2025
ESPE-OSCAR
SCIENCE SYMPOSIUM

Mineralization of bone and growth plate, towards the development of new therapies

PARIS
September 18 & 19

ABSTRACT BOOK

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PARIS 2025

WELCOME MESSAGE

Prof. Agnès LINGLART

Dear colleagues,

We are delighted to welcome you to the **2025 ESPE–OSCAR SCIENCE SYMPOSIUM**, held in Paris, France, on **18 and 19 September 2025**.

This fifth edition of the ESPE Science Symposium is organized jointly by the **European Society for Paediatric Endocrinology (ESPE)** and the French rare disease network **OSCAR**, dedicated to bone, calcium, and cartilage disorders. This high-level scientific event continues the tradition of previous ESPE Science Symposia, which aim to foster collaborative research, bridge the gap between basic science and clinical practice, and support the dissemination of cutting-edge knowledge in paediatric endocrinology.

The 2025 symposium focuses on the theme:

Mineralization of bone and growth plate, towards the development of new therapies

Throughout the two-day programme, international experts will share insights on key topics such as:

- Genetic and developmental skeletal disorders
- Advances in the understanding of short stature and bone growth
- The role of the growth plate and novel imaging/analysis techniques
- New perspectives on vitamin D metabolism and action
- The use of dental structures to study bone pathophysiology
- Clinical and research approaches to fibrous dysplasia

The programme includes keynote lectures, oral communications, posters, a panel discussion, and networking sessions. It offers a unique opportunity for scientists and clinicians to exchange ideas, discuss innovations, and build collaborative efforts across Europe and beyond.
We are honoured to welcome you in **Paris**, a city of knowledge, culture, and scientific inspiration. We wish you a stimulating and productive symposium.

Warmest regards,
On behalf of the Scientific and Local Organizing Committees
Prof. Agnès LINGLART
Scientific President
Le Kremlin-Bicêtre, France

SCIENTIFIC AND LOCAL ORGANIZING COMMITTEE

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The European Society for Paediatric Endocrinology (ESPE) is an international non-profit scientific organisation dedicated to improving the clinical care of children and adolescents with endocrine and metabolic conditions, including diabetes and rare bone disorders, through research, education, and the development of clinical standards. ESPE is a founding member of the International Consortium of Pediatric Endocrinology (ICPE) and actively promotes global collaboration in the field. Its mission is to advance excellence in paediatric endocrinology, diabetes, and bone disorders by fostering scientific discovery, medical education, and high-quality clinical care.

OSCAR - French rare diseases Healthcare Network: bone, cartilage and calcium diseases, officially designated and funded by the French Ministry of Health since 2014 under the National Rare Disease Plan. OSCAR is hosted by Assistance Publique – Hôpitaux de Paris (AP-HP) and coordinates a national network of expert centers, patient associations, research laboratories, and healthcare professionals dedicated to improving care, research, and education in rare skeletal diseases.

ORGANIZER

European Society of Pediatric Endocrinology (ESPE) & OSCAR, The French network of rare bone, calcium and cartilage diseases

EVENT

**2025
ESPE-OSCAR
SCIENCE SYMPOSIUM**

DATES

September 18 & 19, 2025

VENUE / CITY

**PARIS – FRANCE
Hyatt Regency Paris Étoile**

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2025 ESPE–OSCAR SCIENCE SYMPOSIUM

ABSTRACTS

ID: 108 Medical Abstracts / Case Reports / Clinical Cases

ENPP1 DEFICIENCY: BURDEN OF THE DISEASE AND IMPACT ON HEALTH SYSTEM IN FRANCE

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1. Introduction and objectives

ENPP1 deficiency is an ultra-rare genetic disorder due to biallelic mutations in *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1) or *ABCC6* (ATP-binding cassette, subfamily C, member 6) leading to insufficient inorganic pyrophosphate synthesis and consequently, severe calcification of the internal elastic lamina, fibrotic myointimal proliferation of muscular arteries, and subsequent arterial stenosis, starting from birth (Generalized Arterial Calcification of Infancy, GACI). This condition is associated with high mortality due to multivisceral damage during the 1st year after birth and high morbidity later in life. *ENPP1* deficiency may also manifest later in life, particularly through hypophosphatemic rickets.

In France, patients followed in centres for rare diseases are systematically included in the BNDMR database (Banque Nationale des Données Maladies Rare).

The present work is a transversal multicentric study aiming to describe the cartography and burden of *ENPP1* deficiency on the health system in France.

2. Results

Data extracted from the BNDMR identified 38 patients affected with *ENPP1* deficiency in France, of which living 34 were included in the analysis (17 men and 17 females, median age of 21 [9.3-34.5] years). Two thirds of patients (62%, n=21) are recorded as GACI and one third are recorded with hypophosphatemic rickets (38%, n=13). Only one patient is said to present both diagnoses. The median follow-up duration in the reference center was 3 [0.3-7.5] years. During follow-up, each patient had about 11 [4.0-31.8] hospital visits, among which 7 [3.0-19.8] out-patient visits and 1.15 [0-12.8] in-hospital admissions. The time-frame between the different hospital visits was about 1.1 [0.7-3.2] months. Each patient met different healthcare-providers (medical doctors, nurses, nutritionists, psychologists, physiotherapists, orthoptists), mainly medical doctors (96%). During hospital visits, patients underwent clinical examination (22/patient), blood exam (26/patient), and imaging (16/patient).

3. Conclusion and perspectives

Our data demonstrate a very high burden of *ENPP1* deficiency on the patient's life and on French health system. This justifies the development and implementation of an appropriate and efficient treatment for this condition.

**Keywords:* ENPP1, arterial calcification, hypophosphatemic rickets*

ID: 109 Medical Abstracts / Case Reports / Clinical Cases

HIGHER INCIDENCE OF FRACTURE IN ADULTS WITH OSTEOGENESIS IMPERFECTA: IDENTIFICATION OF THE RISK FACTORS

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1. Introduction and objectives

Fractures are recurrent in adults with osteogenesis imperfecta (OI). There are no identified risk factors that predict the occurrence of fracture in adult life. We investigated prospectively the factors associated to the occurrence of fractures in adults with OI followed in a Reference Centre of Rare Bone Diseases.

2. Materials and methods

Among the 106 patients with OI, we included those with BMD measures at one or more skeletal sites (total hip [TH], lumbar spine [LS] or the radius [Rd]), and naïve of bone treatment at baseline. From 2000 to 2022, we collected the clinical data, genotype, BMD and incident fractures from inclusion. We investigated the probability of fracture during follow-up via a logistic regression analysis as a function of age, Z-Score BMD and variant pathogenicity.

3. Results

35 patients were not analyzable because BMD measures were not reliable for technical limitations. 71 patients were included at the initial visit (44 women and 27 men, mean age of 41.4 ± 13.7 years) and were followed for 5.05 years (IQR: 3.18 – 8.75 y). Baseline BMD revealed a low Z-Score (-2.7 ± 1.5 SD) at the LS only affecting mainly men (Z-Score -3 ± 1.6 SD). The mean number of fractures that occurred during the follow-up was higher in the presence of missense variants of COL1 ($p<0.05$). The logistic regression adjusted for the determinants revealed a high probability of fracture with BMD Z-score < -2 SD at any of the 3 skeletal sites (OR 4.38, IC 1.10-21.75, p=0.048) and with missense variants only (stop codon, frameshift variants, OR 29, IC 2.56-1503, p=0.02).

4. Conclusion and perspectives

Our OI cohort revealed a low BMD z-score at the LS. The probability of fractures was higher with low BMD and missense variants. These data identify the risk factors associated with fractures that could be used for treatment decision.

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**Keywords:* Osteogenesis imperfecta, bone density, DXA, rare diseases, bone fragility*

ID: 110 Medical Abstracts / Case Reports / Clinical Cases

PROGRESSION OF SPINAL FIBROUS DYSPLASIA LESIONS IN ADULTS

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Fibrous dysplasia (FD) lesions can enlarge during growth, in cases involving aneurysmal cystic transformation, in association with acromegaly, or during hormonal changes like pregnancy. In adults, structural changes suggest potential sarcomatous degeneration or coexisting malignant lesions. Routine imaging follow-up for adults' dysplastic lesions is generally not recommended, except in specific situations, such as scoliosis[1]. We here present five adult cases of spinal FD who exhibited lesion progression, outside the aforementioned contexts.

Between October 2023 and December 2024, 135 patients consulted at our center; 13 patients (9.6%) with spinal involvement. Among them, five patients (38.5%) had a progression of FD spinal lesions, observed through CT scans performed on average 10.4 ± 2.9 years apart.

Sixty percent are women with an average age of 53.4 years ± 1.1. Eighty percent have a polyostotic form, without McCune-Albright syndrome. The lumbar and cervical spine are affected in 40% each, while the thoracic spine is involved in 20%. Both men exhibit phosphate diabetes without hypophosphatemia. CTX levels average 429.5 pg/mL ± 121.7.

Only one patient received bisphosphonates therapy, last administered in May 2019.
Two underwent intervention due to spinal instability threatening nearby neurological structures: one at the lumbar spine via cementoplasty and one at the thoracic level via extended arthrodesis.
This series of five cases showing progression of spinal lesions of fibrous dysplasia in adults since 2023 prompts us to recommend CT monitoring for patients with axial skeletal dysplastic lesions. The monitoring frequency is not fully determined and should be adjusted based on lesion size and clinical symptoms. Structural progression screening in a larger patient population would help clarify the incidence of this phenomenon and identify potential risk factors.

**Keywords:* fibrous dysplasia, progression, spine*

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ID: 111 Basic and translational research

IMPLICATION OF AUTOTAXINE IN ORAL FIBROUS DYSPLASIA OF BONE

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1. Introduction and objectives
Fibrous Dysplasia (FD) is a benign and rare genetic disease characterized by progressive replacement of normal bone by a non-mineralized matrix. FD is caused by GNAS mutations, causing Gαs constitutive activation, which increases intracellular cAMP levels. While appendicular lesions have been widely studied leading to improvement in understanding and management, craniofacial lesions pathogenesis remains poorly described although these two skeletal regions present embryological, phenotypic and mechanical differences. In addition, bone cells express autotaxin (ATX), a major source of lysophosphaditique acid (LPA), implicating in proliferation, cell differentiation, skeleton development and bone diseases. Of interest, cAMP and LPA pathways are intricated. Our objective was to evaluate the relationship between LPA/ATX and bone homeostasis in craniofacial FD.

2. Materials and methods
Osteoblasts were obtained from FD (n=7) and non-FD (n=8) patients during oral surgery (DC-2014-2262) and cultured in osteogenic medium for 21 days. cAMP level was measured as a hallmark of GNAS mutation. Proliferation assays (DNA, WST-1), osteoblastic phenotype characterization (ALPL, Alizarin red, COLIA1 and osteocalcin immunostaining, RT-qPCR) were evaluated at day 7, 14 and 21. ATX and LPA_{1-6} receptors expression were evaluated by RT-qPCR. Additionally, osteoclast differentiation was performed in FD and non-FD osteoblasts' conditioned supernatants. After 21 days of differentiation, OC were stained (Phalloïdin-AlexaFluor488®, Vinculin-immunofluorescent staining, DAPI) to determine osteoclasts' number and size.

3. Results
Higher intracellular cAMP levels were observed in FD osteoblasts, along with an increased proliferative capacity. Osteoblastic differentiation is reduced and a lack on mineralization capacities marked by a decreased RA staining and osteocalcin immunostaining in FD osteoblasts was evidenced. The expression of ATX and LPA4 receptor tended to be increased under FD conditions. Interestingly, we demonstrated a decrease in osteoclastogenic potential marked by an increase in OPG expression and secretion (3.6fold at day21, $p<0.05$) from craniofacial FD osteoblasts. This observation was sustained by significantly twice less OC formation in FD-conditioned medium as compared to non-FD-conditioned medium at 21-days-culture without any variation of their size.

4. Conclusion and perspectives
Although some characteristics are common between osteoblasts from the craniofacial and appendicular skeleton (increased proliferative capacity and impaired osteoblastic maturation), orofacial lesions are characterized by a reduction in osteoclastogenic potential, marked by an increase in OPG secretion and a decrease in osteoclast formation in conditioned medium. Variations in the expression of autotaxin and LPA4 could be a piece of explanation for understanding the physiopathological phenomena of craniofacial lesions and represent a future therapeutic avenue.

**Keywords:* Fibrous dysplasia of bone, osteoblast, osteoclast, human primary cell culture*

ID: 112 Basic and translational research

ASSESSMENT OF PLACENTAL VITAMIN D TRANSPORT IN A UK COHORT ENRICHED FOR PREGNANCIES WITH SUBOPTIMAL FETAL GROWTH

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1. Introduction and objectives
Vitamin D deficiency in infancy can have severe consequences of hypocalcaemia and seizures. Maternal 25(OH)D was previously thought to diffuse passively across the placenta, and to be hydroxylated in the fetus to $1,25(OH)_2D$. Recent work on human placentas from healthy term pregnancies has shown active placental transport of 25(OH)D3 and synthesis of $1,25(OH)_2D3$ suggesting that fetal supply is dependent on placental function, not availability of maternal 25(OH)D3 alone. Therefore, we wanted to investigate indicators of placental 25(OH)D3 transport in a cohort of pregnancies enriched for suboptimal fetal growth, to determine whether routine measurement of vitamin D status in infants born following these pregnancies is required.

2. Materials and methods
Maternal vitamin D and calcium intake were quantified using Health and Environment-wide Associations based on Large population Surveys-HEALS dietary questionnaires. Samples were taken from the centre, middle and edge of 15 healthy placentas and were formalin-fixed paraffin embedded. 5µm thick sections were cut using a microtome (Leica) and mounted onto slides. Immunohistochemistry (IHC) was performed and used to quantify the expression of vitamin D receptors (VDR) and vitamin D binding protein (VDBP). Δfetal weight was calculated as birthweight centile minus 23-week estimated fetal weight centile/days, and groups were defined based on above and below the median of intrauterine weight gain. Expression levels were compared between groups using Mann-Whitney U tests.

3. Results
53% of the women had inadequate (<600IU/d) dietary vitamin D intake during pregnancy (mean 612.5 (SD 217.4)). For all pregnant women, dietary calcium intake was inadequate (<1000mg/day, 300.5 (114.8)) with 97% having calcium intake below the recommended standard adult amount (700mg/day). Due to image quality limitations, 14 samples underwent VDBP and 12 VDR quantification, with 11 samples having both staining available for quantification. 10/14 (71%) had negative Δfetal weight indicating suboptimal fetal growth and only 4/14 (29%) had positive Δfetal weight. There were no differences in VDBP (p=0.31) or VDR expression between groups with lowest (<-0.078) and highest (>-0.078) intrauterine weight gain (p=0.45).

4. Conclusion and perspectives
Within this small cohort enriched for pregnancies with suboptimal fetal growth, over 50% of mothers had inadequate vitamin D and all had inadequate calcium intake. There were no differences in VDR or VDBP expression between groups of intrauterine weight gain. Further work will involve assessment of the TRPV6 channel to assess calcium transport and could be enhanced through inclusion of a nutritionally-replete control cohort with optimal fetal growth.

**Keywords:* placenta, vitamin D, vitamin D receptor, vitamin D binding protein*

ID: 113 Medical Abstracts / Case Reports / Clinical Cases

IMPACT OF GROWTH HORMONE TREATMENT ON CHILDREN FROM AN EXTENDED FAMILY WITH ACAN VARIENT: A LONG-TERM FOLLOW-UP

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1. Introduction and objectives

Heterozygous *ACAN* gene variants are implicated in approximately 1% of familial short stature cases. This study aimed to characterize the clinical phenotype and response to growth hormone (GH) therapy in members of an extended family harboring an *ACAN* variant.

2. Materials and methods

Seven related children (five males, two females) were included. Clinical data were retrospectively collected, including parental heights, age at genetic diagnosis, anthropometric measurements, pubertal staging, medical treatments, bone age, and laboratory results.

3. Results

The mean age at initial evaluation was 1.7 ± 1.0 years. Mean baseline height, weight, and BMI standard deviation scores (SDS) were −3.4 ± 1.0, −1.6 ± 1.2, and 1.0 ± 1.2, respectively. GH therapy was initiated in five patients at a mean age of 3.2 ± 2.1 years, with a mean treatment duration of 6.4 ± 5.0 years. A significant improvement in height-SDS was observed (−3.3 ± 1.0 to −2.0 ± 1.1; p = 0.001). The most notable increase in growth velocity SDS occurred during the first year of treatment (−0.5 ± 0.6 to 2.1 ± 1.2; p = 0.04). The median increase in height SDS was 1.2 (range 0.8-1.5). No adverse effects were observed, and bone age did not advance significantly during treatment. Three children entered puberty between 10 and 11.6 years and received adjunctive GnRH analog therapy. Genetic testing identified a heterozygous nonsense variant in exon 10 of the *ACAN* gene (c.2023C>T; p.Arg675*).

4. Conclusion and perspectives

GH therapy can improve growth velocity and height in children with *ACAN*-related short stature, though the degree of response varies even within the same family.

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**Keywords:* ACAN, growth hormone therapy, short stature*

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ACHONDROPLASIA AND HYPOCHONDROPLASIA IN FRANCE: A NATIONWIDE EPIDEMIOLOGICAL ANALYSIS

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1. Introduction and objectives

Achondroplasia (ACH) and hypochondroplasia (HCH) are among the most common skeletal dysplasias, characterized by disproportionate short stature and caused by gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene. While the birth prevalence of ACH has been previously described in Europe (3.72 per 100,000)[1] and worldwide (4.6 per 100,000)[2], it is not known whether these figures are applicable to France, given the significant rate of medical terminations of pregnancy due to achondroplasia and increased paternal age. HCH birth prevalence remains poorly defined.

Using data from the French National Registry of Rare Diseases (*Banque Nationale de Données Maladies Rares*, BNDMR), this study provides the first nationwide estimates of birth prevalence for ACH and HCH in France.

2. Materials and methods

We conducted a retrospective analysis of patients recorded with ACH (ORPHA:15) or HCH (ORPHA:429) in BNDMR. Live birth prevalence was calculated using data between 2008 and 2023 from the National Institute of Statistics and Economic Studies (*Institut National de la Statistique et des Études Économiques*, INSEE).

3. Results

As of January 1, 2024, a total of 1,438 patients with ACH or HCH were recorded in BNDMR (998 ACH and 440 HCH). After excluding fetal cases and patients who opposed to data use, 766 ACH and 408 HCH patients formed the full analysis sets. Most patients were followed in expert centers for rare skeletal dysplasias (ACH: 71.3%; HCH: 63.4%). Overall, 85.5% of ACH and 57.2% of HCH cases were related to *de novo* genetic variants. ACH was diagnosed at birth in 40.6% and prenatally in 40.8% of patients; in contrast, HCH was diagnosed postnatally in 65.7% of patients. Molecular diagnostic confirmation was more frequently recorded for ACH (92.9%) than HCH (62.2%). The mean (range) live birth prevalence was 3.27 per 100,000 for ACH (1.90–4.03) and 1.31 per 100,000 for HCH (0.54–2.08).

4. Conclusion and perspectives

This study provides the first national estimates for ACH and HCH in France, leveraging data from the BNDMR. ACH is often identified prenatally and referred to expert centers. In contrast, HCH is frequently diagnosed postnatally. The HCH prevalence may be underestimated because it may remain unrecognized in milder forms. Given the emergence of ACH specific therapies and HCH in the near future, strengthening specialized care pathways is critical to ensure equitable access to timely diagnosis and interventions.

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Keywords: Achondroplasia, Hypochondroplasia, France, prevalence*

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DENOSUMAB TREATMENT IN A CHILD WITH CRANIOFACIAL FIBEROUS DYSPLASIA AND COMPRESSIVE OPTIC NEUROPATHY: A CASE REPORT

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1. Introduction and objectives

Fibrous dysplasia (FD) is a rare, mosaic skeletal disorder caused by postzygotic activating mutations in the *GNAS* gene, leading to altered skeletal stem cell differentiation. This results in expansile, fibro-osseous lesions that can cause fractures, deformities, and functional impairment. Craniofacial involvement may lead to vision or hearing loss due to compression of neural structures.

2. Materials and methods

We present a case of an 11-year-old boy with a known FD lesion in the left maxillary bone since infancy. Over the past two years, he developed progressive proptosis of the left eye and, more recently, transient episodes of monocular blindness upon awakening, lasting 10–45 minutes. He reported no associated pain. He was referred to our center for a second opinion regarding management options.

3. Results

Physical examination revealed expansion of the left maxilla, without café-au-lait spots. Laboratory results showed: calcium 9.7 mg/dL, phosphate 4.2 mg/dL, ALP 679 IU/L, 25-OH vitamin D 9.3 ng/mL, PTH 114 pg/mL, CTX 2146 pg/mL (ref: 393–2131), P1NP 1014 ng/mL (ref:323-1242), GH 0.5 µg/L, IGF-1 12.3 nmol/L (ref: 13.2–61), prolactin-3.8 mcg/l (3-25), FSH-1.3 IU/l, LH<1 IU/l, T<0.4 nmol/l, cortisol-122 nmol/l, TSH-1.45 miu/l, FT4-11.2 pmol/l, FT3-6.2 pmol/l. Eye exam showed left eye proptosis, hypoglobus, and a pale optic disc-consistent with compressive optic neuropathy. Optical coherence tomography demonstrated thinning of the retinal ganglion cell layer. Skeletal survey revealed thickening of the left maxillary and parietal bones. Brain MRI showed expansile bone lesions involving the left orbit, sphenoid, frontal and temporal bones, sella turcica, and clivus, resulting in narrowing of both optic canals, more pronounced on the left. A multidisciplinary team concluded the lesion was not surgically accessible. Due to the risk of permanent vision loss, denosumab therapy was initiated at a dose of 0.25 mg/kg every four weeks.

4. Conclusion and perspectives

Denosumab may offer clinical benefit in pediatric FD patients with craniofacial involvement by reducing lesion activity and relieving compressive symptoms. However, careful monitoring is essential due to risks of hypocalcemia during treatment and rebound hypercalcemia upon cessation.

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Keywords: Fibrous dysplasia, optic neuropathy, denosumab*

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THE ROLE OF BISPHOSPHONATES AND TESTOSTERONE IN ENHANCING QUALITY OF LIFE IN DUCHENNE MUSCULAR DYSTROPHY: A CASE STUDY

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1. Introduction and objectives
Duchenne muscular dystrophy (DMD) is associated with skeletal complications including osteoporosis, growth failure, and delayed puberty, largely due to chronic glucocorticoid (GC) therapy. Managing bone health is crucial, as patients face a high risk of fractures and reduced quality of life. Bisphosphonates are the mainstay for osteoporosis, while testosterone is essential for inducing puberty in affected boys. To illustrate the clinical value of combined bisphosphonate and testosterone therapy in improving bone health, alleviating symptoms, and enhancing quality of life in a 15-year-old boy with DMD.

2. Materials and methods
In June 2024, a 15-year-old boy with DMD (diagnosed at age 3) presented with back pain and low mood. He had been on daily deflazacort (21 mg) since 2019. Examination revealed a cushingoid appearance, bilateral knee contractures, and prepubertal status (Tanner I). The Beck Depression Inventory indicated moderate depression. A DEXA scan revealed low bone mineral density (BMD) with lumbar spine Z-score of -2.7. Hormonal testing confirmed prepubertal gonadotropin and testosterone levels.
Follow-up imaging showed further BMD decline (lumbar Z-score: -3.2, left hip: -3.9) without vertebral fractures. Treatment with 0.1mg/kg zoledronic acid (IV every 6 months) and 50 mg intramuscular testosterone (monthly) was initiated.

3. Results
Six months into treatment, the patient reported resolution of back pain, mood improvement, and excitement about signs of puberty. Depression remitted. A repeat DEXA scan still showed declining BMD (Lumbar Z-score :-3.4, left hip: -3.9), prompting another zoledronic acid infusion. Despite this, pain relief and psychosocial improvements were notable.

4. Conclusion and perspectives
This case highlights the role of dual therapy with bisphosphonates and testosterone in managing skeletal and pubertal complications in DMD. While initial zoledronic acid infusion did not improve BMD, the combination approach alleviated symptoms and improved quality of life.
Preventive and sustained bisphosphonate therapy may be critical not only during acute phases of bone loss but also in long-term management. Broader data collection is needed to guide standardized care and improve outcomes for boys with DMD.

**Keywords:* Duchenne Muscular Dystrophy, bisphosphonates, testosterone, combined therapy*

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EFFECTS OF A CARDIORESPIRATORY REHABILITATION PROGRAMME IN EXERCISE TOLERANCE IN AN ADULT WITH PYCNODYSOSTOSIS: A CASE STUDY

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1. Introduction and objectives

Pycnodysostosis is an ultra-rare autosomal recessive skeletal dysplasia (1-5/1 000 000 births) caused by mutations in the *cathepsin K* gene[1]. Clinical features include disproportionate short stature, facial dysmorphism, bone fragility, and an increased risk of fractures[2]. Individuals with this condition often experience reduced exercise tolerance, impaired mobility, and a heightened risk of falls. The Timed Up and Go (TUG) test is a simple and reliable measure of functional mobility and balance, directly correlating with risk of falls. This study aimed to evaluate the impact of a structured cardiorespiratory rehabilitation program on balance and mobility in an adult with pycnodysostosis, with a particular focus on TUG performance.

2. Materials and methods

A 42-year-old female with genetically confirmed pycnodysostosis (pathogenic variant c.436G C p. (Gly146Arg) in probable homozygosity in *CTSK* gene), with a body mass of 38kg and with 140cm height, was evaluated. The patient had a history of multiple fractures and was recovering from a surgically stabilized left tibial fracture. She underwent a 3-month outpatient cardiorespiratory rehabilitation program, from January to March 2024, consisting of twice-weekly sessions. Each session included a warm-up, strength training, aerobic exercise, balance and flexibility exercises, and monitoring of perceived exertion (RPE) using the modified Borg scale (rated from 0 to 10). The TUG test was administered over a standardized 3-meter distance at baseline, week 4, and week 8, to assess functional mobility and risk of falls.

3. Results

The TUG performance improved considerably throughout the rehabilitation program: from 18 seconds at baseline to 11 seconds at week 4, and 9 seconds at week 8, representing a 50% improvement. In parallel with the TUG test results, the patient reported a reduction in exertional dyspnea, from 5 to 2 RPE, and expressed less fear of falling.

4. Conclusion and perspectives

This case report demonstrates that the TUG test served as a simple, accessible and effective tool for monitoring mobility improvements in an adult with pycnodysostosis. Given the increased risk of fracture associated with this condition, interventions that enhance balance and reduce risk of falls are of particular value. Future research should investigate the long-term sustainability of these improvements and work towards the development of specific rehabilitation guidelines for patients with rare skeletal dysplasias. Multidisciplinary collaboration is essential to optimize care and create standardized rehabilitation protocols for this patient population.

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Keywords: skeletal dysplasia, short stature, bone fragility, functional capacity*

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PREVENTION OF HEIGHT DEFICIT BY BUROSUMAB IN TODDLERS AFFECTED BY XLH

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1. Introduction and objectives

X-linked hypophosphatemia (XLH) is a rare disease caused by *PHEX* mutations. Besides rickets, XLH leads to disproportionately short stature which develops during the first months of life. Burosumab afforded minimal improvement of growth in children above the age of four years. No data are available on growth, including body mass index, of XLH children who started burosumab at a very young age, i.e., between one and four years.

2. Materials and methods

We performed a prospective follow-up of growth and other XLH-related outcomes in XLH children who started burosumab before the age of four years. We compared these children 1:2 with a cohort of XLH children who started vitamin D analogs and phosphate supplements before the age of four years.

3. Results

We included 15 children treated with burosumab and 31 children treated with vitamin D analogs and phosphate supplements. In the burosumab-treated group, mean± SD for age at therapy baseline was 2.1± 0.7. They were treated conventionally for 1.7±0.8 years before switching to burosumab. From birth to burosumab start, they presented a decline in height standard deviation score (SDS) from -0.3±0.7 to -1.4±0.8 (mean± SD), respectively, p<0.001. On burosumab, height SDS did not decline further during the first two years of treatment: mean± SD 0.1±0.6 after one year (p=0.16) and 0.0±0.7 SD after two years (p=0.54). Burosumab did not correct the acquired height deficit as children had a difference in height SDS of -1.5 SDS after two years of therapy when compared to birth length SDS (p=0.04). BMI SDS did not significantly change during the first two years on burosumab. Children treated with vitamin D analogs and phosphate supplements started treatment earlier (1.2±0.8 years old) and presented a continuous decline in height SDS of 0.7±0.9 SDS during the first two years of therapy (p<0.001) and up to four years of age (-1.8 ± 0.9 SDS, to -1.9 ± 0.9, respectively). BMI SDS increased by 0.5±0.9 SDS during the same period (p=0.006).

4. Conclusion and perspectives

We present data from the largest pediatric XLH cohort of very young children treated with burosumab over a follow-up period of two years. Our data suggest that, in contrast to the combination of vitamin D analogs and phosphate supplements, burosumab prevents height deficit in XLH children, even at a period of life associated with a high growth velocity. In addition, burosumab prevents the early and excessive weight gain associated with the development of XLH in children.

**Keywords:* XLH, height, PHEX, short stature, young pediatric population*

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CONFIRMATION OF FGFR1 FRAMESHIFT VARIANTS IN MULTIPLE EPIPHYSEAL DYSPLASIA: EXPANDING THE PHENOTYPIC AND GENOTYPIC SPECTRUM

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1. Introduction and objectives

Multiple Epiphyseal Dysplasia (MED) is a genetically diverse skeletal disorder marked by abnormal and delayed epiphyseal ossification and the early development of osteoarthritis. Individuals affected by MED often experience joint pain and stiffness, particularly in the hips and knees, and may exhibit mild short stature. MED is primarily caused by pathogenic variations in genes involved in cartilage and bone development. According to the International Skeletal Dysplasia Society (ISDS), MED is part of group 9, with the following genes identified: *COMP, MATN3, CANT1, COL9A1, COL9A2, COL9A3,* and *SLC26A2*[1]. Recently, *FGFR1* was reported as a cause of MED in a study published in 2020, identifying terminal frameshift variants in the *FGFR1* gene as a significant contributor to the disorder[2].

Our objective was to confirm the role of *FGFR1* terminal frameshift variants in MED through the study of two new families and additional cases.

2. Materials and methods

We assembled an international cohort of 12 individuals with Multiple Epiphyseal Dysplasia (MED) carrying terminal exon frameshift variants in *FGFR1*. The cohort includes two families (three affected individuals in one, nine in the other) and one previously reported patient.

3. Results

All affected individuals exhibited a consistent phenotype of MED without vertebral involvement. Symptom onset ranged from 3 to 13 years. Complete penetrance was observed, with a very frequent genu valgum, and the majority underwent surgical interventions. Hypogonadotropic hypogonadism was present in approximately half of the cases. Moderate short stature was noted in the majority. In all three families, the frameshift variants are predicted to result in the same 164-amino acid C-terminal elongation tail. This neostructure does not correspond to any known functional domain but we suggest a potential toxic gain-of-function effect.

4. Conclusion and perspectives

Our findings confirm the involvement of *FGFR1* terminal frameshift variants in MED and provide further clinical characterization of this disorder.

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Keywords: FGFR1, MED, Multiple Epiphyseal Dysplasia*

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OVERGROWTH SYNDROMES CAUSED BY DISRUPTIONS OF THE CNP/FGFR3 PATHWAY

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1. Introduction and objectives
Disruptions of the CNP/FGFR3 pathway, caused by activating mutations of the *FGFR3* gene or loss-of-function mutations of the *NPR2* gene, are well known causes of disproportionate short stature. The positive effect on linear growth of CNP pathway stimulation constitutes the proof of principle of Vosoritide, a recombinant CNP-analog which represents the first approved targeted therapy for achondroplasia.
Since 2006, a group of rare disorders characterized by "mirror" clinical features (tall stature, lower limb valgus deformity) and opposite pathogenic mechanisms has been described, including: i) Overgrowth syndrome with 2q37 translocations (t2q37), resulting in hyperactivation of the *NPPC* gene coding for CNP; ii) Boudin-Mortier syndrome (BOMOS), due to biallelic loss-of-function *NPR3* mutations; iii) Epiphyseal Chondrodysplasia Miura type (ECDM), caused by *NPR2* activating mutations; iv) Camptodactyly, tall stature and hearing loss syndrome (CATSHL), secondary to *FGFR3* biallelic loss-of-function variants or monoallelic mutation with possible dominant negative effect. The present study aims to better characterize this group of overgrowth syndromes caused by disruptions of the CNP/FGFR3 pathway.

2. Materials and methods
We launched an international call for collaboration through French and European networks for rare diseases (OSCAR, AnDDI-rares, BOND, ITHACA) and systematically reviewed the relevant literature.

3. Results
We recruited 6 previously unreported patients, including one patient t2q37, two BOMOS siblings carrying previously undescribed *NPR3* mutations, two CATSHL siblings and their affected mother. Literature review showed five t2q37 and five BOMOS patients as well as five ECDM and four CATSHL families. A specific pattern of common abnormalities emerges, including a marfanoid habitus (tall stature, arachnodactyly, low BMI), and variable degree of hip dysplasia. Useful clues for differential diagnosis include striking long hallux (less severe in CATSHL), scoliosis (less severe in BOMOS), tibial bowing and ankle valgus deformity (not reported in BOMOS) and pseudoepiphyses (especially in ECDM and BOMOS). CATSHL appears to be characterized by a milder skeletal involvement, almost constant arachnodactyly, sensorineural hearing loss and impaired neurodevelopment. A minority of patients shows myopia; no lens dislocation has been observed. Previously unreported features include congenital epiphysiodesis of femoral capital epiphysis in t2q37 and aortic dilatation in two CATSHL individuals (previously observed only in two BOMOS patients).

4. Conclusion and perspectives
Our study provides new insights into the clinical and molecular spectrum of CNP/FGFR3 related overgrowth syndromes, which share a common pattern of skeletal abnormalities as well as a striking wasting of muscular and adipose tissues.

**Keywords:* overgrowth, C-type natriuretic peptide, FGFR3*

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TRISOMY 9P PRESENTING WITH DEVELOPMENTAL DYSPLASIA OF THE HIP: A DIAGNOSTIC CHALLENGE MIMICKING TURNER SYNDROME

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1. Introduction and objectives

Trisomy 9p is a rare chromosomal disorder characterized by variable expression and significant phenotypic overlap with other syndromes. We present a case of a girl with short stature and dysmorphic features and was initially suspected of havingTurner syndrome. Genetic evaluation later confirmed Trisomy 9p. This case highlights how orthopedic findings such as developmental dysplasia of the hip (DDH) and Turner-like features can mask a rarer chromosomal disorder, reinforcing the importance of advanced genomic diagnostics.

2. Materials and methods

The patient was born at term with normal weight and length. Early clinical concerns included growth retardation, delayed motor milestones, and bilateral DDH, diagnosed at 4 months of age with an absence of the femoral heads on imaging. Brain MRI revealed corpus callosum hypoplasia; cardiac and pelvic ultrasounds were normal. She underwent bilateral hip reduction at age 4.5 years and did not walk independently until 6 years. She had persistent growth retardation (height −3.8 SDS), delayed bone age, late closure of fontanels, and mild intellectual disability. At age 7, based on her phenotype and short stature, Turner syndrome was suspected and karyotyping was performed, which revealed a 46,XX chromosomal constitution. Afterwards, chromosomal microarray identified a 38.6 Mb pathogenic copy number gain in region 9p24.3–p13.1, confirming the diagnosis of Trisomy 9p. Over time, spontaneous puberty progressed from Tanner stage I to stage IV (age 12) and stage V (age 13). The patient experienced two menstrual cycles with normal duration and flow.

3. Results

GH therapy was initiated at 0.034 mg/kg/day, later adjusted to 0.025 mg/kg/day (Omnitrope). After four months of treatment, IGF-1 remained low at −2.11 SDS, indicating a suboptimal biochemical response at that stage. A total height gain of 15 cm was observed in the first 21 months. At age 13, her height reached 144 cm and weight 45 kg. GH therapy was continued at 4 units of Growtropin daily. The patient showed steady growth.

4. Conclusion and perspectives

This case underlines the phenotypic overlap between Trisomy 9p and Turner syndrome, emphasizes the importance of chromosomal microarray analysis in the context of short stature and intellectual disability. The presence of early and significant orthopedic pathology, such as DDH, should prompt consideration of a chromosomal disorders, even when traditional karyotyping is normal. GH therapy supported linear growth and spontaneous puberty, although long-term developmental outcomes remain to be followed. Early genetic confirmation enables tailored management and appropriate family counseling.

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Keywords: Trisomy 9p, short stature, hip dysplasia, growth hormone therapy, Turner syndrome mimic*

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LOWER LIMB LENGTHENING OUTCOMES IN ACHONDROPLASIA: TIMING OF SURGERY AND IMPACT ON HEIGHT AND FUNCTIONALITY

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1. Introduction and objectives

Lower limb lengthening (LL) surgery is an option for individuals with achondroplasia to increase height[1]. Surgical techniques offered for LL differ globally[2], with a gap between outcomes expectations from families and published medical papers. Despite recommendations for childhood intervention[3], evidence comparing outcomes between early versus later intervention remains limited. This study analysed the impact of surgical timing on height outcomes and functionality in patients with achondroplasia.

2. Materials and methods

A cross-sectional online survey on LL experiences was conducted in 2024 across 11 languages. A total of 614 responses from 16 countries were collected through REDCap, a secure web application, and 50 met inclusion criteria (diagnosis of achondroplasia, >12 years for self-respondents or be a parent of a child with achondroplasia <12 years, history of LL surgery) and were categorized by timing of first LL surgery: childhood (<12 years, n=27, 15 females) or adolescence (≥12 years, n=23, 11females). Outcomes included added length per limb, final adult height and functionality across 8 daily activities (bathing, brushing hair, wiping after toileting, dressing, driving, putting on shoes, walking upstairs and downstairs). Statistical analysis employed Student's t-tests and Fisher's exact tests (significance: $p<0.05$).

3. Results

Timing of surgery showed no statistically significant advantage between groups. Added length per lower limb was comparable as females gained 12.3 cm (childhood) versus 12.6 cm (adolescence), males gained 8.0 cm versus 11.0 cm, respectively. Final adult heights for female were 134.3 cm (childhood) versus 137.7 cm (adolescence), while males showed an inverse relationship at 145.0 cm (childhood) versus 140.7 cm (adolescence). Functionality assessments showed similar improvements in daily activities regardless of timing of LL surgery.

4. Conclusion and perspectives

This study challenges the assumption that early LL surgery yields superior outcomes. Our findings suggest no significant differences in final height or functional improvements based on time of LL surgery. Importantly, the timing of surgery involves some trade-offs, with later intervention allowing greater patient involvement in decision-making, but may coincide with key academic periods, posing psychological and practical challenges due to prolonged immobilization[4,5]. These results support a flexible approach to surgical timing, emphasizing individualized, patient-centered care and informed consent. While limited by sample size, this study provides real-world evidence to guide decision-making in achondroplasia.

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**Keywords:* skeletal dysplasia, growth, surgery, bone*

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TALL STATURE, LONG HALLUCES AND EXTRA EPIPHYSES: REPORT OF A NEW CASE WITH DISCUSSION OF THE PHENOTYPE AND ITS GENETIC CAUSES

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1. Introduction

Natriuretic peptides and their receptors play a crucial role in regulating endochondral ossification and linear bone growth. Genetic alterations in these pathways can lead to either short or tall stature, depending on the nature of the pathogenic variants. Decreased activity of the natriuretic peptide receptor B (NPR-B) signaling pathway results in short stature phenotypes, such as acromesomelic dysplasia Maroteaux type (MIM: 602875) or "idiopathic" short stature (MIM: 616255), while increased activity causes tall stature, such as epiphyseal chondrodysplasia, Miura type (MIM: 615923).

2. Clinical case

We describe an 11-year-old girl born to non-consanguineous parents. She was born at 37 3/7 weeks with a weight of 3070 g (+0.2 SDS) and length of 50 cm (+0.8 SDS). She had a normal psychomotor development. Her tall stature and diagnosis of polyarticular juvenile idiopathic arthritis led to referral to the genetic department at the age of 4 years. Whole exome sequencing analysis revealed the presence of a heterozygous pathogenic variant in *NPR2*: c.2647_2649delinsTTT; p.Val883Phe. Substitution of the same residue (p.Val883Met) has been reported in the original patient described by Miura et al. (PMID 22870295). Her current physical examination shows tall stature (length of 163 cm, +2.2 SDS), with long fingers and toes, especially affecting the halluces. She is slender with a body mass index of 12.8 kg/m^2 (-2.8 SDS). Extra epiphyses of the phalanges are noted on radiographs of the hands and feet. Mono-allelic gain-of-function variants in *NPR2* lead to increased activity in the NPR-B signaling pathway, resulting in a phenotype characterized by tall stature, long halluces and extra epiphyses (MIM: 615923). In addition, bi-allelic loss-of-function variants in *NPR3* (MIM: 619543) result in a similar phenotype due to the impaired clearance of natriuretic peptides by NPR-C and the increased availability of C-type natriuretic peptide (CNP) that signals through NPR-B. This highlights the critical role of the NPR-B/CNP signaling pathway in skeletal development. The presence of extra epiphyses in the hands and feet is particularly intriguing, as it may indicate the impact of aberrant natriuretic peptide signaling on endochondral ossification. This feature also serves as an important diagnostic marker, enabling clinicians to differentiate this disorder from other heritable connective tissue diseases characterized by tall stature and long fingers/toes (arachnodactyly), such as Marfan syndrome and Loeys-Dietz syndrome.

By comparing these two genetic conditions, this study aims to elucidate the shared and distinct mechanisms by which alterations in the NPR-B/CNP signaling pathway contribute to abnormal skeletal growth.

**Keywords:* Tall stature, extra epiphyses, natriuretic peptides*

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A NEW NOTCH2 VARIANT IN HAJDU-CHENEY SYNDROME: A CASE REPORT AND LITERATURE UPDATE

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1. Introduction

Hajdu-Cheney syndrome (HCS) is a rare (< 1/1 000 000 live births) connective tissue disorder, in most cases autosomal-dominant, due to pathogenic variants in exon 34 of Notch homolog protein 2 gene (*NOTCH2*). NOTCH signalling pathway is implicated in bone development and homeostasis by controlling cell proliferation and differentiation. In HCS, truncated NOTCH2 protein accumulation leads to continuous excessive signalling responsible of developmental skeletal disorders as acroosteolysis, osteoporosis with short stature, unique craniofacial features and other systemic abnormalities. To date, approximately 100 cases have been documented in the literature. We propose an updated comprehensive review including 40 new clinical cases published after 2020.

2. Clinical case

A 43-year-old female presented multiple fractures, joint hypermobility, severe osteoporosis, distal phalanx and nails shortening with acroosteolysis and pseudoclubbing, dysplastic facies, dental anomalies and hearing loss. Her sister and father had also progressive distal fingers deformities, joint hypermobility and mitral insufficiency. X-ray survey demonstrated skull irregularities with open sutures, absent frontal sinuses, and acroosteolysis. Genetic analysis identified the c.6187delG,p.(Asp2063Metfs*5) heterozygous *NOTCH2* frameshift class 4 variant in exon 34. This variant leads to the deletion of the PEST domain sequence, which regulates proteosomal destruction of the protein and results in excessive osteoclastogenesis, contributing to a « gain of function » bone destruction.

Comparatively to previous reports, our patient encompassed all the typical bone features. The diagnosis delay is quite representative of the condition with 32.5% of the patients diagnosed after 25 years (n=13/40). A prevalence of 32.5% cardiovascular (n=13/40) and 27.5% pulmonary involvement (n=11/40) in addition to the bone features is estimated based on an extensive literature review highlighting the need of a systematic systemic follow-up for HCS patients.

3. Conclusion

A novel *NOTCH2* variant was found in our patient with typical HCS manifestations. A delayed diagnosis is common due to the rarity of HCS. Our review provides new descriptive data that would improve the latest descriptive retrospective cohort published in 2020. Specific treatment guidelines for HCS are not currently established and need to be supported especially by accurate genotype-phenotype correlations. The current therapeutic objectives are to minimize complications and reduce symptoms. Antiresorptive (biphosphonates, denosumab) and anabolic (teriparatide) agents have been used without evidence of real efficacy.

**Keywords:* Hajdu-Cheney syndrome, bone disease, osteoporosis, NOTCH2*

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CNV ANALYSIS REVEALS STX16 DELETION IN TWINS PRESENTING WITH PREMATURE PUBARCHE AND PRECOCIOUS PUBERTY

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1. Introduction and objectives

Autosomal dominant Pseudohypoparathyroidism 1B (AD-PHP1B, MIM# 603233) with loss of methylation at the maternal *GNAS A/B*: TSS-DMR alone can be caused by maternal deletions involving *STX16*.

2. Materials and methods

Here we report twins diagnosed with PHP1B via exome sequencing (ES) Copy number variation (CNV) analysis, presenting with premature pubarche, early puberty, and short predicted adult height.

3. Results

Female twins were referred at 7 years of age due to recent onset of pubic hair. They were born preterm at 32 weeks of gestation, with birth weights of 2180 g (+1.5 SDS) for Case 1 and 1400 g (−1.2 SDS) for Case 2. Parents were related.

At age 7, Case 1 weighed 29.2 kg (+1.4 SDS), with a height of 114.5 cm (−1.4 SDS) and a BMI of 22.2 kg/m^2 (+2.2 SDS). She had Tanner stage 2 pubic hair and stage 2–3 breast development. Case 2 weighed 28.9 kg (+1.4 SDS), with a height of 116.5 cm (−1.0 SDS) and BMI of 21.2 kg/m^2 (+2.1 SDS), showing similar pubertal findings (P2, B2–3).

Mid-parental height (MPH) was 149.5 cm (−2.3 SDS), based on maternal (150 cm) and paternal (162 cm) heights. Bone age was advanced. Clinical and laboratory evidence of central precocious puberty, with pubertal responses on LHRH stimulation tests (peak LH 7.5 IU/L and 6.8 IU/L, respectively). Brain MRI was normal. Ambulatory blood pressure monitoring demonstrated systolic hypertension with suppressed plasma renin activity. Cardiac, renal, and adrenal evaluations were unremarkable. Malar hypoplasia, retrognathia, hypertrichosis, and bilateral 5th metacarpal shortening were demonstrated. Both cases showed suboptimal growth velocities under GnRH analogue therapy and were subsequently initiated on rhGH treatment.

ES - CNV analysis identified a 2 kb deletion at Chr20:58669286–58671302 (exons 5–7 of *STX16*), classified as a VUS per ACMG criteria. RT-PCR confirmed the deletion in both affected twins and their mother. It was observed that both cases initially demonstrated mildly elevated parathyroid hormone (PTH) concentrations, more pronounced during periods of low 25-hydroxyvitamin D (25-OHD). However, overt PTH resistance and a more typical PHP phenotype became evident during follow-up.

4. Conclusion and perspectives

Recent advancements in next-generation sequencing technologies, including the integration of CNV analysis, have enabled the identification of diagnoses in patients with atypical or subtle clinical manifestations.

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**Keywords:* Imprinting disorders, PHP1B, STX16 deletion, CNV analysis*

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LONG TERM EVOLUTION OF XLH UNDER BUROSUMAB AND DETERMINANTS OF BUROSUMAB DOSE

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1. Introduction and objectives
X-linked hypophosphatemia (XLH) is a rare phosphate-wasting disorder with progressive skeletal and growth impairments. Burosumab, a human monoclonal antibody targeting FGF23, offers a targeted treatment option. This study aimed to evaluate the long-term evolution of burosumab treatment in a pediatric XLH cohort and identify the clinical and biochemical predictors of burosumab dosing.

2. Materials and methods
We conducted a prospective monocentric longitudinal observational study including 67 children (63% were female) with XLH treated with burosumab between February 2018 and August 2023. Inclusion criteria were a confirmed diagnosis of XLH, and initiation of burosumab therapy. The primary endpoint was cumulative burosumab dose at months 12, 24, and 36 (M12, M24, M36). Quantitative data were expressed as mean ± SD. Univariate analyses were performed using Student's t-test, Mann-Whitney, or chi-squared tests. Multiple linear regression models were used to assess predictors of cumulative dosing at each time point based on variables from the previous timepoint. Analyses were performed using R software.

3. Results
Mean cumulative burosumab doses increased progressively from 982.5 ± 483.8 mg at M12 to 3521.6 ± 1656.3 mg at M36. At each timepoint, patient weight was significantly associated with cumulative dose. In multivariate models, additional independent predictors included serum phosphate (negative association), $1,25(OH)_2D$ (positive), parathyroid hormone (PTH, positive), and sex (higher doses in males). At M12, significant predictors of higher dose included lower phosphate ($p < 0.01$), higher PTH ($p < 0.05$), and male sex ($p < 0.05$). These associations remained consistent through M24 and M36.

4. Conclusion and perspectives
While weight remains the main determinant of burosumab dosing, several clinical and biochemical parameters—including serum phosphate, $1,25(OH)_2$ vitamin D, PTH, and sex—play a significant role in dose adjustment over time. These findings support the need for individualized dose titration in XLH treatment to optimize outcomes. Prospective multicenter validation of these predictors and exploration of pharmacogenetic influences may further refine burosumab therapy in XLH.

**Keywords:* XLH, PHEX, weight, pediatric population, burosumab*

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EMPIRIC VITAMIN D SUPPLEMENTATION: A POTENTIAL STRATEGY TO PREVENT TYPE 2 DIABETES?

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1. Introduction and objectives

Type 2 diabetes mellitus (T2DM) is a growing global health burden. Vitamin D has been implicated in glucose metabolism through its influence on pancreatic β-cell function, insulin sensitivity, and inflammation, largely mediated by the vitamin D receptor (VDR). Recent research suggests that subclinical vitamin D deficiency may contribute to T2DM development. This narrative review aims to evaluate whether empiric vitamin D supplementation could serve as a preventive strategy against T2DM, with attention to genetic factors such as VDR polymorphisms.

2. Materials and methods

A narrative review was conducted, focusing on randomized controlled trials (RCTs), meta-analyses, cohort studies, and clinical guidelines published between 2022 and 2024. Emphasis was placed on studies addressing vitamin D supplementation, glycemic outcomes, T2DM risk reduction, and the influence of VDR gene polymorphisms, specifically the *FokI* (rs2228570) variant.

3. Results

Meta-analyses[1] show modest improvements in insulin resistance and glycemic control with vitamin D supplementation, particularly among individuals with prediabetes. Post hoc analysis from the D2d study[2] indicated that participants with severe vitamin D deficiency (<12 ng/mL) derived the greatest benefit from supplementation. Additional trials[3] confirmed enhanced insulin sensitivity in obese, vitamin D-deficient individuals.

Genetic studies suggest that the f allele of the VDR *FokI* polymorphism is associated with reduced VDR activity, impaired insulin secretion, and higher T2DM risk. Emerging mechanistic research[4] reinforces the role of VDR signaling in glucose homeostasis. The Endocrine Society's 2024 guidelines advocate for vitamin D supplementation in high-risk populations, with recommended serum 25(OH)D levels of 30–50 ng/mL.

4. Conclusions and perspectives

Although universal vitamin D supplementation for T2DM prevention is not currently endorsed, growing evidence supports empiric supplementation in individuals at elevated metabolic risk. Early correction of vitamin D deficiency and consideration of genetic susceptibility may enhance preventive strategies against T2DM. Further research is needed to refine personalized supplementation approaches.

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**Keywords:* Vitamin D, type 2 diabetes, VDR Polymorphism, empiric eupplementation, global health*

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GROWTH HORMONE THERAPY IN PATIENT WITH OVERLAP SYNDROME: GROWTH OUTCOME AFTER ONE YEAR OF TREATMENT

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1. Introduction

SET domain-containing 5 (SETD5) is a member of the protein lysine-methyltransferase family that regulates gene expression. *SETD5* gene mutations cause disorders of the epigenetic machinery which determinate phenotypic overlap characterized by several abnormalities. Recently, *SEDT5* gene variants have been described in patients with KBG and Cornelia de Lange syndromes. Pathogenic variants of *SETD5* gene are primarily associated with intellectual delay and other several manifestations including severe short stature. Only a few reports are available on the use of recombinant growth hormone therapy (rhGH) in the aforementioned syndromes, none in the overlap syndrome.

2. Case description

A 9-year-old female child was admitted to the pediatric endocrinology clinic for assessment of severe short stature. Her height was 103.3 cm (-5.46 SDS), weight 15.1 kg (-5.08 SDS), BMI 16.3 kg/m^2 (-1.71 SDS). The target height for the proband was 151.65 cm (-1.80 SDS). Her bone age (BA) was 8 years. She had a prepuberal stage (Tanner stage 1).Physical examination revealed dysmorphic features, including a long triangular face, low-set and protruding ears, macrodontia of the central incisors and pointed palate. Biochemical examinations, including thyroid function and calcium homeostasis, were normal. The clonidine stimulation test revealed a normal GH peak (9,24 ng/ml). She had an intellectual disability with a total IQ of 68 (WISC-R). CHG-array detected a *de novo SETD5* gene mutation (*c.890_891delTT*) classified as pathogenic variant. The *SETD5* gene mutation is consistent with our patient's phenotype in the context of an overlap syndrome between the phenotype of KBG and Cornelia de Lange syndromes. Recombinant growth hormone therapy (rhGH) (at dose of 0,03 mg/kg/die) was started at the age of 12 years (pre-therapy data: height 114 cm, -5.22 SDS; growth velocity 3.9 cm/year, -3.6 DS; pubertal stage B1P1; bone age 10 years). After one year of treatment there was a significant increase in the growth velocity (7.2 cm/year, +3.2 DS), even though pubertal development has not yet begun.

3. Conclusion

To the best of our knowledge, this is the first case of a patient with overlap syndrome due to *SETD5* mutation treated with rhGH. The initial response to rhGH therapy was satisfactory in terms of growth rate, although the effective response to therapy in terms of height outcome should be assessed during long-term follow-up.

**Keywords:* SETD5 gene mutation, overlap syndrome, KBG syndrome, Cornelia de Lange syndrome*

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MOSAIC TURNER SYNDROME PRESENTING WITH SHORT STATURE AND DELAYED PUBERTY IN A 13-YEAR-OLD GIRL: A CASE REPORT

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1. Introduction
Turner syndrome (TS) is a chromosomal disorder in phenotypic females, often associated with short stature, gonadal dysgenesis, and congenital anomalies. Mosaic forms often present with variable phenotypes and may lack classic features, leading to diagnostic delays. This case illustrates the diagnostic challenge of mosaic TS without dysmorphic features and highlights the importance of considering TS in females with unexplained growth failure and delayed puberty.

2. Case description
A 13-year-old girl presented with short stature, delayed puberty, and low body weight. Growth failure had been noted since early childhood. She reported occasional headaches and one episode of loss of consciousness. On examination, her height was 145 cm (Percentile <5), Body mass index (BMI) 17.0 kg/m^2, and Tanner staging revealed breast development at stage 2, axillary hair at stage 2, pubic hair at stage 3, and absence of menarche. No dysmorphic or Turner-specific features were observed.
Laboratory results showed normal liver, renal and thyroid function. Growth factors and hormonal assays were within reference ranges: insulin-like growth factor-1 (IGF-1) 300 µg/L, IGF-binding protein-3 (IGF-BP3) 4.9 mg/L, follicle-stimulating hormone (FSH) 3.09 mIU/mL, luteinizing hormone (LH) 0.63 mIU/mL, estradiol (E2) 43.17 pg/mL, and prolactin (PRL) 17.7 ng/mL. Bone age corresponded to chronological age (13 years). Echocardiography showed a 1 mm patent foramen ovale, mild mitral insufficiency, and mild mitral valve prolapse. Pelvic ultrasound showed a non-visualized left ovary, with a 10.5 x 7 mm hypoechoic fluid-filled structure in its projection. The right ovary measured 23 x 14.5 x 19.5 mm. Pelvic Magnetic resonance imaging (MRI) showed altered adnexal structures, a cystic formation (12 mm) in place of the left ovary, a fluid-filled right ovary with a 3 mm inclusion, a heterogeneous myometrium, and a small amount of free fluid in the pouch of Douglas. Cytogenetic analysis of peripheral blood revealed 45, X/46, XX mosaicism.
The diagnosis of mosaic TS was confirmed. Recombinant human growth hormone therapy (45 mcg/kg/day) was initiated, resulting in a positive auxological response. Pubertal development progressed spontaneously, and estrogen/progestogen therapy was not required. The patient continues under multidisciplinary follow-up. Diagnostic laparotomy has been recommended based on MRI findings.

3. Conclusions and perspectives
This case highlights the need to consider mosaic Turner syndrome in girls presenting with short stature, even when classic dysmorphic features are absent. Early cytogenetic evaluation facilitates appropriate therapeutic interventions and enables effective multidisciplinary management to ensure the best outcomes and improve the patient's quality of life.

**Keywords:* Turner syndrome, mosaicism, short stature, delayed puberty, growth hormone therapy*

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BIALLELIC CSGALNACT1 VARIANTS AS A RARE CAUSE OF SHORT STATURE: CLINICAL COURSE AND LONG-TERM RESPONSE TO GROWTH HORMONE THERAPY IN THREE SIBLINGS

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1. Introduction
Mutations in genes encoding enzymes responsible for the biosynthesis and structural diversity of glycosaminoglycans cause a variety of disorders affecting bone and connective tissues. Biallelic variants in *CSGALNACT1* have been associated with a mild skeletal dysplasia, often accompanied by advanced bone age.

2. Case description
Three siblings with complaints of short stature were referred to the pediatric endocrinology clinic at the age of 27 days (Patient 1, male), at the age of 1 year (Patient 2, male), and 3.6 years (Patient 3, female), respectively. Their parents had first-degree consanguineous marriage. All patients were born at term with normal birth weight; however, birth lengths were low in Patient 1 (-2.4 SDS) and Patient 2 (-2.2 SDS), and normal in Patient 3 (-1.03 SDS). At presentation, height SDS values were -2.0, -2.0, and -2.4, respectively. BMI SDS of all patients were normal. Target heights were 177 cm (0.13 SDS) for Patient 1 and 2, and 164 cm (0.15 SDS) for Patient 3. On physical examination, mild facial dysmorphism and pectus excavatum were noted in Pateint 1 and 2. Additionally, Patient 1 had attention deficit, Patient 2 had mitral valve prolapse, and Patient 3 had psoriasis. Body proportions were normal in all siblings.
First step biochemical investigations for short stature were normal. No skeletal dysplasia was detected on skeletal survey, and bone ages were slightly delayed. All three patients had normal responses to growth hormone stimulation tests. Due to suboptimal growth velocity, growth hormone treatment was initiated at follow-up. Treatment was well-tolerated without complications, and IGF-1 levels remained within normal limits. Body proportions were normal throughout follow-up. The durations of growth hormone treatment were 13.2, 12.5, and 8 years, respectively. At final evaluation, height SDS values had improved to -1.7 in Patient 1, -1.6 in Patient 2, and -1.2 in Patient 3. Whole exome sequencing revealed a homozygous pathogenic *CSGALNACT1* variant, c.429T>G (p.Tyr143*), in all three siblings. Both parents were found to be heterozygous carriers.

3. Conclusion
Children with biallelic *CSGALNACT1* variants may present with mild phenotypes. These cases may be found among children diagnosed with idiopathic short stature or those considered small for gestational age based on height. Without genetic testing, the underlying etiology may remain undiagnosed. Long-term follow-up is essential to better understand the clinical impact of *CSGALNACT1* variants.

**Keywords:* CSGALNACT1, growth hormone, short stature*

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GENERALIZED ARTERIAL CALCIFICATION OF INFANCY SYNDROME TREATED BY RECOMBINANT HUMAN EPP1 AT 8 MONTHS OF AGE: REPORT OF A CASE DUE TO *ABCC6*

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1. Introduction

GACI (Generalized Arterial Calcification of Infancy) syndrome is a rare, severe vascular disease linked to abnormal regulation of inorganic pyrophosphate, secondary to biallelic mutations of *ENPP1* or, more rarely, *ABCC6*.

We report here the case of a patient affected by GACI syndrome linked to *ABCC6* mutation, treated by recombinant human *ENPP1*.

2. Case description

The patient was born at 35 SA to consanguineous parents. Myocardial hypertrophy was diagnosed since the fetal stage and monitor during the neonatal period. At two months of age, moderate impairment of left ventricular function was suspected with no signs of clinical heart failure. The body chek-up (coronary and cerebral CT scan, renal ultrasound and cardiac catheterization) revealed diffuse vascular calcifications (pulmonary arteries, aorta, coronary branches) leading to GACI syndrome diagnosis, due to *ABCC6* biallelic mutation.

Clinically, he presented only hypertension, resolved under converting enzyme inhibitor and anti-aldosterone therapy. At 4 months of age, treatment with biphosphonate was attempted, with no effect on body calcifications. The child demonstrated harmonious growth, with stable body calcifications. Nonetheless, because of potential risks described in the literature, treatment with recombinant human *ENPP1* (named INZ-701), a PPi hydrolysis inhibitor, was proposed in may 2025 at 8 months of age.

Clinical, biochemical and radiological evolution will be presented during the meeting.

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**Keywords:* calcification, novel therapy, ABCC6, enzyme replacement*

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GENETIC INSIGHTS INTO SHORT STATURE: AN EVALUATION OF CLINICAL, HORMONAL, AND GENETIC PARAMETERS IN A REAL WORLD PAEDIATRIC COHORT

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1. Introduction and objectives
To assess the identification of genetic causes of short stature (SS) in children and to identify diagnostic patterns and inheritance in the real-world.

2. Materials and methods
A total of 193 children (113 males) referred for SS were evaluated. Genetic testing was based on clinical presentation. Patients were grouped as: genetic diagnoses (GH-axis-related, n=6; bone-related, n=28; non-GH/bone-related, n=16; possibly SS-related variant-of-unknown-significance, n=11, pre-referral genetic diagnoses, n=21); no genetic diagnosis (non-SGA, n=65; SGA, n=39; atypical Growth-Hormone-deficiency GHD, n=7). Typical GHD, Turner syndrome, and Constitutional-Delay-of-Growth-and-Puberty were excluded.

3. Results
At referral, boys were aged 6.37±4.65 and girls 6.61±4.17 years. Mean height SDS was -2.96±1.27 in boys and -3.10±1.57 in girls. A genetic diagnosis was found in 36.8% of patients, with an additional 5.7% showing VUS. Bone-related conditions were the most common (15%), including in those with pre-referral diagnoses (52.4%). Genetic diagnoses were realized in: 42.2% patients with severe SS (height <-2.5SD), which were most frequently bone-related (16.5%), 32.6% with mild SS (-2.5 to -2.0SD), 60% patients short for their parents with a height > -2SD (28% had pre-referral diagnoses). Patients with bone-related conditions had most severe SS (height SDS -3.77±2.42 vs others -2.89±1.07; ANOVA p=0. 0017), and higher BMI SDS (0.16±2.02 vs others -0.94±1.74; ANOVA p=0.0028). Patients with microcephaly had mostly a non-GH/non-bone diagnosis (13.6%) or a bone-related diagnosis (10.6%); patients with normocephaly had mostly bone-related diagnoses (19.4%). Macrocephaly was rare. Patients with bone-related conditions had mostly an high IGF1 concentration (25%), followed by patients with GH-axis-related diagnoses. Patients with atypical GHD had mostly low IGF1 concentration (43%). Multivariate regression analyses were performed on the entire cohort and on patients with height SD≤-2 only (excluding those short for parents with height>-2 SD), using clinical and biochemical parameters. In both groups height SDS, learning difficulties/developmental disabilities and dysmorphic features were significant predictors of genetic diagnoses. In the second cohort, there was a trend for high IGF-1, low head circumference SDS and high BMI SDS to be a significant predictor.

4. Conclusion and perspectives
Genetic testing is critical in identifying the underlying causes of SS, even in patients with mild SS or those with normal height short for parents. Bone-related genetic variants are associated with more severe SS. Key predictors of genetic diagnoses include height SDS, learning difficulties/developmental disabilities and dysmorphic features. High IGF1 levels, observed in 25% of patients with bone-related conditions, highlight an area requiring further investigation.

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**Keywords:* short stature, bone-related genetic variants, genetic predictors*

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GACI SYNDROME: A RARE PATHOLOGY OF INTRAFAMILIAL PHENOTYPIC VARIABILITY

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GACI (Generalized Arterial Calcification of Infancy) syndrome is a rare, severe vascular disease linked to abnormal regulation of inorganic pyrophosphate, secondary to biallelic mutations of *ENPP1* or, more rarely, *ABCC6*.
The first child of the family was born at term with joint limitations, linked to peri-articular calcifications of the hips and elbows. The evolution was spontaneously favorable, with persistence of moderate hip flessum. At the age of 3 years and 2 months, the diagnosis of GACI syndrome by mutation of the *ENPP1* gene was made, when the younger brother presented at 10 days of age a cardiogenic shock, linked to severe cardiac calcifications. The body chek-up showed calcifications of all the arterial axes responsible for severe renal arterial stenosis leading to arterial hypertension. Genetic investigation revealed ENPP1 mutation in the two children, leading to familial GACI syndrome diagnosis. The state of cardiac emergency of the young boy led to purpose iterative courses of biphosphonates, that allow progressive improvement of general condition and courses continued for 17 months. Currently at 4 years of aged, the boy is doing well on cardiogenic treatment (aspirin, ACE inhibitor and anti-aldosterone); follow-up imaging shows the persistence of moderate generalized calcifications with no clinical repercussions.
The older sister is actually 7 years old, she display discrete genu varum and moderate school difficulties. Body checkup revealed aortic and retinal calcifications without clinical impact.
Biologically, the 2 children presented slights signs of hypophosphatemic rickets treated by oral phosphorus and UN ALPHA.
The 3rd child of this family was followed for an IPEX syndrome (global immune deficiency) treated by bone marrow transplantation and follow-up revealed recently at 5 years of age, cardiac calcifications without any clinical repercussions. Genetic investigation confirmed similar familial *ENPP1* mutation, leading to the diagnosis of pauci-symptomatic GACI syndrome.

In conclusion, GACI syndrome can present great phenotypic heterogeneity, ranging from a pauci-symptomatic to severe life-threatening form. This familial description argues against a genotype-phenotype correlation, and better understanding of the pathophysiology is needed to optimize management and target therapies.

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**Keywords:* calcification, rachitism, cardiogenic shock, ENPP1*

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TUMOUR-INDUCED OSTEOMALACIA (TIO) IN AN ADOLESCENT: DIAGNOSTIC CHALLENGES, SURGICAL MANAGEMENT, AND POSTOPERATIVE COURSE

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1. Introduction and objectives

TIO is a rare cause of hypophosphataemia in children, usually resulting from phosphaturic mesenchymal tumours (PMTs) secreting excess FGF23. Early diagnosis is essential to prevent long-term morbidity, but diagnosis is often delayed. Tumour localisation and excision is frequently difficult. We present a case of adolescent-onset TIO, outlining the diagnosis, surgical treatment, and biochemical recovery.

2. Materials and methods

A 14-year-old boy presented with a one-year history of generalised bone pain and a previous distal radius/ulna fracture. Growth and development were normal, with no relevant family history or physical abnormalities.

3. Results

Investigations showed hypophosphataemia (0.48 mmol/L), renal phosphate wasting (TMP/GFR 0.26 mmol/L), mild hypocalcaemia (2.15 mmol/L), elevated ALP (791 U/L), high-normal PTH (6.5 pmol/L), low urinary calcium, raised FGF23 (177 RU/mL), and low 1,25-dihydroxyvitamin D (38 nmol/L).
X-rays showed no evidence of longstanding rickets. Renal ultrasound was normal. Bone mineral density was low (L1–L4 Z-score –2.5). Targeted genetic panel and whole genome sequencing were negative. TIO was diagnosed after excluding other causes. A skeletal survey did not reveal a tumour. Whole-body MRI detected a likely lesion (33mm) in the distal left femur.
Ga-68 DOTATATE PET-CT confirmed a somatostatin-avid juxtacortical mass. A dedicated MRI measured a 35×14×9mm lesion.
Peripheral venous FGF23 sampling from limbs revealed high circulating levels (898–1019 mU/mL) but failed to localise the source. Burosumab was considered but is not available for TIO. The lesion was surgically excised, and histopathology was consistent with a PMT. Tumour RNA sequencing (TruSight RNA Pan Cancer panel) detected an *FN1–FGFR1* fusion gene.
Postoperative recovery was marked by FGF23 reduction to 24RU/mL (day 14), normalisation of phosphate concentration (day 16-phosphate treatment discontinued). Transient rise in PTH (14.9 pmol/L), severe increase in 1,25-dihydroxyvitamin D (919 pmol/L), rise in ALP (415 U/L), alongside worsening bone pain, indicated bone remodeling. Symptoms resolved over 2–3 months and alphacalcidol was also stopped. Three months postoperatively, biochemical parameters had mostly normalised, except for persistently elevated 1,25-dihydroxyvitamin D.

4. Conclusion and perspectives

TIO should be considered in paediatric patients with unexplained hypophosphataemia and high FGF23. Localisation of the tumour is often unsuccessful. Ga-68 DOTATATE PET-CT (most sensitive diagnostic tool in adults) was the most effective modality for tumour localisation in this case. Surgical removal of the PMT was curative but a rapid increase in 1,25-dihydroxyvitamin D, possibly due to rapid fall of FGF23, and bone pain occurred post-operatively. Molecular characterisation confirmed an *FN1–FGFR1* fusion gene, which has been described previously in adult patients. Burosumab has been approved as TIO treatment in some countries but not the UK.

**Keywords:* hypophosphataemia, osteomalacia, tumour, FGF23*

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GENETIC INSIGHTS INTO SHORT STATURE AND BONE-RELATED CONDITIONS: EVALUATION IN A REAL-WORLD PAEDIATRIC COHORT

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1. Introduction and objectives

This study aimed to assess the identification of genetic causes in children with short stature (SS) and determine diagnostic and inheritance patterns in real-world presentations of growth/bone disorders.

2. Materials and methods

A total of 193 children (113 males) referred for SS were evaluated. Based on clinical presentation, patients underwent genetic testing: chromosomal microarray, syndrome-specific testing, a 66-gene SS panel, a 442-gene skeletal dysplasia panel, or duo/trio whole genome sequencing. Patients were grouped as: genetic diagnoses (GH-axis-related, n=6; bone-related, n=28; non-GH/bone-related, n=16; possibly SS-related variant-of-unknown-significance VUS, n=11, pre-referral genetic diagnoses, n=21); no genetic diagnosis (non-SGA, n=65; SGA, n=39; atypical Growth Hormone deficiency, n=7). Typical GHD, Turner syndrome, and Constitutional Delay of Growth and Puberty were excluded.

3. Results

At referral, mean height SDS was −2.96 ± 1.27 in boys and −3.10±1.57 in girls. Genetic diagnoses were established in 36.8% of patients (71/193), with another 5.7% (11/193) showing VUS. Bone-related gene variants were the most frequent (39%, 28/71).

The most represented bone-related diagnoses were 3M syndrome (*CUL7* ×3, *CCDC8, OBSL1*), XLH (*PHEX* ×4, including 2 of 4 siblings), Meier-Gorlin syndrome (*CDC45* ×2, siblings), Myhre syndrome (*SMAD4* ×2). Among 21 patients with a pre-referral genetic diagnosis, 11 had bone-related conditions; most frequent were acromesomelic dysplasia, Maroteaux type (*NPR2* ×2, siblings), 3M syndrome (*CUL7, OBSL1*), osteogenesis imperfecta (*COL1A2, P3H1*). VUS were also detected in genes implicated in skeletal development (*ACAN, FGFR1, FGFR2*, and *KMT2A*). Missense genetic variants prevailed in bone-related variants. Patients with bone related gene variants showed the lowest mean height SDS (−3.77 vs −2.89; p = 0.0017) and highest BMI SDS (0.16 vs −0.94; p = 0.0028). IGF1 levels were often elevated in bone-related conditions (25%). Normocephaly was most common in these patients (64%), followed by microcephaly (25%), with no one having macrocephaly; head circumference was not available 11% (3/28).

Predictors for identification of an underlying gene variants in the cohort were severe short stature, a learning disability and dysmorphic features. Gene variants were often inherited.

4. Conclusion and perspectives

Genetic testing revealed a substantial yield (36.8% with genetic diagnoses and 5.7% with VUS) in a real-world SS cohort, with bone-related conditions accounting for most diagnoses, and showing the most severe short stature and specific growth profiles with severe SS, high BMI and frequent high IGF1 concentration. Early and comprehensive genetic evaluation, is crucial to accurate diagnose and appropriately manage children with SS.

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**Keywords:* short stature, bone-related genetic variants, genetic predictors*

ID: 138 Basic and translational research

CONTINUOUS SUBCUTANEOUS PARATHYROID HORMONE (PTH 1-34) INFUSION (CSPI) IN CHILDREN AND YOUNG PEOPLE (CYP) WITH SEVERE AUTOSOMAL DOMINANT HYPOCALCAEMIA TYPE 1 (ADH1); LONG TERM FOLLOW-UP

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1. Introduction and objectives

Autosomal Dominant Hypocalcaemia Type 1 (ADH1) is caused by gain-of-function mutations in the calcium-sensing receptor (CaSR) gene resulting in hypoparathyroidism with persistent hypocalcaemia, hyperphosphataemia, hypomagnesaemia, and severe hypercalciuria. Conventional therapy using activated vitamin D and oral calcium can exacerbate nephrocalcinosis and frequently fails to adequately control hypocalcaemia and seizures. Continuous subcutaneous infusion of PTH via an insulin pump is an alternative treatment option. Previous data from our centre on six patients demonstrated that CSPI improved calcium concentrations and reduced seizures (mean duration: 3.2±0.6 years). This study presents long-term follow-up data on the safety and efficacy of CSPI in CYP with ADH1.

2. Materials and methods

This retrospective observational analysis included five patients with genetically confirmed ADH1 (aged 6–30 years) who received CSPI for an average duration of 8.22±1.26 years, each with a history of frequent hypocalcaemic seizures and hospitalisations on conventional therapy or PTH injections before CSPI initiation. A sixth patient was excluded due to discontinuation CSPI following renal and parathyroid transplantation. We evaluated biochemistry, seizure frequency, hospital admissions, calciuria, nephrocalcinosis, growth and bone mineral density (BMD). Serum and urinary mineral levels were assessed biannually from January 2018, with results presented as mean ± standard deviation.

3. Results

CSPI therapy maintained mean adjusted calcium between 1.90 and 2.27 mmol/L for all patients. Mean 24h urinary calcium excretion was between 1.7 and 4.5 mmol/day and mean calcium-phosphate product between 2.34 and 4.48 for all patients. Seizure frequency and hospital admissions were reduced. Two patients experienced no seizures, while two had a single episode during the entire follow-up period. Only one patient exhibited progression of nephrocalcinosis. Notably, individuals who commenced CSPI before the age of one showed normal neurodevelopmental outcomes. Growth and BMD remained in the normal range. Treatment-emergent adverse events (TEAEs) included autoimmune hypothyroidism, gastrointestinal symptoms, anxiety/depression, dental enamel defects, and central precocious puberty.

4. Conclusion and perspectives

CSPI is a safe and effective long-term treatment for CYP with ADH1, maintaining serum calcium, reducing seizures and hospital admissions, and normalizing calcium excretion and BMD. Only one patient developed mild nephrocalcinosis. The relationship between CSPI and TAEAs remains unclear, but CSPI is a viable option for severe ADH1 in the absence of other effective treatments.

**Keywords:* pump, hypocalcaemia, ADH1*

ID: 139 Medical Abstracts / Case Reports / Clinical Cases

MCCUNE-ALBRIGHT SYNDROME WITH FIBROUS DYSPLASIA AND HYPOPHOSPHATEMIC RICKETS

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1. Introduction and objectives
McCune-Albright Syndrome (MAS) is a rare genetic disorder characterized by fibrous dysplasia (FD), skin pigmentation, and multiple endocrinopathies. This case highlights the complex clinical course of a child with MAS, emphasizing the challenges of managing skeletal complications, particularly the development of hypophosphatemic rickets, and exploring potential therapeutic strategies.

2. Materials and methods
We report the case of a patient diagnosed with MAS, initially referred to our skeletal dysplasia clinic for evaluation and surveillance of fibrous dysplasia lesions, who subsequently developed hypophosphatemic rickets. Clinical data were retrospectively collected from medical records, encompassing endocrine assessments, radiologic imaging, biochemical profiles, and therapeutic interventions.

3. Results
The patient exhibited early-onset endocrine features, including neonatal Cushing's syndrome requiring bilateral adrenalectomy and gonadotropin-independent precocious puberty, managed with an aromatase inhibitor. FD was diagnosed at 3.5 years with multifocal skeletal involvement, leading to progressive deformities and recurrent fractures. At 5 years and 7 months, she developed hypophosphatemic rickets, compounding skeletal fragility. Despite conventional treatment including phosphate and vitamin D supplementation, bisphosphonate therapy, and orthopedic interventions, hypophosphatemia and bone fragility persisted. Burosumab, a targeted therapy for hypophosphatemia, was considered but remains off-label in MAS.

4. Conclusion and perspectives
This case illustrates the multifaceted nature of MAS and its significant impact on skeletal health. A multidisciplinary approach is essential for effective management. While current therapies provide symptomatic relief, emerging treatments like Burosumab may offer new hope for addressing the underlying phosphate metabolism defects. Further clinical research is needed to assess its efficacy and safety in MAS patients.

**Keywords:* McCune-Albright Syndrome, Fibrous dysplasia, hypophosphatemic rickets, burosumab*

ID: 140 Basic and translational research

ENAMEL PHENOTYPE OF MOUSE MODELS OF FAMILIAL HYPOCALCIURIC HYPERCALCEMIA TYPES 2 AND 3

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1. Introduction and objectives

Amelogenesis Imperfecta (AI) is a heterogeneous group of rare inherited disorders that affect the enamel structure of both dentitions. While AI has been associated with normocalcemic and hypocalcemic conditions, no link has yet been made between AI and hypercalcemia.

We aim to investigate the impact of FHH-associated genetic variants (*Gna11* and *Ap2s1*) on amelogenesis *in vivo*.

2. Materials and methods

Three transgenic *Gna11* (KO and KI) and *Ap2s1* (KI) mouse strains were studied. All animal procedures were approved by the ethics committee. Mice of both sexes were grouped by genotype (WT, heterozygous and homozygous, n=16 per genotype) and age: young adults (2–4 months) and older adults (6–8 months). Serum calcium levels were measured. Immunohistochemistry was used to assess the expression of *GNA11* and *AP2S1* in tooth germs. Enamel volume and density were assessed using high-resolution µCT scans.

3. Results

Hypercalcemia was confirmed in all mutant strains, with results consistent with previous studies[1,2]. *Ap2s1* HTZ and KO mice exhibited the highest calcium levels, mirroring FHH3 phenotype in humans. Both $G\alpha_{11}$ and Ap2s1 proteins were detected in molar germs. In *Ap2s1* mutants, enamel volume in incisors was significantly reduced in both HTZ (0.66 ± 0.03 mm^3) and KO (0.563 ± 0.0278 mm^3) compared to WT (0.77 ± 0.0229 mm^3), with $p = 0.0481$ and $p = 0.0092$, respectively. A similar reduction was observed in *Gna11* heterozygotes (0.6905 ± 0.0129 mm^3 vs. 0.7445 ± 0.0180 mm^3; $p = 0.0424$). Molars of older mutant mice displayed more wear and damage than controls, aligning with the dental findings reported in patients.

4. Conclusion and perspectives

This study provides the first evidence that FHH-associated variants impair enamel development. These findings highlight a previously unexplored link between hypercalcemia and amelogenesis and showcases two new genes potentially linked with AI.

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**Keywords:* tooth, enamel, biomineralization, Gα11, AP2S1*

ID: 141 Basic and translational research

IDENTIFICATION OF AMELOGENESIS IMPERFECTA IN PATIENTS WITH HYPERCALCEMIA DUE TO GNA11 LOSS-OF FUNCTION MUTATIONS

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1. Introduction and objectives

Amelogenesis Imperfecta (AI) is a diverse group of rare inherited disorders that impact the enamel structure of both primary and permanent teeth. Although AI has been linked to normocalcemic and hypocalcemic conditions, no association has yet been identified with hypercalcemia. In this study, we aimed to determine whether Familial Hypercalcemia Hypocalciuria 2 (FHH2) due to loss-of function mutations in *GNA11* is a cause of AI.

2. Materials and methods

Dental examination of patients with FHH2

We diagnosed hypomineralized AI in the affected patients of two unrelated families with FHH2. This manifested by high susceptibility to caries and enamel wear.

Dental tissue studies of FHH2 teeth

First, we collected and prepared deciduous teeth from 2 FHH2 patients and age-matched controls. We performed several techniques to study the microanatomy of the dental tissues (SEM, Synchrotron ID19, EDS, Raman micro-spectroscopy, TOF-SIMS). Second, we studied the expression of *GNA11/ Gna11* in the human and mouse tooth germ via scRNAseq atlas. Third, we investigated more in depth the expression of *Gna11*/Gα11 in the mouse tooth germ (RT-qPCR, RNA Scope, Western blot, immunohistochemistry).

3. Results

SEM analysis showed slightly more looser enamel prisms in FHH2 teeth and abnormal dentin. EDS showed a significant difference in mineralization of both enamel and dentin (lower Ca/P ratio for both tissues in the FHH2 teeth). Synchrotron acquisitions at 3 um revealed punctual patches of enamel demineralization following no set pattern in the FHH2 enamel. Raman microscopy highlighted the demineralized patches and confirmed the loss of mineral phase in the patches. Further analysis by TOF-SIMS confirmed that the defect area had a lower Ca, and therefore mineral, content compared to a defect-free enamel area of the same tooth.

Single-cell transcriptome atlas analysis of human and murine tooth germ revealed that *GNA11/ Gna11* was expressed at all stages of amelogenesis. We performed RT-qPCR and western blot analyses on molar and incisor germs from WT mice, showing robust *Gna11*/Gα11 expression. We next performed RNA Scope and immunofluorescence on OCT-included frontal and sagittal postnatal tooth germ sections. We found *Gna11*/Gα11 expression in both ameloblasts and odontoblasts.

4. Conclusion and perspectives

This study shows that *GNA11* pathogenic variants responsible for hypercalcemia, are a new cause of AI. Abnormal mineralization of enamel and also dentin were identified and the expression of *Gna11*/Gα11 in the murine tooth germ was confirmed.

**Keywords:* tooth, enamel, biomineralization, Gα11, Ap2s1*

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