommended daily dose of 15 µg/kg/day for up to 5-weeks. No signs, symptoms or adverse reactions associated with the higher than intended dose were observed. In the event a patient takes more than they should, the patient should contact their healthcare professional. **Summary of the safety profile:** The most common adverse reactions to vosoritide were injection site reactions (85%), vomiting (27%), and decreased blood pressure (13%). **Tabulated list of adverse reactions:** Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. See the Voxzogo SmPC for full details of adverse reactions.

Special precautions for storage: Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store in the original package in order to protect from light. VOXZOGO® may be stored at room temperature below 30 °C fora single period up to 90 days, but not beyond the expiry date. Do not return VOXZOGO® to refrigeratorafter storage at room temperature. If not used immediately, VOXZOGO® must be administeredwithin 3 hours of reconstitution. **Marketing authorisation holder:** BioMarin International Limited. Shanbally, Ringaskiddy, County Cork, Ireland. **Marketing authorisation number(s):** EU/1/21/1577/001 - EU/1/21/1577/002 - EU/1/21/1577/003 Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/ - **Date of first authorisation:**August 2021. Latest aPI revision: June 2024. VOXZOGO® is a trademark of BioMarin Pharmaceutical Inc. from whom further information is available. **Legal classification:** Prescription-Only Medicine.

Healthcare professionals should report adverse events in accordance with their local requirements.

Adverse events should also be reported to BioMarin on

+ 1 415 506 6179 or drugsafety@bmrn.com

NOTES

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