

Case Report: A novel de novo pathogenic variant in COL1A1 causing osteogenesis imperfecta (OI) in a Chinese girl

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Case Report

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Abstract

Background

Osteogenesis imperfecta (OI) is a group of hereditary connective tissue disorders characterized primarily by increased bone fragility, recurrent fractures, and reduced bone mass. The clinical phenotype is highly heterogeneous, and some children may lack typical extra-skeletal manifestations in the early stages, making clinical identification and diagnosis challenging.

Case

This report presents a case of a 4-year-and-9-month-old female patient. The patient had normal growth and development from infancy, with no significant birth history or family history of genetic disorders. She was repeatedly brought in for medical care due to multiple fractures, which successively involved the clavicle, feet, and forearms. Physical examination revealed bilateral scleral blue staining, but no signs of dentin hypoplasia, hearing loss, joint laxity, scoliosis, or marked short stature. Genetic testing revealed a heterozygous non-synonymous variant (c.406G > T [p.Gly136Ter]) in the COL1A1 gene. Neither parent carried this variant, suggesting a *de novo* mutation. According to ACMG criteria, this variant was classified as pathogenic. Based on the patient's recurrent fractures and blue sclera, a diagnosis of OI was made.

Conclusion

We report, for the first time, the clinical presentation of a patient with OI caused by a missense variant (c.406G > T) in exon 5 of the COL1A1 gene. This case highlights the importance of remaining vigilant for the possibility of OI in patients with recurrent childhood fractures who lack some typical associated phenotypes, and of promptly conducting genetic testing to confirm the diagnosis. The identification of the COL1A1 c.406G > T (p.Gly136Ter) mutation also provides new clinical evidence to expand the spectrum of associated genetic variants and phenotypes.

Introduction

Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disorder with an incidence of approximately 1 in 15,000–20,000 [1]. The clinical features of OI include brittle bones, skeletal deformities, recurrent fractures, blue sclera, dentin hypoplasia, short stature, and progressive hearing loss [2]. In addition to skeletal involvement, some patients may also present with extra-skeletal manifestations such as blue sclera, dentin hypoplasia, hearing loss, joint laxity, and spinal deformities [3]. Due to the significant clinical heterogeneity of OI, its severity can range from perinatal lethal forms to cases presenting only with mild fracture susceptibility; therefore, early identification and accurate diagnosis are of great clinical importance.

OI is predominantly inherited in an autosomal dominant pattern. Currently, approximately 85%–90% of OI cases are known to be associated with mutations in the COL1A1 and COL1A2 genes, which encode type I collagen [4]. Type I collagen is one of the most important structural components of the bone matrix; mutations in COL1A1/COL1A2 can lead to reduced levels or structural abnormalities of type I collagen, resulting in clinical phenotypes of varying severity [5]. The clinical spectrum of COL1A1/COL1A2-related OI is broad; patients may present with mild fracture susceptibility or severe skeletal deformities, limited mobility, and marked short stature. Fractures can occur in any bone, but are most common in the long bones of the limbs [6]. The timing of OI diagnosis varies depending on disease severity and may be identified prenatally, at birth, during childhood, or even in adulthood [7]. Previous studies have shown that the incidence of fractures is highest during childhood in OI patients, and the risk of fractures persists into adulthood, particularly in middle and older age [8].

Although well-established genotype-phenotype studies exist, significant clinical overlap persists among different types of OI, particularly in early childhood. Some children lack typical extra-skeletal manifestations or present only with recurrent fractures, thereby increasing the difficulty of clinical identification and classification [9]. Furthermore, the high fracture rate and long-term skeletal complications associated with OI not only increase the medical burden on patients but also have a lasting impact on caregivers' psychological well-being, financial resources, and quality of life [10]. Therefore, for patients lacking a typical phenotype, early identification of suspected cases and confirmation of diagnosis through molecular genetic evidence are of practical significance for optimizing treatment strategies and improving prognosis.

This report presents a 4-year-and-9-month-old female patient who presented with recurrent fractures and bilateral blue sclerae. Genetic testing revealed a *de novo* heterozygous missense mutation (c.406G > T [p.Gly136Ter]) in the COL1A1 gene, leading to a diagnosis of OI.

Case presentation

Female, 4 years and 9 months old. Unremarkable birth history; normal growth and development. No history of drug allergies. No family history of recurrent fractures, blue sclera, hearing abnormalities, or other hereditary bone disorders.

The patient was first admitted to our hospital on April 22, 2022, for a “follow-up examination 4 weeks after fixation of a right clavicle fracture with a figure-8 bandage (brace).” Physical examination revealed no significant swelling or tenderness in the right clavicular region, no significant restriction of shoulder joint movement, and no swelling, pain, or deformity in the upper limb. Radial artery pulsation was good, and finger movement was normal. A preliminary diagnosis of a right clavicle fracture was made. The patient was advised to continue treatment with an “8” figure bandage or brace and was scheduled for a follow-up visit with the orthopedic specialist in one week. The results of the imaging studies are shown in Fig. 1A.

On May 22, 2023, the patient presented again with a complaint of “limping for one week following a right foot injury.” Physical examination revealed a limp in the right lower limb. There was no significant swelling or tenderness in the right foot, no local lacerations or ecchymoses, and peripheral circulation was adequate. Following anteroposterior and oblique DR imaging of the foot, a preliminary diagnosis of a right foot sprain was made. A cast was applied, and the patient was instructed to return for a follow-up visit in one week. The results of the imaging studies are shown in Fig. 1B.

On July 1, 2023, the patient returned for a follow-up visit due to “a fracture of the fifth metatarsal bone of the right foot, more than one month post-injury.” The patient had previously undergone surgical treatment; at this follow-up, there were no obvious symptoms such as fever or pain. Physical examination revealed the patient was in generally good condition, alert, and responsive; the affected limb was under external fixation with a brace, and peripheral blood supply was adequate. Anterior-posterior and oblique DR images of the foot showed an indistinct fracture line. The preliminary diagnosis was a postoperative follow-up for a fracture of the fifth metatarsal bone of the right foot. The patient was advised to avoid strenuous activities and re-injury, and to return for follow-up as necessary. The imaging results are shown in Fig. 1C.

On July 18, 2023, the patient returned for a follow-up visit due to “swelling, pain, and limited mobility in the right foot following trauma.” Physical examination revealed swelling and pain in the affected limb, primarily in the foot. There were no open wounds or ecchymoses locally, but tenderness was present, and joint mobility was limited. The dorsalis pedis artery pulse was faint, peripheral circulation was adequate, and sensation was slightly numb. Anterior-posterior and oblique DR images of the foot, along with X-ray examination, showed good alignment and reduction at the original fracture site of the fifth metatarsal bone of the right foot, with local callus formation and the fracture line largely resolved. A preliminary diagnosis of foot injury was made. The foot was immobilized with a brace, and the patient was advised to protect the area and avoid trauma. The results of the imaging studies are shown in Fig. 1D.

On March 16, 2024, the patient presented with “abnormal weight-bearing in the left foot following a fall.” Physical examination revealed good mental status; no redness or swelling was observed in either lower limb, and there were no obvious tender points; no redness, swelling, or tenderness at the hip, knee, or ankle joints, with good range of motion; no redness, swelling, or tenderness on the sole of the foot, with normal lower limb muscle strength; and good upper limb mobility. The left foot showed no significant swelling or tenderness, with good joint mobility and negative longitudinal percussion pain. The preliminary diagnosis was abnormal gait. The patient was advised to undergo observation for the time being, avoid weight-bearing on the lower limb, enhance protection, and avoid re-injury.

On February 18, 2025, the patient presented to our hospital following two weeks of external fixation treatment at another facility for a “left forearm injury.” Physical examination revealed the patient was in generally good condition, with bilateral scleral icterus; the external fixation had been removed by the patient, and the distal left forearm was slightly swollen with tenderness. Imaging studies revealed

abnormalities on anteroposterior and lateral radiographs of the radius and ulna. A preliminary diagnosis of a left ulnar fracture was made, with osteogenesis imperfecta to be ruled out. The patient was treated with a plaster cast. Follow-up X-rays showed good alignment and union of the fracture, with evidence of callus formation. It was recommended to continue plaster immobilization and perform further investigations. The radiographic findings are shown in Fig. 1E.

On August 25, 2025, the patient presented again with “recurrent fractures of the extremities.” Given the history of multiple fractures following low-energy trauma and the presence of a blue sclera noted on physical examination, OI was strongly suspected clinically, and genetic testing was performed. A preliminary diagnosis of osteogenesis imperfecta was made, and the patient was treated with a plaster cast for the fracture.

On September 22, 2025, the patient returned for a follow-up visit regarding “the left foot four weeks after fracture casting.” Physical examination revealed: the left foot appeared normal with no obvious deformity, and the exposed distal phalanges exhibited good blood perfusion. X-ray findings showed no significant displacement at the fracture site of the left foot, with local callus formation visible. Overall, this patient presented with onset in the preschool years, recurrent fractures, and a blue sclera as the primary manifestations. There were no typical associated phenotypic features such as dentin hypoplasia, hearing loss, joint laxity, scoliosis, or short stature; therefore, a preliminary diagnosis of osteogenesis imperfecta was made.

Genetic Testing

To determine the genetic cause of the patient’s recurrent fractures, peripheral blood samples were collected from the patient and his parents. Genetic testing was performed using high-throughput sequencing, and the variants were validated via Sanger sequencing (Fig. 2). Quality control for the high-throughput sequencing is shown in Table 1. The results revealed a heterozygous variant in the patient’s COL1A1 gene: c.406G > T (NM_000088.4), located in exon 5. This variant causes the 136th amino acid of the protein to change from glycine to a stop codon, resulting in the p.Gly136Ter variant, which is classified as a nonsense mutation.

Conservation analysis showed that the amino acid sequence at position 136 is highly conserved in human and Pan troglodytes mullatta (Fig. 3). Prediction of this mutation using MutationTaster (<https://www.genecascade.org/MutationTaster2021/>) indicates that the COL1A1 c.406G > T (p.Gly136Ter) variant is deleterious, with a model vote of 200/0, suggesting that this variant has clear potential for harm. The COL1A1 amino acid chain consists of 1,465 amino acids; the c.406G > T (p.Gly136Ter) mutation prematurely introduces a stop codon at position 136 of the protein, causing the translation of the normal COL1A1 protein to terminate significantly earlier, which is highly likely to affect the functional region of the protein (Table 2). Further analysis suggests that this mutation may trigger nonsense-mediated mRNA decay (NMD), leading to the degradation of the abnormal transcript and resulting in loss of COL1A1 function. Prediction of this mutation using CADD

(<https://cadd.gs.washington.edu/snv>) yielded a RawScore of 6.25 and a PHRED score of 33, indicating a very high likelihood of deleteriousness, with its potential harm ranking among the top 0.1% of all possible variants across the entire genome. Overall, the results from MutationTaster and CADD support that the COL1A1 c.406G > T (p.Gly136Ter) variant likely causes significant functional impairment, and its molecular consequences are consistent with the known pathogenic mechanisms of osteogenesis imperfecta.

According to the ACMG variant interpretation criteria, this variant is classified as pathogenic, with evidence entries PVS1, PS2_Moderate, and PM2_Supporting. Specifically, PVS1 indicates that this variant is a null variant leading to loss of gene function; PS2_Moderate indicates that the same variant was not detected in either of the patient's parents at this locus, suggesting that the variant is *de novo*; PM2_Supporting indicates that the variant is absent or extremely rare in population databases; this variant is not included in population databases (gnomAD, ExAC, 1000 Genomes), nor are there explicit reports of it in ClinVar or HGMD. COL1A1 is one of the most common disease-causing genes for osteogenesis imperfecta, encoding the type I procollagen $\alpha 1$ chain. Given that the patient's clinical presentation is characterized primarily by increased bone fragility and blue sclera, without significant skeletal deformities or growth and developmental delays, the clinical phenotype is consistent with mild OI.

Discussion

To our knowledge, this case report is the first to describe a female pediatric patient with osteogenesis imperfecta (OI) who carries a nonsense mutation (c.406G>T, p.Gly136Ter) in exon 5 of the COL1A1 gene. Osteogenesis imperfecta (OI) is a group of hereditary connective tissue disorders primarily characterized by increased bone fragility and reduced bone mass. In addition to skeletal involvement, it may be accompanied by blue sclera, conductive or sensorineural hearing loss, dentin hypoplasia with malocclusion, basal skull depression, scoliosis, pulmonary dysfunction, cardiac valve abnormalities, muscle weakness, and ligament laxity [11]. This patient experienced multiple fractures during early childhood, involving the clavicle, metatarsals, ulna, and feet, suggesting persistent increased bone fragility. At the same time, the patient presented with bilateral blue sclerae but did not exhibit common associated manifestations such as dentin hypoplasia, hearing loss, joint laxity, scoliosis, or marked short stature. Furthermore, there was no clear family history, nor was there a history of typical low-energy trauma or spontaneous fractures. This “partially typical, partially atypical” phenotypic combination suggests that this case aligns more closely with the clinical spectrum of mild or early-stage OI, reflecting the complexity of identifying OI in childhood. Previous studies have also noted that identifying OI in early childhood is often challenging, and a single fracture or limited clinical signs may not be sufficient to make a timely diagnosis [12].

Based on the above clinical findings, we performed whole-exome sequencing on the patient and his parents. The results revealed that the patient carried only one heterozygous variant in the COL1A1 gene: c.406G>T (NM_000088.4), located in exon 5, which causes the 136th amino acid of the protein to change

from glycine to a stop codon, i.e., p.Gly136Ter, classified as a nonsense mutation. This finding explains the patient's clinical presentation, which is characterized primarily by increased bone fragility and blue sclera. It also highlights the critical role of molecular genetic testing in establishing a diagnosis in pediatric cases lacking a complete, typical phenotype and a clear family history.

The COL1A1 gene is located on chromosome 17 at q21.33 and consists of 51 exons [13–14]. This gene encodes the $\alpha 1$ chain of type I collagen, which is the most abundant collagen in mammals and a key component in maintaining the structure and function of various tissues, including bones, teeth, skin, and the sclera [14]. Consequently, pathogenic variants in COL1A1 can directly affect the synthesis, assembly, and functional stability of type I collagen, leading to varying degrees of bone fragility and skeletal phenotypes. The most common molecular basis of OI is mutations in type I collagen-related genes, accounting for approximately 80%–85% of cases in Western countries and about 60% in populations with higher rates of consanguinity, suggesting that the proportion of non-collagen-related pathogenic mechanisms may vary across different populations. In this case, to the best of our knowledge, c.406G>T (p.Gly136Ter) is a *de novo* mutation that has not been previously reported. A study of 146 OI patients from diverse populations showed that 56.16% of OI cases were caused by *de novo* pathogenic variants [15]; therefore, the *de novo* occurrence in this case is not uncommon and further underscores the importance of prioritizing the detection and interpretation of *de novo* variants in sporadic cases.

From the perspective of pathogenic mechanisms, COL1A1-related OI can generally be classified into two molecular patterns: the first is a “quantitative defect” that leads to a reduction in the amount of type I collagen; this is commonly seen in nonsense mutations, frameshift mutations, splice site mutations, or whole-gene deletions, and is typically associated with a relatively mild clinical phenotype; The second is a “qualitative defect” that leads to abnormal collagen molecular structure, commonly seen in missense mutations that alter the stability of the triple-helix structure, particularly glycine substitutions, and is more frequently associated with severe or even lethal phenotypes [3]. Previous studies have suggested that quantitative defects in type I collagen are typically associated with milder OI phenotypes, whereas qualitative defects are more likely to result in moderate to severe progressive deformities and are even associated with type III, type IV, and lethal type II OI [3,11]. Therefore, determining whether a mutation represents a “quantitative defect” or a “qualitative defect” is of great significance for understanding the clinical severity of the affected child.

The c.406G>T (p.Gly136Ter) mutation in this case is a classic nonsense mutation that introduces a premature stop codon at position 136 of the protein. Since this mutation is located in the early part of the coding sequence, its molecular consequence is more likely to trigger nonsense-mediated mRNA decay (NMD), thereby clearing the abnormal transcripts before they produce large amounts of truncated proteins, ultimately resulting in COL1A1 monogenic deficiency rather than the generation of abnormal collagen chains with significant disruptive effects. Previous studies have shown that COL1A1 variants capable of generating a premature stop codon and causing haploinsufficiency via NMD are typically associated with milder phenotypes such as type I OI [16]. Similarly, haploinsufficiency resulting from the inactivation of a single COL1A1 allele is often associated with mild forms of osteogenesis imperfecta,

with the core mechanism involving premature stop codons induced by nonsense, frameshift, or certain splicing mutations, followed by mRNA degradation [17]. Amino acid conservation analysis in this case further revealed that the 136th amino acid is highly conserved across different species, suggesting that this site has significant biological importance; Bioinformatics analysis also predicts that this variant introduces a premature stop codon and triggers NMD. Consequently, the most likely pathogenic mechanism in this case is COL1A1 haploinsufficiency, leading to reduced levels of type I collagen and establishing a molecular pathophysiological basis consistent with mild OI. Given the correspondence between the clinical phenotype and genotype, the phenotype in this case shows a high degree of consistency with the aforementioned mechanism. The patient primarily presented with recurrent fractures and blue sclera during childhood, without evident skeletal deformities, growth retardation, or multisystem involvement, suggesting a diagnosis of mild osteogenesis imperfecta. According to ACMG criteria, this variant is classified as pathogenic; furthermore, family testing confirmed that neither of the patient's parents carried the same variant at this locus, supporting the conclusion that it is a *de novo* mutation.

This case further underscores the significant value of genetic testing in cases of atypical OI. In children presenting with multiple, recurrent fractures and suggestive features such as blue sclera, hereditary bone fragility disorders should not be readily ruled out, even in the absence of clues such as dental abnormalities, hearing impairments, or a history of low-energy fractures. Molecular diagnosis can significantly improve diagnostic accuracy and aid in genetic counseling and prognosis assessment.

In summary, the patient in this case presented primarily with recurrent fractures and blue sclera during early childhood. Although some classic skeletal phenotypes and a clear family history were absent, genetic testing revealed a heterozygous missense variant in COL1A1 (c.406G>T [p.Gly136Ter]), leading to a definitive diagnosis of osteogenesis imperfecta. This case provides valuable insights into the clinical and molecular spectrum of OI associated with rare COL1A1 nonsense variants and highlights the need for early consideration of genetic testing in cases of recurrent fractures with atypical childhood phenotypes. Of course, this study currently relies primarily on clinical manifestations and genetic testing results, and lacks more systematic bone density assessments, radiographic follow-up of the spine, and long-term treatment outcome data. Therefore, the precise phenotypic spectrum and long-term natural history of this variant remain to be further clarified by future research.

Declarations

Data availability statement

The original contributions presented in the study are included in the article/ Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics approval and consent to participate

The human research involved in this study has been approved by the Shenzhen Children's Hospital. Ethics Committee (Ethics Approval No.202009002). The study was conducted in compliance with local laws, regulations and institutional requirements. Written informed consent was obtained from the legal guardians/next of kin of all participants. For any potentially identifiable images or data contained in this article, written informed consent was obtained from the relevant individuals and their minor guardians/next of kin.

Author contributions

Xf Wang: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

W Wang and Gb Fu: Conceptualization, Data curation, Investigation, Writing – review & editing.

Lf Xie: Data curation, Formal analysis, Writing – original draft.

B E: Investigation, Writing – original draft.

Yh Liu: Data curation, Investigation, Writing – original draft.

Js Wang: Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

Conflict of Interest Jiansheng Wang, Xinfeng Wang, Wei Wang, Liangfu Xie, Bing E, Yuhuan Liu and Guibing Fu declare that they have no conflict of interest.

Clinical trial number: not applicable.

Consent to publish:

Written informed consent were obtained from the patient/legally authorized representative and/or guardian's of all patients for publication of this case report.

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Tables

Table 1 Quality control data of exome sequencing

Average sequencing depth	Target region coverage	
	10X	20X
312.37	99.73	99.63

Table 2 Wildtype amino acid chain and mutated amino acid chain.

Wildtype AA sequence (1465)	MFSFVDLRL LLLAATALLT HGQEEGQVEG QDEDIPPITC VQNGRLRYHDR DVWKPEPCRI CVCDNGKVLC DDVICDETKN CPGAEPVEGE CCPVCPDGSE SPTDQETTGV EGPKGDTGPR GPRGPAGPPG RDGIPGQPL PGPPGPPGPP GPPGLGGNFA PQLSYGYDEK STGGISVPGP MGPSGPRGLP GPPGAPGPQG FQGPPGEPGE PGASGPMGPR GPPGPPGKNG DDGEAGKPGR PGERGPPGPQ GARGLPGTAG LPGMKGHRGF SGLDGAAGDA GPAGPKGEPG SPGENGAPGQ MGPRGLPGER GRPGAPGPAG ARGNDGATGA AGPPGPTGPA GPPGFPGAVG AKGEAGPQGP RGSEGPQGV RGEPPGPAG AAGPAGNPGA DGQPGAKGAN GAPGIAGAPG FPGARGPSGP QGPGGPPGPK GNSGEPGAPG SKGDTGAKGE PGPGVGVQGP GPAGEEGKRG ARGEPTGL PGPPGERGGP GSRGFPGADG VAGPKGPAGE RGSPGPAGPK GSPGEAGRPG EAGLPAGKGL TGSPGSPGPD GKTGPPGPAG QDGRPGPPGP PGARGQAGVM GFPGPKAAG EPGKAGERGV PGPPGAVGPA GKDGEAGAQQ PGPAGPAGE RGEQGPAGSP GFQGLPGPAG PPGEAGKPGE QGVPGDLGAP GPSGARGERG FPGERGVQGP PGAPGPRGAN GAPGNDGAKG DAGAPGAPGS QGAPGLQGMP GERGAAGLPG PKGDRGDAGP KGADGSPGKD GVRGLTGPPI PGPAGAPGD KGESGPSGPA GPTGARGAPG DRGEPGPPGP AGFAGPPGAD QPGAKGEPG DAGAKGDAGP PGPAGPAGPP GPIGNVAGAPG AKGARGSAGP PGATGFPGAA GRVGPGPSG NAGPPGPPGP AGKEGGKGP GETGPAGRPG EVGPPGPPGP AGEKGSPGAD GPAGAPGTPG PQGIAGQRGV VGLPGQRGER GFPGLPGPSG EPGKQGPSGA SGERGPPGPM GPPGLAGPPG ESGREGAPGA EGSPGRDGSP GAKGDRGETG PAGPPGAPGA PGAPGPVGPA GKSGDRGETG PAGPTGPVGP VGARGPAGPQ GPRGDKGETG EQGDRGIKGH RGFSGLQGP GPPGSPGEQG PSGASGPAGP RGPPGSAGAP GKDGLNGLPG PIGPPGPRGR TGDAGPVGPP GPPGPPGPPG PPSAGFDFSF LPQPPQEKAH DGGRYRADD ANVVRDRDLE VDTTLKSLSQ QIENIRSPEG SRKNPARTCR DLKMCHSDWK SGEYWIDPNQ GCNLDAIKVF CNMETGETCV YPTQPSVAQK NWYISKNPDK KRHVWFGESM TDGFQFEYGG QGSDPADVAI QLTLRLMST EASNITYHC KNSVAYMDQQ TGNLKKALLL QGSNEIEIRA EGNSRFTYSV TVDGCTSHTG AWGKTVIEYK TTKTSRLPII DVAPLDVGAP DQEFQFDVGP VCFL*
Mutated AA sequence (136)	MFSFVDLRL LLLAATALLT HGQEEGQVEG QDEDIPPITC VQNGRLRYHDR DVWKPEPCRI CVCDNGKVLC DDVICDETKN CPGAEPVEGE CCPVCPDGSE SPTDQETTGV EGPKGDTGPR GPRGPAGPPG RDGIP*

Figures

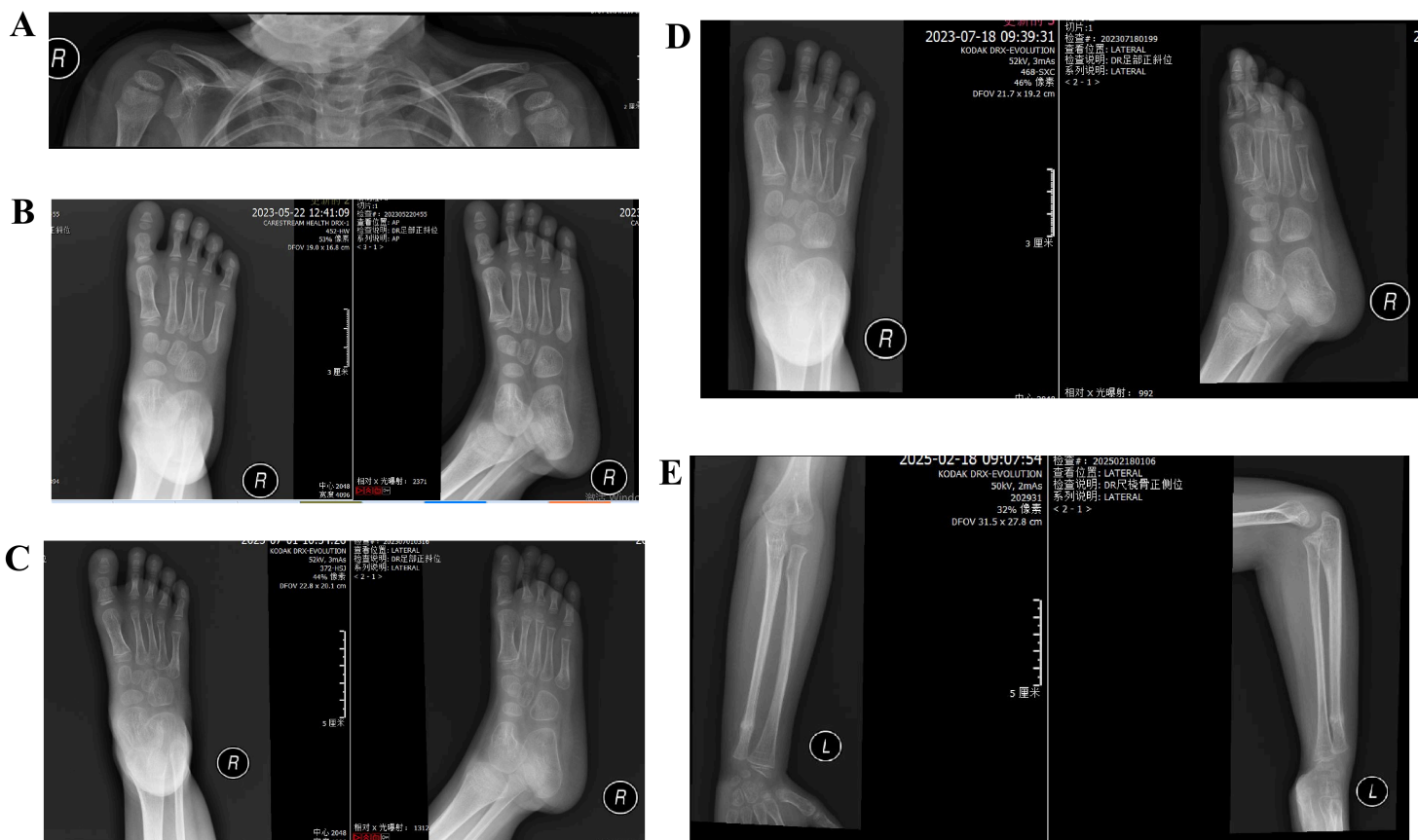


Figure 1

Radiographs of the patient. (A) Radiograph of the patient's clavicle fracture on April 2, 2022; (B) Radiograph of the patient's proximal fifth metatarsal fracture on May 22, 2023; (C) Radiograph of the patient's distal fifth metatarsal fracture on July 1, 2023; (D) Radiograph of the patient's fifth metatarsal at the site of the original fracture on July 18, 2023; (E) Radiograph of the patient's ulnar fracture on February 18, 2025

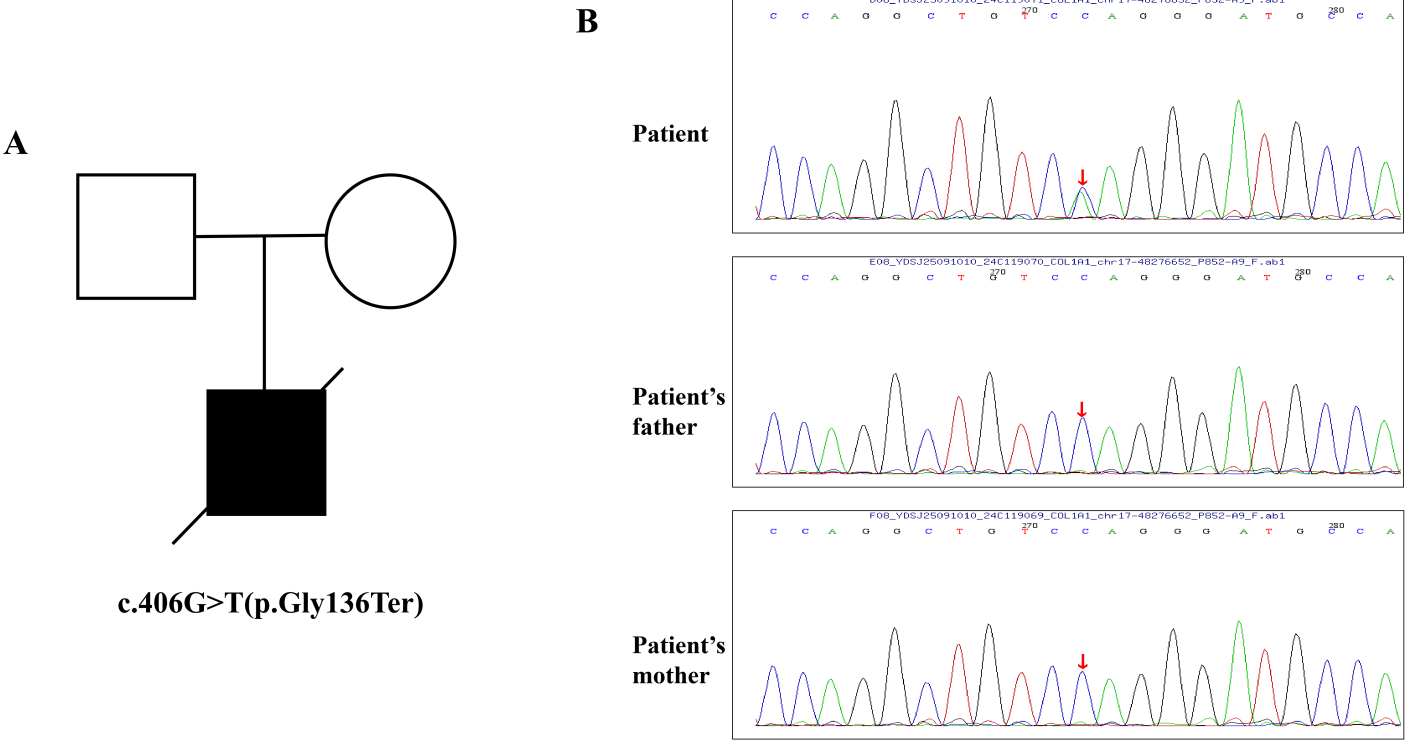


Figure 2

Molecular genetic analysis. (A) Family tree; (B) Mutation sites in this family were validated by Sanger sequencing. A novel missense variant (c.406G>T) in the COL1A1 gene was identified in the patient.

Species	Amino acid Sequence
Human	136 PAGPPGRDGIPG QPGLPGPPGPPGPPGLGGNFAPQLSYGYDEKSTGGISVPGPMGSPGRGLPGPPGAPGPQGFQGPPEPGE PGASGPMGPRGPPPGKNGDDGEAGKPGR
Pan troglodytes	136 PAGPPGRDGIPG QPGLPGPPGPPGPPGLGGNFAPQLSYGYDEKSTGGISVPGPMGSPGRGLPGPPGAPGPQGFQGPPEPGE PGASGPMGPRGPPPGKNGDDGEAGKPGR
Mmulatta	136 PAGPPGRDGIPG QPGLPGPPGPPGPPGLGGNFAPQLSYGYDEKSTGGISVPGPMGSPGRGLPGPPGAPGPQGFQGPPEPGE PGASGPMGPRGPPPGKNGDDGEAGKPGR

Figure 3

Conservation analysis of the missense variant (c.406G>T) in the COL1A1 gene.