Case Report

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Osteogenesis Imperfecta with Pes Equinovarus: A Rare Combination and a Rare Col1a1 Variant

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ABSTRACT
Variants in the *COL1A1* gene typically lead to a connective tissue disorder called osteogenesis imperfecta (OI), which is characterized by increased bone fragility that may be associated with blue sclera, dentinogenesis imperfecta and hearing loss. However, the coexistence of pes equinovarus and OI is rare, and to date, no genetic basis has been described. We report a female patient who was admitted with short stature, and growth hormone replacement treatment was initiated following a diagnosis of growth hormone deficiency. She also had blue sclera, a bulbous nose, flexion contractures in both knee joints, tightness of Achilles tendons and hamstrings and bilateral pes planovarus. In infancy casting had also been applied due to bilateral pes equinovarus and she had experienced one bone fracture. Whole exome sequencing revealed a heterozygous pathogenic variant (c.2956G>A) in the *COL1A1* gene. Pathogenic variants in the *COL1A1* gene have been associated with OI. This rare variant of the *COL1A1* gene should be considered in cases presenting with both pes equinovarus and joint contractures, particularly when accompanied by signs of increased bone fragility.
Keywords: osteogenesis imperfecta, pes equinovarus, bone fragility, joint contractures

What is already known on this topic?
Pathogenic variants in the COL1A1 gene are most commonly associated with osteogenesis imperfecta. However, these pathogenic variants can lead to a wide range of clinical manifestations.

What this study adds?
The identified variant has been reported in only one father-son pair. Increased bone fragility, blue sclera, and short stature along with the presence of pes equinovarus and joint contractures in all three cases carrying this variant, have been considered noteworthy.

Introduction
The *COL1A1* gene is essential for the synthesis of type 1 collagen, a major structural component of connective tissues so its variants have been associated with various hereditary connective tissue disorders, such as osteogenesis imperfecta (OI) (1,2), Ehler-Danlos Syndrome (EDS) (3), Caffey Disease, osteoporosis and fracture risk (4). Pathogenic variants in the *COL1A1* gene most commonly cause OI, with a clinical spectrum ranging from mild to perinatally lethal forms. OI is characterized by an increased susceptibility to bone fractures, reduced bone density and bone deformities. Other skeletal features for OI are short stature, scoliosis and skull deformities. Additionally, cases have been reported with cardiovascular and pulmonary system anomalies, skin fragility, hearing loss, sight impairment, blue sclera and dentinogenesis imperfecta (1,2). Certain *COL1A1* variants are associated with classical EDS, which presents with skin hyperextensibility and generalized joint hypermobility (3). In Caffey disease (infantile cortical hyperostosis), cortical thickening (hyperostosis) and subperiosteal new bone formation are the main findings on radiological imaging (2). Certain variations have been related to osteoporosis or fracture risk (4).
Moreover, variants in *COL1A1* gene may be related to clinical features of both OI and EDS, a condition referred to as OI/EDS overlap syndrome (5). Joint hypermobility is commonly observed in OI and EDS (6); however, joint contractures -including isolated contractures such as pes equinovarus (also known as clubfoot) -have also been reported in EDS (7).
The present case had proportionate short stature, blue sclera, a bulbous nose, flexion contractures in both knee joints, tightness of Achilles tendons and hamstrings and bilateral pes planovarus. Bilateral pes equinovarus was present at birth. The patient had a history of a single forearm fracture sustained during childhood.
There is limited literature regarding the association between *COL1A1* variants and joint contractures or pes equinovarus.
Methods
Whole-exome sequencing (WES) was performed at an accredited clinical genetics laboratory using the Illumina NovaSeq platform with Exome 2.0/2.5 Plus Enrichment (Illumina). Sequencing reads were aligned to the GRCh38/hg38 human reference genome, and variant calling was carried out with validated in-house bioinformatics pipelines (VarSome Clinical and related tools). The average sequencing depth exceeded 100×, with >98% of the target regions covered at ≥20×.
Variant annotation and filtering included multiple databases: ClinVar, OMIM, dbSNP, gnomAD, and in silico prediction tools (MutationTaster, SIFT, PolyPhen-2, REVEL). Variants with a minor allele frequency greater than 1% in population databases were excluded. Candidate variants were evaluated in the context of the proband's phenotype, pedigree, and Human Phenotype Ontology (HPO) terms.
Variant classification followed ACMG/AMP 2015 guidelines, together with ACGS 2020 and ClinGen recommendations. Reported variants were confirmed by Sanger sequencing. Copy number variants were additionally assessed using ExomeDepth CNV calling algorithms. Annotation of COL1A1 was performed using RefSeq transcript NM_000088.4.
AI- assisted tools (Open AI's ChatCPT) were used for language and editorial support. The author takes full responsibility for the scientific content and the interpretation of the manuscript.

Case report

An 11.5-year-old female patient was admitted with short stature. Her weight was 38.1 kg (-0.45 SDS); height was 132.5 cm (-2.5 SDS); mother's height was 0.32 SDS; father's height was 0.13 SDS, and her target height was 0.24 SDS. She had a proportionate short stature, Tanner stage 2 puberty, blue sclera, bulbous nose, yellow teeth, and a slight limp while walking. She was born at term, with normal height and weight. There was no reported maternal smoking, exposure to teratogenic medication use, physical trauma, oligohydramnios, or fetal malposition during the intrauterine period that could have contributed to the development of clubfoot deformity. A cast was applied for 1 week due to bilateral clubfoot in infancy. She had experienced a bone fracture in her forearm. As reported by parents, a greenstick fracture of the forearm occurred at the age of 1 during an attempt to walk, due to a fall onto the arm. Her tooth eruption and anterior fontanelle closure were late. She also had hamstring and Achilles tendon contractures, bilateral knee flexion contracture, mild scoliosis, and pes planovarus. Her family history was unremarkable. Chronic disease tests were normal, bone age was 11 years (Figure-1), basal IGF-1:-1.2 SDS, IGFBP3:-3.28 SDS. Karyotype was 46, XX and microarray was normal. In the ten-month follow-up, the patient's annual growth velocity (GHV) was 2.4 cm, height was -3.19 SDS, growth hormone (GH) peak response was 2.2 ng/mL in clonidine stimulation test, and GH peak response was 0.3 ng/mL in L-dopa stimulation test. Other anterior pituitary hormones were normal, and a 2 mm micronodule was detected in the pituitary on Magnetic Resonance Imaging (MRI). Growth hormone replacement therapy (GHRT) was initiated and genetic examination was planned due to dysmorphic findings. At the 11th month of GHRT (age 13.4 years), her weight was 49.6 kg (-0.23 SDS), height was 145.1 cm (-2.3 SDS), GHV was 9.8 cm/ year, puberty was Tanner stage 3-4, and bone age was 12.

In whole exome sequencing, a heterozygous pathogenic variant NM_000088.4: c.2956G>A; p.(Gly986Ser) was found in *COL1A1* gene. Segregation analysis performed on both parents revealed that neither the mother nor the father carried this variant, confirming its de novo occurrence in the proband. In addition, the WES data were systematically evaluated for other genes known to be associated with Bruck syndrome and congenital pes equinovarus (e.g., FKBP10, PLOD2, COL27A1, FLNB, HOXD10, PITX1). No pathogenic or likely pathogenic variants were identified in these genes.

Discussion

Type 1 collagen is the most prevalent form of collagen, found in nearly all connective tissues and essential for maintaining tissue integrity in collagen (8). Variants in genes encoding type I collagen, particularly *COL1A1* and *COL1A2*, can lead to either quantitative defects (reduced collagen synthesis) or qualitative defects (abnormal collagen structure). Clinical severity typically correlates with the nature of the mutation: structural defects often result in more severe phenotypes, including frequent fractures, skeletal deformities, and significant short stature. In contrast, variants leading to decreased collagen production usually present with milder clinical forms. According to Marini et al. (2007), glycine substitutions in the triple helix domain of *COL1A1* often produce structurally abnormal collagen and are associated with severe forms of osteogenesis imperfecta (OI), while haploinsufficiency variants typically lead to type I OI, the mildest form of the disease (1). In type I collagen, the most frequent structural abnormality leading to OI involves the substitution of glycine residues within the triple-helical domain, a region critical for proper folding and stability of the collagen molecule. Given glycine's essential role in maintaining the tight packing of the triple-helix, its replacement with bulkier amino acids disrupts the helix structure and impairs collagen function (9). Furthermore, variants occurring at specific loci within the type I procollagen molecule result in distinct clinical phenotypes (9). The COL1A1 (NM_000088.4):c.2956G>A (p.Gly986Ser) variant leads to replacement of a glycine residue within the critical Gly-X-Y repeat of the collagen type I triple helix. Glycine, due to its minimal size, enables the close packing that is essential for stable helix formation. When substituted by a larger amino acid, helix folding is delayed and the collagen chains undergo abnormal post-translational modification. This disturbance decreases thermal stability, interferes with fibril assembly, and weakens the extracellular matrix (9). Pathogenic glycine substitutions in COL1A1 are well-recognized cause of OI (1). The same missense change has been described in individuals with characteristic clinical features of OI (10). In the affected father-son pair reported by McVey et al., the father was the second child of unrelated parents. He had fixed hips and contractures of the right elbow, left hip and left knee at birth. He sustained a right femoral fracture at the age of 11 months. The anterior fontanel remained open until the age of three. During childhood, he developed severe short stature, thoracolumbar scoliosis, bilateral sensorineural hearing loss, and myopia. He had blue sclera, hypotelorism, a short philtrum, prominent ears and opalescent dentition. Also he suffered from recurrent shoulder dislocations due to glenoid fossa dysplasia. The patient reached a final adult height of 148 cm. His son had bilateral shortening and bowing of the femur at 22 weeks gestation. At the age of 2 months, the son exhibited facial features resembling those of the father, along with blue sclera, and contractures of the right elbow and left knee. At the evaluation at 19 months of age, the patient presented with severe short stature, normal hearing, and no history of fractures. The clinical features of the current case and the father-son cases are presented in Table-1.

Unlike typical presentations, our patient with the identical pathogenic variant exhibited bilateral congenital pes equinovarus in infancy, a rare finding in OI. Initially, Munns et al. (2004) reported a case of type IV OI presenting with bilateral congenital clubfoot. In this case, whose mother was also affected by type IV OI, it was suggested that the clubfoot deformity might have been a consequence of maternal bisphosphonate therapy (11). Persiani et al. (2016) reported another case of bilateral congenital clubfoot and type IV OI in a newborn whose mother was also affected by type IV OI. They emphasized that the potential association between these two rare conditions should be considered (12). In 2022, Srivastava et al. reported an 8-month-old patient diagnosed with type III OI who presented with bilateral congenital clubfoot and multiple fractures (13). Most recently, in 2025, Barnett et al. reported two cases in which bilateral pes was identified during first-trimester fetal ultrasonography, and osteogenesis imperfecta ~~was~~ diagnosed in the second trimester. In both cases, multiple fractures were observed, and loss-of-function variants in the *COL1A1* gene were detected (14). In OI, joint contractures are generally milder compared to those associated with FKBP10 and PLOD2 variants (15). Variants in FKBP10 and PLOD2, which are involved in collagen folding and cross-linking, generally result in phenotypes that are clinically indistinguishable (16). In these cases, congenital large-joint contractures are observed, followed by fractures during growth and subsequent skeletal deformities. Spinal deformities may also develop during the growth period (16).

Short stature in OI is thought to result from collagen defects and is typically observed in more severe cases (9). These abnormalities interfere with endochondral ossification and long bone growth, as defective collagen fibrils compromise both the structural integrity of bone and the function of growth plates, ultimately leading to disproportionate growth failure (17-19). In addition to the OI, in our patient with proportionate short stature, GH deficiency was also considered to contribute to clinical picture, as the patient demonstrated persistently low growth velocity and showed markedly low responses in two separate GH stimulation test. The patient was started on GH replacement therapy and referred to another center for genetic examination. No side effects were observed under GH treatment. The annual growth velocity was calculated as 9.8 cm/ year over 11 months, and during this period, no progression of scoliosis or disproportionate growth was observed.

In our case, GH therapy was initiated based on the consideration of GH deficiency, without taking bone mineral density (BMD) into account. There are also reports in the literature suggesting that GH therapy may improve BMD in OI patients (20). However, conflicting evidence exists in the literature regarding the efficacy of GH therapy in OI, treatment decisions should therefore be tailored to each patient's individual characteristics and current clinical findings (21,22). Bisphosphonate therapy was not initiated, as the patient had a history of only a single bone fracture at the age of one and showed no evidence of vertebral compression fractures. Since there was no major indication for bisphosphonate therapy, a DEXA scan was not performed prior to initiating GH treatment, which represents an important limitation in our OI case.

Moreover, both the patient's audiometric evaluation and ophthalmologic examination were unremarkable. She had sustained only a single bone fracture, no vertebral compression fracture was detected on X-ray, but mild scoliosis was observed (Figure-2). An operation was planned due to hamstring and Achilles tendon contracture, and orthopedic follow-up was ongoing. Additionally, she had 10-degree flexion contracture in bilateral knees and was receiving physiotherapy.

Our observation adds further detail by showing congenital clubfoot and early joint contractures, thereby broadening the clinical spectrum linked to this variant and underscoring the phenotypic variability that can accompany identical molecular defects. In this newly identified variant, unlike classical OI, there were no recurrent bone fractures or skeletal deformities. Although the family history was unremarkable, segregation analysis provided critical additional evidence confirming a de novo status. Moreover, comprehensive review of the WES dataset excluded other candidate genes previously linked to Bruck syndrome or congenital clubfoot, further supporting the pathogenic contribution of the COL1A1 variant in this patient. All these data collectively demonstrate that the identified COL1A1 variant is the underlying cause of the patient's phenotype.

In conclusion, variants in the *COL1A1* gene can give rise to a broad spectrum of phenotypic manifestations. Thorough clinical characterization of these genetic variants is essential for defining accurate genotype–phenotype correlations.

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Table 1: The clinical features of the current case and the father-son cases reported in the literature

Current case	**Father (Mcvey's case)**	**Son (Mcvey's case)**
Short stature (height at 11.5 years:-2.5 SDS)	Short stature (adult height:148 cm, height at 5 years: -3.52 SDS)	Short stature (height at 19 months: -3.24 SDS)
Blue sclera	Blue sclera	Blue sclera
Yellow teeth	Opalescent and eroded dentitation	Same features
Forearm fracture (at age 1)	Femur fracture (11 months)	No fructures
Contractures (hamstring- achilles tendons and bilateral knees)	Contractures (right elbow, left hip, left knee)	Contractures (right elbow and left knee)
Bilateral clubfoot		
Pes planovarus		Bilateral shortening and bowing of the femora (at 22 weeks gestation)
Late fontanelle closure	Large fontanelle and late fontanelle closure	
Late tooth release		

	Hypotelorism, short philtrum, prominent ears	Same features
Scoliosis	Thoracolumbar scoliosis (at age 5)	
No sensorineural deafness	Bilateral sensorineural deafness and myopi (at age 6)	
No joint laxity	Leg length discrepancy with joint laxity (adulthood)	

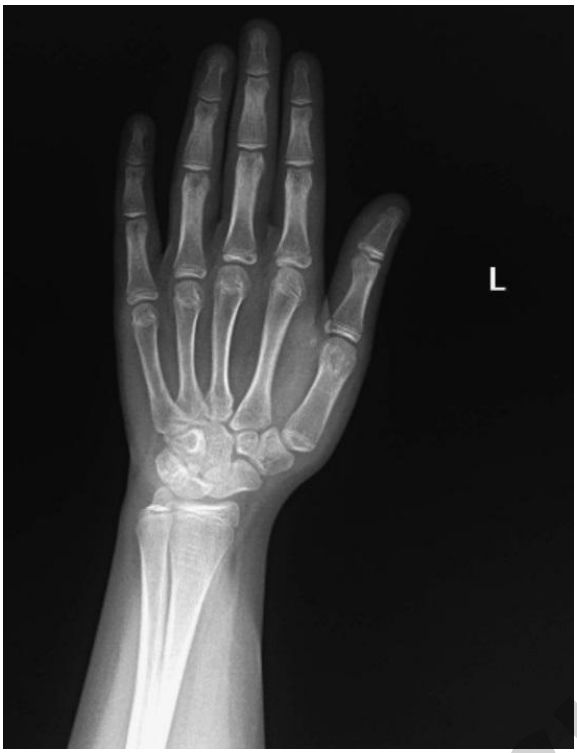

Figure 1: Left wrist radiography

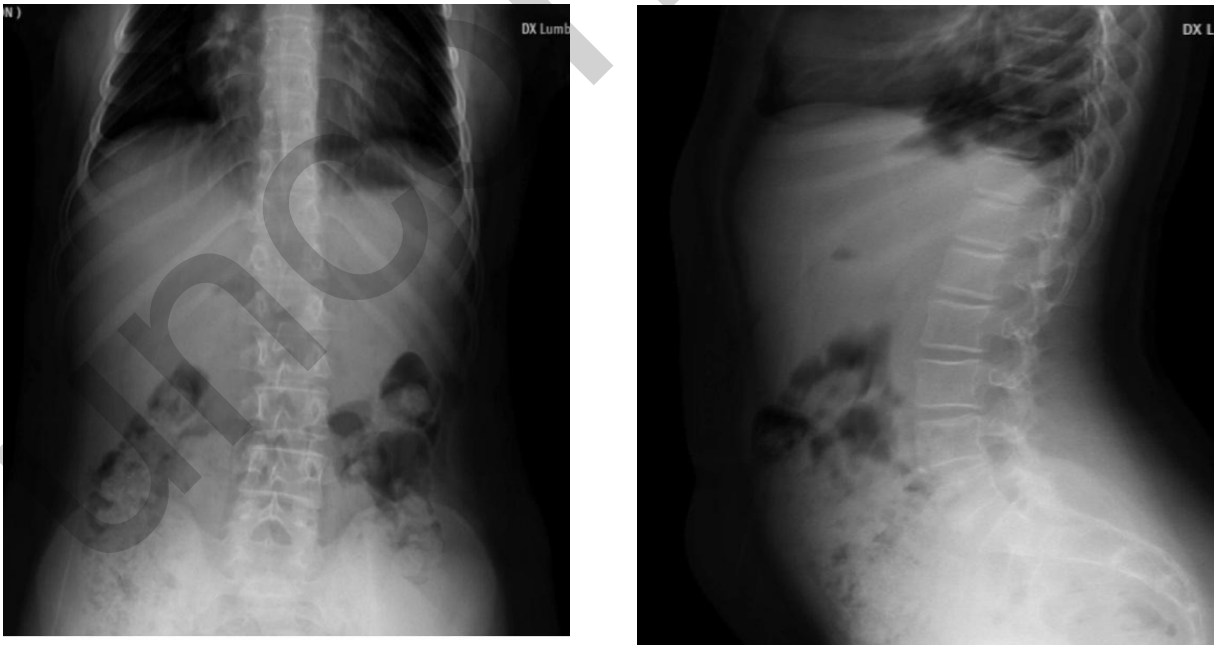

Figure 2: Vertebral compression fracture was not detected. Mild scoliosis was observed