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CASE REPORT

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Two cases of primary hypertrophic osteoarthropathy caused by *HPGD* variants: a case report and literature review

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Abstract

Background Primary hypertrophic osteoarthropathy (PHO) is a rare genetic disorder primarily characterized by digital clubbing, pachydermia, and periostitis. The rarity of this disease often leads to misdiagnosis or delayed diagnosis.

Methods We describe the clinical and genetic findings of two pediatric PHO cases caused by *HPGD* variants and perform a systematic literature review of *HPGD*-related PHO cases.

Results Both patients exhibited congenital digital clubbing and patent ductus arteriosus from birth. Radiographs revealed cortical bone thickening and a periosteal reaction. Patient 1 displayed gait abnormalities and delayed cranial suture closure, while Patient 2 had bilateral leg swelling. Whole exome sequencing identified a compound heterozygous variant (NM_000860.6: c.189C > A, p.C63* and NM_000860.6: c.310_311delCT, p. L104Afs*3) in Patient 1 and a homozygous splice-site variant (NG_011689.1(NM_000860.6): c.324 + 5G > A) in Patient 2. All variants were classified as pathogenic based on the American College of Medical Genetics and Genomics criteria. Among 89 reviewed cases, the c.310_311delCT variant accounted for 37.1% (33/89), predominantly in homozygous form (60.6%, 20/33). The median urinary prostaglandin E2 (PGE2)-to-creatinine ratio in PHO patients was 627.1 ng/mmol (normal: 61.49 ng/mmol). Notably, the median age of symptom onset was 5.1 years, while diagnosis occurred at 22.1 years, with a male predominance (male-to-female ratio: 2.2:1).

Conclusion We report the first *HPGD* c.189C > A variant, expanding the genetic spectrum of PHO. The c.310_311delCT variant represents a recurrent hotspot, predominantly in homozygosity. Our findings highlight the importance of early genetic testing and multidisciplinary management to reduce diagnostic delays and improve outcomes.

Keywords Primary hypertrophic osteoarthropathy, *HPGD*, Gene variant, Early diagnosis, Genetic disorder

Introduction

Primary hypertrophic osteoarthropathy (PHO) is a rare genetic disorder primarily characterized by the classic triad of digital clubbing, pachydermia, and periostitis. The variants in the 15-Hydroxyprostaglandin Dehydrogenase (*HPGD*, OMIM:601,688, NM_000860.6) gene or the Solute Carrier Organic Anion Transporter Family Member 2A1 (*SLCO2A1*, OMIM:601,460, NM_005630.3) gene have been identified in PHO patients. However, the exact prevalence of PHO remains unclear. Friedreich first described this disorder in 1868 as a condition

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of widespread skeletal hyperostosis [1]. Touraine et al. (1935) introduced the term "hypertrophic osteoarthropathy" to differentiate primary forms from secondary cases, which are often linked to pulmonary, cardiac, or neoplastic diseases [2]. PHO exhibits both autosomal recessive (AR) and autosomal dominant (AD) inheritance patterns. Variants in *HPGD* causing PHOAR1 (MIM:259,100) follow an autosomal recessive pattern. In contrast, *SLCO2A1* variants can result in autosomal recessive (PHOAR2, MIM:614,441) and dominant forms (PHOAD, MIM:167,100).

The pathogenesis of PHO centers on dysregulated prostaglandin E2 (PGE2) metabolism, leading to excessive PGE2 accumulation. Elevated PGE2 promotes angiogenesis via vascular endothelial growth factor-mediated increases in vascular permeability [3]. It also stimulates osteoblast activity and migration, driving pathological bone proliferation [4, 5]. Pathogenic variants in *HPGD* and *SLCO2A1* disrupt PGE2 metabolism through distinct mechanisms. *HPGD* encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme that oxidizes PGE2 in an NAD-dependent manner. Conversely, *SLCO2A1* encodes the prostaglandin transporter OATP2A1, facilitating intracellular PGE2 transport for degradation.

Beyond the classic triad, PHO may manifest with joint, cutaneous, or cardiovascular complications. For instance, joint pain, effusion, and swelling are frequently misdiagnosed as arthritis, leading to inappropriate therapies such as methotrexate or corticosteroids [6, 7].

This study reports the clinical and genetic features of two Chinese children with *HPGD*-associated PHO and synthesizes existing literature on *HPGD*-related cases from PubMed. By highlighting key diagnostic clues and genetic findings, we aim to improve clinical recognition of PHO and reduce diagnostic delays.

Materials and methods

This study presents the clinical features and genetic test results of two children diagnosed with PHO caused by *HPGD* gene variants. A comprehensive review was conducted to identify reported cases of PHO associated with the *HPGD* gene variants in PubMed using the following search strategy: ((Hypertrophic Osteoarthropathy) OR (PHO)) AND ((HPGD) OR (15-Hydroxyprostaglandin Dehydrogenase)). Only reports specifically related to HPGD-associated PHO cases were included.

Case description

Patient 1

A 19-month-old male infant presented with delayed motor development. He was born prematurely at 32^{+2} weeks of gestation via cesarean section due to excessive amniotic fluid. His birth weight was 2.5 kg. The mother, aged 32 years at delivery, had a history of three miscarriages with unknown causes. The father was 30 years old at conception. No consanguinity was noted between the parents. The mother denied exposure to known teratogens during pregnancy and did not smoke, drink alcohol, or use recreational drugs. Prenatal check-ups were regular, with no other complications noted.

The patient achieved independent sitting at eight months and crawling at ten months. He began walking at 14 months, though his gait remained abnormal. Speech and cognitive development were appropriate for his age. Physical examination revealed a notably large head and abnormal cranial bone development, with an anterior fontanelle measuring 2.5×2.5 cm. His body weight was 12.5 kg, and his height was 82 cm at his first visit. No chest deformities were observed. A grade II systolic murmur was detected along the left sternal border of the second intercostal space. Muscle strength and tone in the extremities were normal. Prominent digital clubbing was observed in both hands, along with X-shaped legs. An echocardiogram confirmed the presence of patent ductus arteriosus (PDA). X-rays of both tibiae showed bilateral cortical bone thickening (Fig. 1A, B). The family history was unremarkable for any genetic disorders or congenital anomalies. The patient is 7 years old, with a height of 125 cm (75th percentile for age), a weight of 25 kg (75th percentile for age), and a head circumference of 52.5 cm (75th percentile for age).

Patient 2

An 11-month-old male infant was admitted to our hospital with bilateral lower-limb swelling. The patient had exhibited bilateral digital clubbing since birth and had a PDA that spontaneously closed at six months of age (Fig. 1J-L). His 4-year-old sister had a history of PDA, atrial septal defect (ASD), ventricular septal defect (VSD), and digital clubbing. However, digital clubbing persisted despite surgical correction of the ASD and VSD.

The patient was born at 35^{+6} weeks of gestation via vaginal delivery due to excessive amniotic fluid, with a birth weight of 2.2 kg. The mother, aged 29 years at the time of delivery, had a normal pregnancy with regular prenatal check-ups. No significant complications were reported during the pregnancy. The father, aged 30 years at conception, had a mild form of digital clubbing. There was no consanguinity between the parents. The mother denied exposure to known teratogens during pregnancy and did not smoke, drink alcohol, or use recreational drugs.

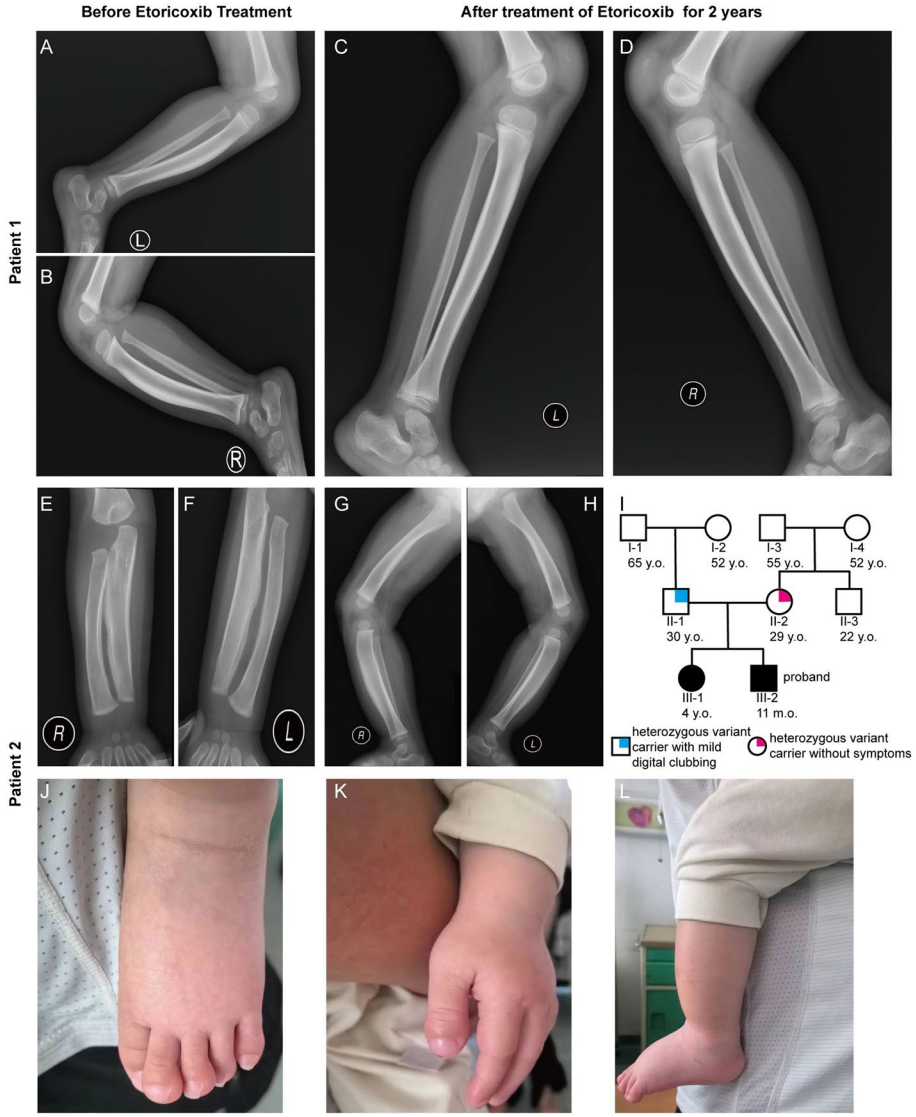

Fig. 1 Radiographic and clinical imaging of both patients. **A-B** X-rays of Patient 1 showed 'onion skin-like' cortical thickening of the tibiae and fibulae, particularly on the medial side, along with narrowing of the medullary cavity. **C-D** After 2 years of etoricoxib treatment, Patient 1 displays a significant reduction in the cortical thickening of the tibiae, with less pronounced 'onion skin-like' features compared to earlier images. **E–H** The diaphyses of the ulnae, radii, femurs, and tibiae/fibulae are thickened in Patient 2, accompanied by bilateral bowing deformities in the ulnae and radii. Layered periosteal reactions are also visible around these bones. **I** The Pedigree for Patient 2. **J-L** Patient 2 exhibits clubbing of the distal extremities and noticeable skin swelling in the lower limbs

Upon admission, the patient was alert but irritable. Physical examination revealed pronounced non-pitting edema in both lower limbs. Digital clubbing was evident in the extremities, but muscle strength and tone remained normal. Radiographs of the long bones demonstrated bilateral thickening of the humeri, ulnae, radii, femora, and tibiae, with layered periosteal reactions and spinal scoliosis (Fig. 1E-H). The patient is 18 months old now, with a height of 80 cm (25th percentile for age), a weight of 9.9 kg (25th percentile for age), and a head circumference of 47 cm (25th percentile for age).

Diagnostic assessment

Both patients presented with digital clubbing and skeletal abnormalities. Patient 2 had an extensive family history of related symptoms (Fig. 1I), demonstrating the possibility of a genetic disorder. Therefore, whole-exome sequencing was conducted to identify genetic anomalies.

In accordance with the institutional guidelines, informed consent was obtained from the parents of the patients.

Genomic DNA was extracted from peripheral blood leukocytes of the probands. Standard Illumina library preparation techniques, including end repair, adapter ligation, and polymerase chain reaction (PCR) amplification, were used. Sequencing was performed using the Illumina NovaSeq 6000 platform (Illumina Inc., San Diego, CA, USA). The data were subsequently analyzed, with clean reads aligned to the human reference genome (hg19) using the Sentieon software BWA parameter (https://www.sentieon.com/). Sequence variations, including single nucleotide polymorphisms and InDels, were identified using the Genome Analysis Toolkit (https://www.broadinstitute.org/gatk/). Potentially pathogenic variants were defined as those with allele frequencies less than 0.01, as determined by the 1000 Genomes Project and ESP6500 databases. These included nonsense, missense, splice-site, and InDel variants.

PCR and Sanger sequencing were conducted to validate the variants. For Sanger sequencing in Patient 1, the primers for variant NM_000860.6: exon2: c.189C > A (p.C63*) were as follows: Forward (F) 5′-ACAGCTATT GGGCTGTCAGAAG-3′ and Reverse (R) 5′-TGTGAG CACACCTCAGAAGTG-3′. For variant NM_000860.6: exon3: c.310_311delCT (p. L104Afs*3), the primer pair used was: Forward (F) 5′-TCTGCCAATCCCTGAGTT AAGC-3′ and Reverse (R) 5′-CAGTTAGTCTGTGGT GTCTGCA-3′. For Patient 2, PCR amplification was performed using the primer pair: Forward (F) 5′-TGTTTC CATGACTCCAAGAACC-3′ and Reverse (R) 5′-TGC TTCTAGTCCACAAACCACAC-3′. The PCR products were sequenced using an ABI3730XL DNA Analyzer (Applied Biosystems, Waltham, MA, USA) (Fig. 2A-C).

HPGD is highly conserved across species, particularly at amino acid residues 63 (Cysteine, C) and 104 (Leucine, L), as highlighted by the red and purple arrows in Fig. 3, respectively. Comparative sequence alignment demonstrates that these residues are highly conserved in 15-hydroxyprostaglandin dehydrogenase from Homo sapiens (UniProt: P15428), Mus musculus (UniProt: Q8VCC1), Rattus norvegicus (UniProt: O08699), Cavia porcellus (UniProt: P70684), Bos taurus (UniProt: Q3T0C2), Cynomolgus monkey (UniProt: Q8MJY8), and Zebrafish (UniProt: E7F258). Whole-exome sequencing identified a compound heterozygous *HPGD* variant in Patient 1. The first variant was a novel single-nucleotide substitution at position 189 (NM_000860.6: c.189C > A, p.C63*). The second variant was a deletion of cytosine and thymine at positions 310 and 311 (NM_000860.6: c.310_311delCT, p. L104Afs*3), resulting in a frameshift after codon 104 and premature termination at codon 106, as documented in previous studies. In Patient 2, genetic testing identified a homozygous splice-site variant at position 324 in *HPGD*, five nucleotides downstream of the splice site (NG_011689.1(NM_000860.6): c.324 + 5G > A). The exact effect of this variant on the protein change is unclear, as it likely leads to a splicing alteration (p.?), with no definitive protein change predicted. This variant disrupts the protein-coding sequence and has been reported in previous study [8]. All variants identified in our patients were classified as pathogenic based on the criteria of the American College of Medical Genetics and Genomics.

Literature review

Given the limited reports of *HPGD*-related PHO, we thoroughly reviewed the cases published in PubMed. Our search identified 67 articles, of which 26 met the inclusion criteria (Supplemental Fig. 1). To date, 89 PHO cases attributed to *HPGD* variants have been documented. The c.310_311delCT variant accounted for 37.1% (33/89) of cases (Fig. 4), predominantly in homozygous form (60.6%, 20/33). Heterozygous *HPGD* variants can also cause PHO, albeit with milder PGE2 elevation and later symptom onset [9–11]. Notably, the homozygous 577T > C variant exhibits variable penetrance linked to isolated clubbing or full PHO phenotypes [12, 13], though this variability is not observed in other variants.

Ethnic distribution analysis revealed that 38% (34/89) of cases were Han Chinese, followed by Pakistani (13.5%, 12/89). Among cases with sex data, males outnumbered females (2.2:1 ratio). While previous studies linked male-biased PHO prevalence to *SLCO2A1* variants, sex differences in *HPGD*-related PHO were previously considered insignificant [14]. Our findings, however, suggest a potential male predominance in *HPGD*-associated cases. The median symptom onset age was 5.1 years (vs. 7.5 years historically reported [15]), with digital clubbing often apparent at birth, implying earlier disease initiation than previously recognized [11]. The median age at diagnosis is 22.1 years, with a significant difference between symptom onset and diagnosis. This delay underscores clinicians' potential lack of awareness, leading to delayed diagnosis or misdiagnosis [6, 7].

Beyond the classic triad (digital clubbing, skin thickening, osteophytes), common symptoms included joint pain (46.1%), joint swelling (37.1%), osteolysis (30.3%), and hyperhidrosis (60.1%). Less frequent manifestations encompassed joint effusion (11.3%), delayed closure of cranial sutures (16.9%), acne (21.3%), skin hyperkeratosis (7.9%), Wormian bones (7.9%), and knee valgus (4.5%), watery diarrhea (5.6%), and anemia (5.6%). Cardiac anomalies included PDA (15.7%, $n = 14$), ASD (2.2%, $n = 2$), and pulmonary artery stenosis (2.2%, $n = 2$). Tumors were identified in two patients:

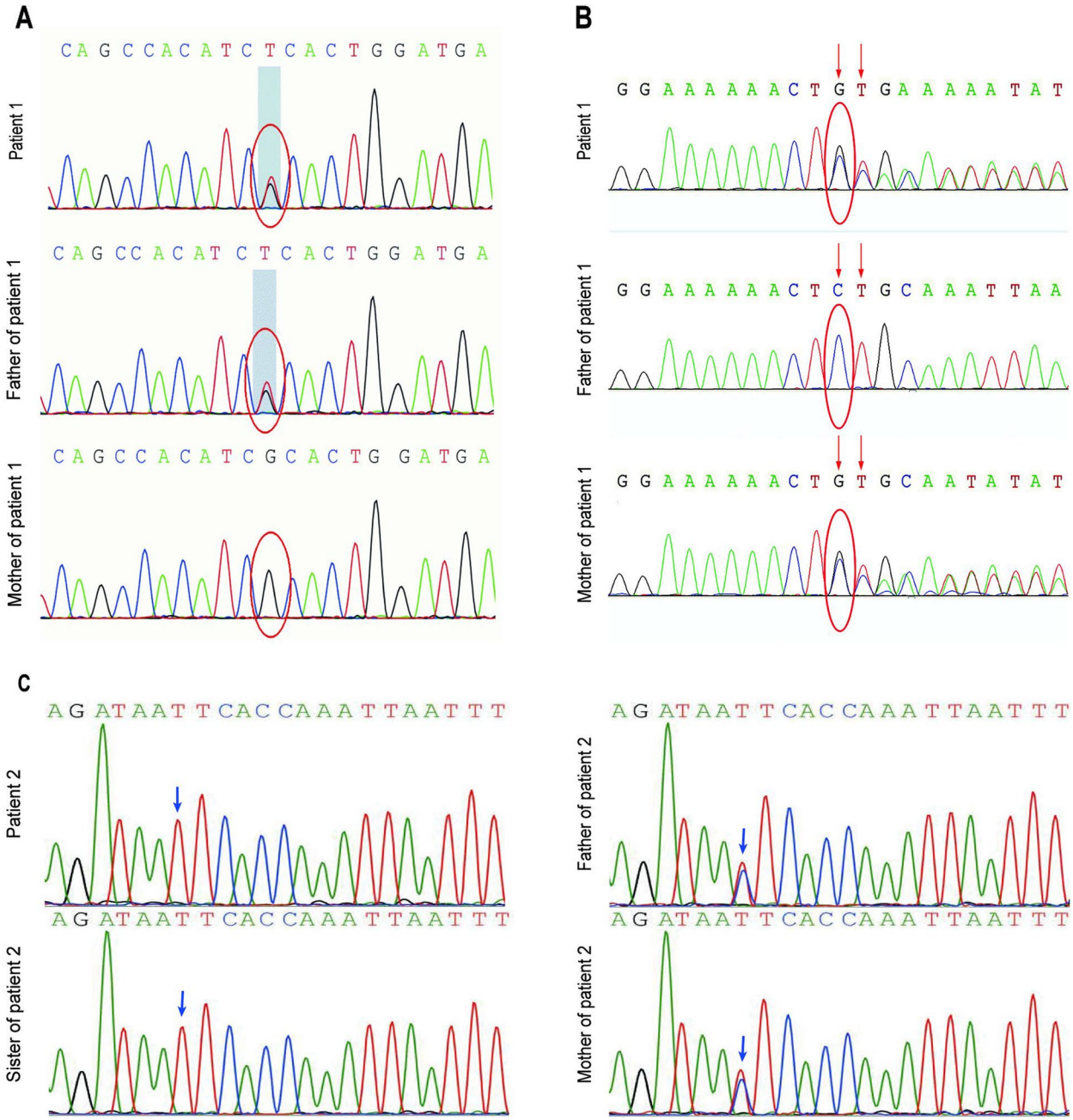

Fig. 2 Sanger sequencing analysis of the variants in both patients. **A** A heterozygous c.189C > A (p.C63*) variant was identified in Patient 1 and his father. **B** A heterozygous c.310_311delCT (p. L104Afs*3) variant was identified in Patient 1 and his mother. The red arrow indicates the position of deleted nucleotides (CT). **C** The homozygous c.324 + 5G > A variant was absent in the asymptomatic parents of Patient 2

one with a diffuse tumor in the medial left tibia [16], and the other with abdominal fibromatosis [17]. Other notable symptoms included recurrent severe calf ulcers in one patient and inflammatory bowel disease in another. Although *HPGD* was previously identified as a tumor suppressor [18–20], only two cases of tumors have been reported in the literature. However, these cases did not meet the conventional criteria for tumor suppressor genes [9]. The urine PGE2-to-creatinine ratio in PHO patients was tenfold higher than normal (median 627.1 vs. 61.49 ng/mmol [15]), confirming profound PGE2 dysregulation.

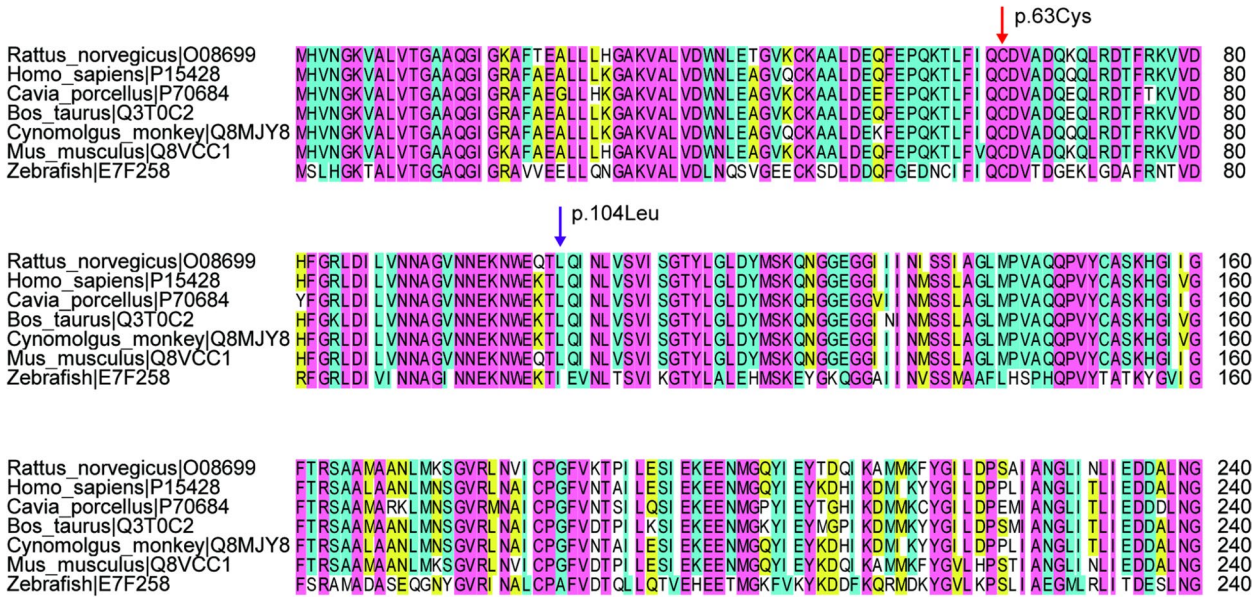

Fig. 3 Comparative genomics demonstrates the conservation of residue 63 (Cysteine, red solid arrow) and residue 104 (Leucine, purple solid arrow) in 15-hydroxyprostaglandin dehydrogenase across species, highlighting their functional importance

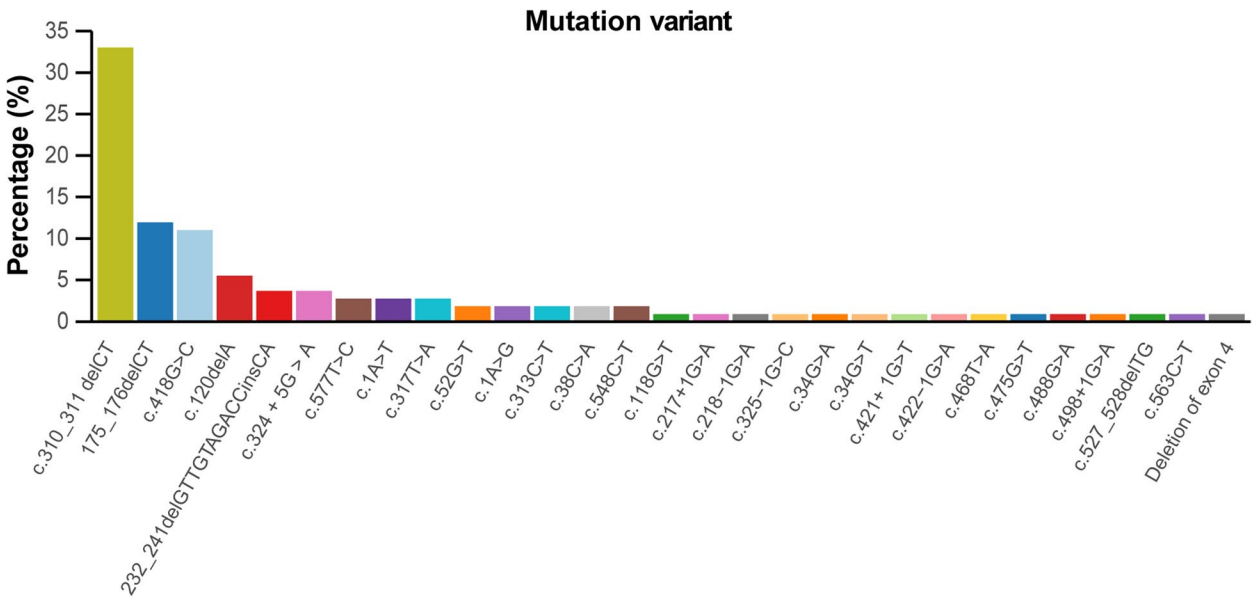

Fig. 4 Distribution of variant variants in *HPGD*, highlighting the predominance of c.310_311delCT

Discussion

We present two cases of PHO attributed to variants in *HPGD*. Both patients exhibited digital clubbing and cortical bone changes. The early onset of symptoms raised suspicion for PHO and whole-exome sequencing confirmed the diagnosis. Genetic testing classified the variants in both patients as pathogenic, consistent with the clinical presentations. In Patient 1, a previously unreported single-nucleotide substitution (NM_000860.6: c.189C > A, p.C63*) was identified. Interestingly, Patient 2 initially presented with bilateral leg edema. However, clinical signs, physical examination, or laboratory tests do not find evidence of a common cause of edema. The presence of digital clubbing since birth and a positive family history further led us to suspect a genetic disorder, particularly one affecting

the musculoskeletal system. The bilateral leg edema was determined to result from skin thickening rather than fluid redistribution.

Uppal et al. [9] identified *HPGD* as the causative factor for PHO, mapping it to the chromosomal region 4q33–q34. This gene encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a key enzyme in PGE2 metabolism. Normally, 15-PGDH metabolizes and inactivates PGE2, maintaining homeostasis. Pathogenic variants in *HPGD* reduce or eliminate the activity of 15-PGDH, leading to the accumulation of PGE2.

The diverse clinical manifestations of PHO are closely associated with the various physiological roles of PGE2 [9]. PGE2 acts through the E-proteinoid receptor family and is involved in multiple physiological processes. It can increase vascular permeability [21, 22], promote inflammatory cell infiltration, and enhance the release of inflammatory mediators [23]. In addition, PGE2 stimulates bone resorption, inhibits bone formation, and leads to osteolysis [24]. It also mediates skeletal homeostasis through sensory nerves and promotes bone regeneration and deposition [25]. PGE2 plays a crucial role in pain signaling, with elevated levels intensifying pain perception [26]. Its effect on cell proliferation and differentiation may also contribute to the regeneration of bone and other tissues [27–29].

PGE2 accumulation can result from genetic variants that disrupt its metabolism, such as pathogenic variants in *HPGD* and *SLCO2A1*. Additionally, PGE2 elevation can be secondary to chronic pulmonary/cardiovascular diseases or malignancies [30]. Primary PHO presents unique features, including delayed cranial suture closure, PDA, and early onset of digital clubbing. These features help distinguish PHO from secondary causes, as similar changes typically appear later in life[9].

PHO caused by *HPGD* variants often presents with digital clubbing at the onset. Patients with this type of PHO typically usually do not have a history of chronic hypoxia. This highlights the need for clinicians to consider this condition with similar presentations. Long-bone X-rays are recommended to evaluate periosteal reactions and hyperostosis. Additionally, measurement of urinary PGE2-to-creatinine ratios and PGE2 metabolite (PGE2-M) concentrations can assist in the diagnosis. It can also help monitor treatment efficacy in facilities with appropriate resources. Unfortunately, we were unable to measure these indices due to technical limitations.

Genetic studies have linked impaired PGE2 metabolism to PHO. This suggests that targeting PGE2 synthesis is a promising therapeutic strategy. Current treatment options, including nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen, indomethacin) and cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib, etoricoxib), have demonstrated clinical efficacy in symptom management [31, 32]. However, NSAIDs carry risks of gastrointestinal complications (e.g., bleeding, ulcers) due to their non-selective inhibition of COX-1, especially with prolonged or high-dose use. COX-2 inhibitors are therefore preferred for long-term therapy. In patients with osteolysis, bisphosphonates like pamidronate may alleviate bone loss and pain, though their effectiveness requires further validation [33]. Other experimental approaches include selective estrogen receptor modulators (SERMs) for joint pain and botulinum toxin type A (BTX-A) for facial pachydermia, although their mechanisms of action remain unclear [34–36]. Supportive therapies such as physical rehabilitation and arthroscopic synovectomy can improve joint function and mobility [37]. Patient 1 exhibited reduced tibial cortical thickening in our study after two years of etoricoxib therapy. In contrast, Patient 2 declined pharmacological treatment and developed knee valgus, requiring corrective footwear and physiotherapy. Early intervention with COX-2 inhibitors may mitigate pain sensitivity and joint symptoms in PHO [15].

Conclusion

In this study, we report a novel c.189C>A variant that expands the known variant spectrum of PHO. The c.310_311delCT variant is the most prevalent and is typically homozygous. Beyond the classic triad, patients with PHO frequently present with joint pain, arch osteolysis, and cardiovascular and skin abnormalities. These findings highlight the importance of early diagnosis and comprehensive disease management.

Abbreviations

PHO	Primary hypertrophic osteoarthropathy
PHOAR1	Autosomal recessive primary hypertrophic osteoarthropathy-1
PHOAR2	Autosomal recessive primary hypertrophic osteoarthropathy-2
PHOAD	Autosomal dominant primary hypertrophic osteoarthropathy
PDA	Patent ductus arteriosus
ASD	Atrial septal defect
VSD	Ventricular septal defect
PGE2	Prostaglandin E2
15-PGDH	15-Hydroxyprostaglandin dehydrogenase
PGE2-M	PGE2 metabolite

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05590-z.

Supplementary Material 1.

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Authors' contributions

All the authors contributed significantly to this work. J.L. drafted the manuscript. S.J., J.G., W.X., Y.M., and X.G. analyzed the genetic data and prepared

figures. M.G. is the corresponding author and was responsible for critical revision of the manuscript. All authors have reviewed and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available in the ClinVar repository, under the accession number SCV005397935. Additionally, the raw FASTQ data is available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Board of Shenzhen Children's Hospital, Shenzhen, Guangdong Province, China.

Consent for publication
Written Informed Consent was obtained from the parents to publish images, medical information, and genetic analyses.

Competing interest
The authors declare no competing interests.

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