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Research Article

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Homozygous Synonymous Variant in *CCDC134* with Osteogenesis Imperfecta Type XXII in a Three-Generation Chinese Family

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Abstract

Background: Osteogenesis imperfecta (OI) type XXII is an ultra-rare autosomal recessive disorder caused by biallelic pathogenic variants in *CCDC134*. To date, only six cases have been reported worldwide: five harboring the c.2T>C (p.Met1Thr) variant and one with the synonymous c.492G>C (p.Leu164Leu) change. We report two siblings carrying the c.492G>C variant, thereby expanding the clinical and therapeutic phenotype spectrum of this ultra-rare condition.

Methods: Two siblings presenting with recurrent fractures and low bone mineral density (BMD) underwent comprehensive evaluation. Trio-based whole-exome sequencing was performed, followed by Sanger sequencing for segregation analysis. The impact of the variant on pre-mRNA splicing was assessed by reverse transcription PCR (RT-PCR) and Sanger sequencing of cDNA. Clinical, radiological, and densitometric data were collected at baseline and during follow-up after intravenous zoledronic acid therapy.

Results: Both siblings were homozygous for the *CCDC134* c.492G>C variant. RT-PCR and cDNA sequencing confirmed complete skipping of exon 5. The proband (11 years) exhibited multiple long-bone fractures, severe osteopenia (femoral neck Z-score = −5.0), and persistent non-union of a right femoral fracture despite three cycles of zoledronic acid, although BMD showed modest improvement. His younger sister (7 years), who was fracture-naïve at presentation, had low BMD (femoral neck Z-score = −2.9) and demonstrated a more pronounced BMD response after a single treatment cycle.

Conclusions: Our findings confirm that the synonymous c.492G>C variant causes OI type XXII through exon 5 skipping and significantly broaden the clinical and therapeutic phenotype spectrum, including variable expressivity and differential responses to bisphosphonate therapy. Early initiation of treatment may improve BMD; however, established non-union appears refractory to zoledronic acid.

Keywords: Osteogenesis imperfecta type XXII; CCDC134; synonymous variant; exon skipping; splicing defect; zoledronic acid; bone mineral density.

Introduction

Osteogenesis imperfecta (OI), often termed brittle bone disease, is a genetic disorder with an incidence of approximately 1 in 15,000 to 20,000 births[1]. Clinically, it is characterized by bone fragility leading to an increased propensity for fractures and deformities[2].

The majority of OI cases, approximately 85-90%, result from autosomal dominant variations in the *COL1A1* and *COL1A2* genes, which encode the abundant type I collagen in bone and skin[3]. An additional 5-10% of cases are inherited through autosomal recessive or X-linked patterns. Furthermore, in 2-5% of cases, the genetic basis remains unidentified, highlighting the genetic heterogeneity of OI[4].

In the most recent literature, *CCDC134*-related OI has emerged as a novel and exceptionally rare genetic subtype, with only six cases documented globally to date [5,6,7,8]. *CCDC134* encodes a secreted protein widely expressed and implicated in the regulation of select mitogen-activated protein kinase (MAPK) signaling cascades [9]. Among the five reported patients who carry the homozygous initiation-codon variant c.2T>C, gracile long bones, multiple fractures ranging from 10 to 50, poor response to bisphosphonate therapy, and short stature were documented [5,6,7]. Functional analyses confirmed complete loss of CCDC134 protein in fibroblasts and osteoblasts, leading to enhanced Erk1/2 phosphorylation and reduced COL1A1 and osteopontin (OPN) expression [5].

Nevertheless, a sixth patient with the synonymous *CCDC134* variant c.492G>C (p.Leu164Leu) exhibited only a single non-union fracture [8], indicating that distinct variant sites can produce divergent clinical phenotypes.

In this study, we report a three-generation Chinese family with two siblings affected by osteogenesis imperfecta type XXII due to a homozygous synonymous variant in *CCDC134* (c.492G>C; p.Leu164Leu). We describe their clinical, radiological, biochemical, and genetic features, and outcomes following bisphosphonate therapy.

Methods

Evaluation of the families with osteogenesis imperfecta

The proband was an 11-year-old Chinese boy who presented to the Department of Pediatric Endocrinology and Inherited Metabolic Disorders due to recurrent fractures. The proband, his sister, both parents, and all four grandparents participated in this study.

Clinical data and serum biochemical parameters were analyzed retrospectively. Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry (DXA), with regions of interest including the lumbar spine (L1–L4), femoral neck, and total hip. BMD Z-scores adjusted for age, sex, and ethnicity were calculated using normative reference data [10]. Radiographic examinations of the oral cavity, spine and limbs were conducted for both the proband and his sister.

Genomic DNA analysis

Following the acquisition of informed consent from the proband's parents, genomic DNA was extracted from peripheral blood samples of the proband and both parents. Trio-based whole-exome sequencing (WES) was performed to identify the underlying genetic etiology. The

average sequencing depth of the target region was ≥150×, with >99.5% of target bases covered at a depth of at least 20×. The candidate pathogenic variant identified by WES was confirmed by Sanger sequencing in the proband, his parents, and other available family members. The pathogenicity of the novel variant was assessed using in silico prediction tools, including MutationTaster, FATHMM, NetGene2, and RNA Splicer.

RNA transcript analysis by reverse transcription PCR (RT-PCR)

Total RNA was extracted from peripheral blood samples preserved in lysis buffer using a magnetic bead-based method. The quality and concentration of the total RNA were assessed by measuring absorption values at 260 and 280 nm. By using AccurSTART One Step RT-PCR Kit (Vazyme), total RNA was reversely transcribed to cDNA which was then amplified by using specific primers, the sequence of the primers was as follows: Forward: 5'-CTTCAATTCCTGGCCTTCCT-3', Reverse: 5'-TTCTGGAAAGGGTCAGTGCT-3'. The PCR products were separated by agarose gel electrophoresis and sequenced by the Sanger method.

Treatment and Follow-up

Following confirmation of the genetic diagnosis in our department, the proband received intravenous zoledronic acid every six months, along with daily supplementation of calcium (1,000 mg/day) and vitamin D (1,000 IU/day). The proband's sister has not experienced any fractures to date. However, given her femoral neck bone mineral density (BMD) Z-score of –2.9, she is at elevated risk for future fragility fractures. Consequently, she was initiated on intravenous zoledronic acid every six months, combined with daily calcium (1,000 mg/day) and vitamin D (400 IU/day) supplementation. Clinical follow-up is scheduled every six months, with measurements including height, weight, bone metabolic markers, skeletal X-rays, and bone mineral density conducted at appropriate intervals.

Results

Subjects and clinical presentation

The proband, of Han Chinese descent, presented to our clinic with a primary complaint of recurrent fractures. His younger sister, who had not experienced any fractures at the time of evaluation, was also enrolled in the study owing to low bone mineral density (BMD). Both siblings, together with their parents and all four grandparents, participated in the study(Fig. 1A).

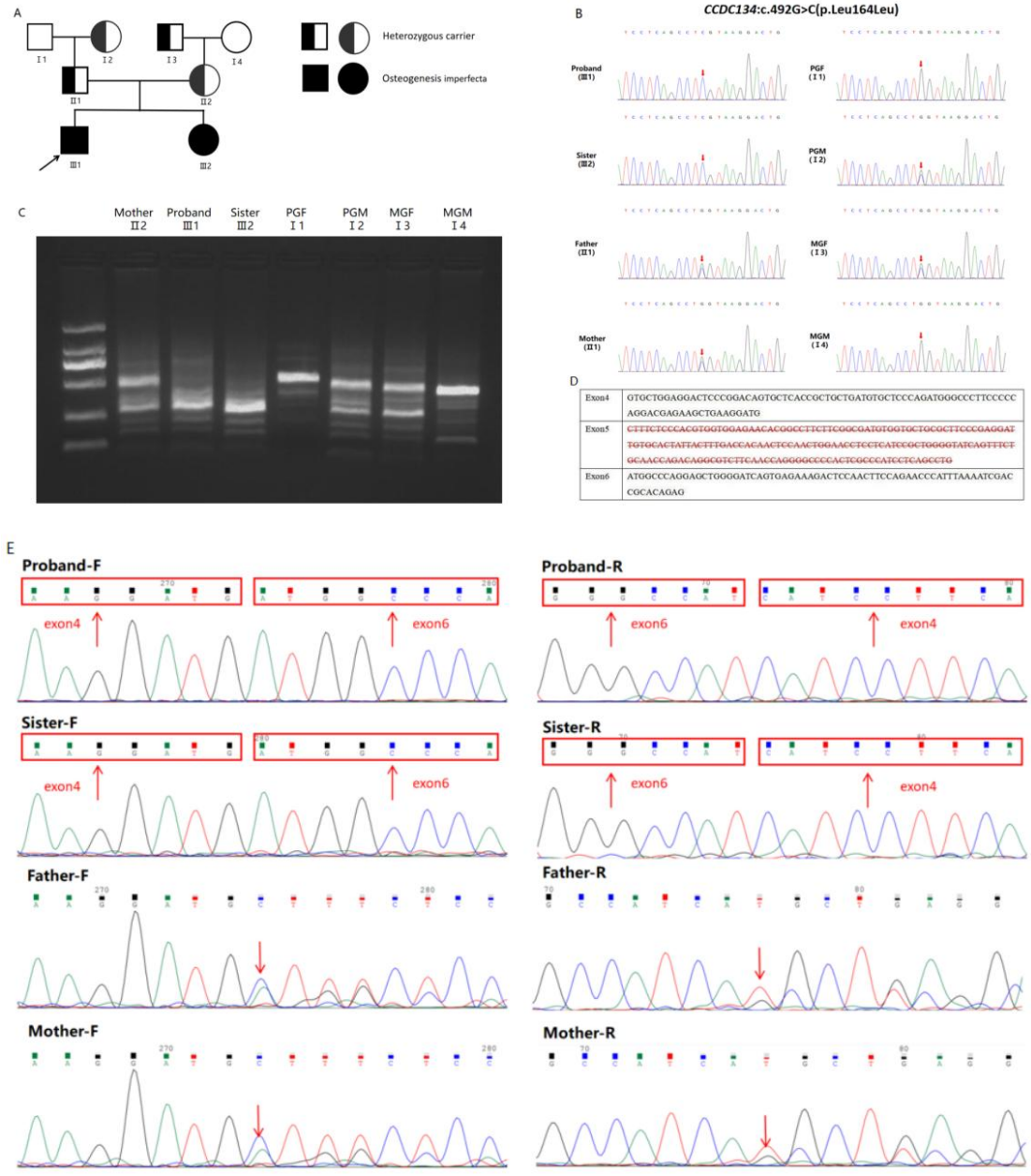


Figure 1. (A) Pedigree of the family showing autosomal recessive inheritance. (B) Sanger sequencing of genomic DNA confirmed that the proband (III:1) and her sister (III:2) were homozygous for the CCDC134 c.492G>C variant, the parents (II:1, II:2), PGM (I:2), and MGF (I:3) were heterozygous, and PGF (I:1) and MGM (I:4) were homozygous for the wild-type allele. (C) Gel image showing RT-PCR products of *CCDC134* cDNA fragments. (D, E) Sanger sequencing of *CCDC134* cDNA confirmed the absence of exon 5 in the transcripts of the proband and her sister, and co-expression of wild-type and exon 5–skipped isoforms in the parents.

The proband is an 11-year-old boy, the firstborn child of consanguineous parents (four th cousins). No other family members reported skeletal abnormalities. Intrauterine growth restriction was noted during the third trimester. He was delivered at term (40 weeks' gestation) via cesarean section, with a birth weight of 2,250 g (−3.11 SD) and birth length of 45 cm (−2.75 SD).

At 7 years and 4 months of age, he sustained a right femoral fracture following a m inor fall and underwent open reduction with elastic intramedullary nailing. Subsequent non union with progressive femoral bowing necessitated a second surgery—open reduction and plate fixation—with restoration of bony continuity. One year later, a refracture occurred dis tal to the plate screws, prompting plate removal and conversion to external fixation. Altho ugh bony continuity was maintained, the femoral shaft remained markedly slender, leading to a fourth procedure: transverse diaphyseal osteotomy with segmental overlap to stimulat e callus formation and promote diaphyseal thickening. Despite this intervention, the right f emoral shaft remained extremely slender, prompting referral to our center. A left femoral f racture at 9 years and 9 months healed with union.

At 11 years and 4 months of age, physical examination revealed a weight of 35 kg (−0.69 SD) and height of 127 cm (−3.06 SD), with no facial dysmorphism and white scle rae. Audiological testing demonstrated bilateral low-frequency conductive hearing loss. Dent al radiographs, echocardiography, and renal ultrasonography were unremarkable. Skeletal su rvey revealed bilaterally thin ribs with downward bowing originating from the costal angle s, pelvic obliquity, gracile long bones, and a healed right femoral fracture (Fig. 2 a–b). D ual-energy X-ray absorptiometry (DXA) demonstrated low bone mineral density (BMD) at the lumbar spine (Z-score −2.3), femoral neck (Z-score −5.0), and total hip (Z-score −3.1) (Table 1).

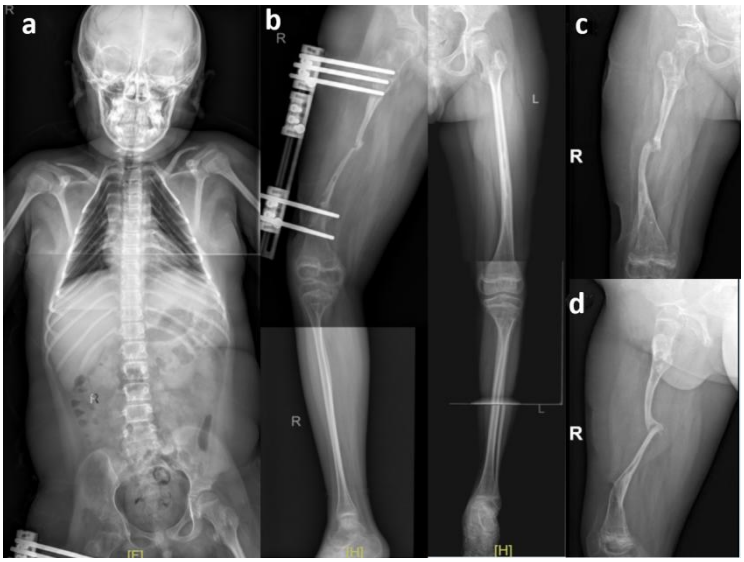


Fig.2 a-b Skeletal radiographs of the proband. c-d X-rays 12months after zoledronic acid treatment.

Table1. Clinical characteristics of the family members

	Proband	Sister	Mother	Father	Reference
Age at first visit (years)	11	7	36	35	
Height (cm)	127	114	162	164.6	
Weight (kg)	35	19	59.6	81.4	
LS BMD Z-score	-2.3	-1.4	2.9	1	

	Proband	Sister	Mother	Father	Reference
FN BMD Z-score	-5.0	-2.9	0.6	0.6	
TH BMD Z-score	-3.1	-1.8	1.3	0.3	
Age of first fracture	7 years	-	-	-	
Blue sclerae	-	-	-	-	
Dentinogenesis imperfecta	-	-	-	-	
Joint Hyperlaxity	-	-	-	-	
Ca (mmol/L)	2.51	2.68	-	-	2.1-2.80
P (mmol/L)	1.61	1.6	-	-	1.25-1.93
25OHD (nmol/L)	79.4	58.2	-	-	50-250
ALP(U/L)	166	205.1	-	-	143-406
PTH (pmol/L)	7.8	2.2	-	-	1.3-6.8
β-CTX (ng/ml)	0.739	0.588	-	-	0.7-1.9
P1NP(ng/ml)	357	576	-	-	300-950
BGP(ng/ml)	25.78	30.1	-	-	-

His sister also had evidence of intrauterine growth restriction and was delivered at term (40 weeks' gestation) by cesarean section, with a birth weight of 2,350 g (−2.47 SD) and birth length of 47 cm (−1.51 SD). She has not sustained any fractures to date. Physical examination at age 7 years revealed a weight of 19.0 kg (−1.43 SD), height of 114 cm (−1.92 SD), absence of facial dysmorphism, and white sclerae. Radiographic skeletal findings were similar to those of her older brother but less severe (Fig. 3A–D). Dual-energy X-ray absorptiometry (DXA) demonstrated low bone mineral density (BMD) at the lumbar spine (LS; Z-score −1.4), femoral neck (FN; Z-score −2.9), and total hip (TH; Z-score −1.8) (Table 1).

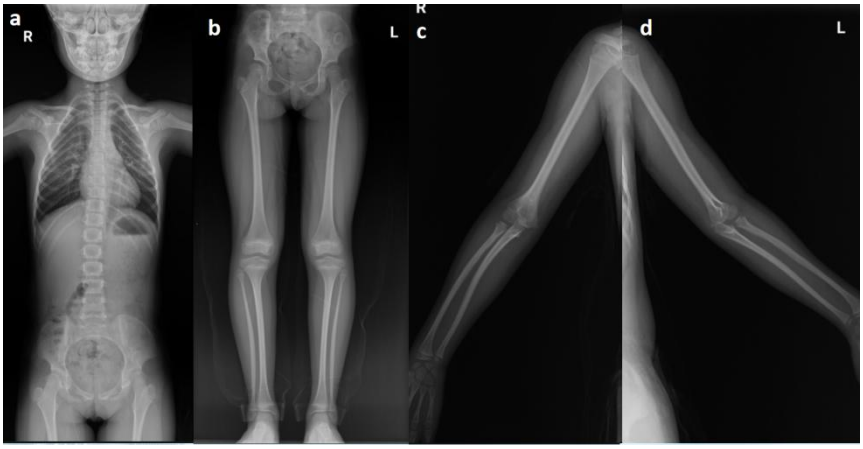


Fig.3 a-d Skeletal radiographs of the proband's sister

Genetic analysis

To delineate the genetic etiology of the observed phenotype, trio-based whole-exome sequencing (trio-WES) was performed in the proband-parent trio. A homozygous c.492G>C (p.Leu164Leu) variant in *CCDC134* was identified in the proband, with both parents confirmed as heterozygous carriers. This variant has an East Asian population frequency of 0.000653 (gnomAD). The bioinformatics software RNA Splicer predicted that this variant might affect splicing. Sanger sequencing revealed that the proband's sister was homozygous for the variant, and the parents and grandparents were heterozygous (Fig. 1B).

RT-PCR and cDNA Sanger sequencing demonstrated that the synonymous *CCDC134* variant

c.492G>C (p.Leu164Leu) disrupts normal splicing, resulting in complete skipping of exon 5. The proband and her sister, who are homozygous for the variant, exhibited only the exon 4–6 junction in their cDNA, whereas both heterozygous parents showed overlapping peaks at the splice site, consistent with co-expression of wild-type and exon 5-skipped transcripts (Fig. 1C-E).

Follow-up

After three courses of zoledronic acid treatment, the proband's BMD Z-score changed from -2.3 in LS to -1.0, from -5.0 in FN to -2.7, and from -3.1 in TP to -2.7 (Table 2). However, the right femoral fracture showed persistent non-union with progressive deformity.(Fig. 2 c-d)

After one course of treatment with zoledronic acid, the sister's BMD Z-score changed from -1.4 in LS to -0.0, FN from -2.9 to -1.3, and TP from -1.8 to 0.1, and height from 114(-1.92SD) to 116.6 (-1.84SD) (Table 2).

Table 2. BMD and Height Changes in Proband and Sister

		Pre-treatment	6-months	12-months	18-months
Proband	Height(cm)	127	130	133	135.5
	LS($g/cm^{2)}$	0.467	0.543	0.592	0.643
	Z-score	-2.3	-1.6	-1.3	-1.0
	FN($g/cm^{2)}$	0.300	0.347	0.406	0.536
	Z-score	-5.0	-4.5	-3.9	-2.7
	TP($g/cm^{2)}$	0.506	0.540	0.615	0.575
	Z-score	-3.1	-2.9	-2.2	-2.7
Sister	Height(cm)	114	116.6		
	LS($g/cm^{2)}$	0.452	0.551		
	Z-score	-1.4	0.0		
	FN($g/cm^{2)}$	0.390	0.505		
	Z-score	-2.9	-1.3		
	TP($g/cm^{2)}$	0.475	0.626		
	Z-score	-1.8	0.1		

Discussion

Osteogenesis imperfecta type XXII (OI22; OMIM #619795), caused by pathogenic variants in *CCDC134*, represents an exceedingly rare genetic subtype. To date, only six cases have been documented worldwide: five harbour the missense variant c.2T>C (p.Met1Thr), and one carries the synonymous change c.492G>C (p.Leu164Leu)[5,6,7,8].

According to previous reports, individuals harboring the homozygous *CCDC134* c.2T>C variant exhibit intrauterine growth restriction, gracile and bowed long bones, multiple fractures (between 10 and 50), pseudarthroses, short stature, and a poor response to bisphosphonate treatment[5,6,7]. In contrast, the single reported patient with the homozygous c.492G>C variant sustained only one fracture, which occurred after a fall at age 6 years and progressed to nonunion [8].

The proband in this study also harbors the homozygous *CCDC134* c.492G>C variant. Notably, a left femoral fracture sustained at 9 years and 9 months healed with radiographic union, indicating that bone repair remains feasible in this genotype under favorable conditions. In contrast, the right femur fractured first at 7 years and 4 months and was initially managed with

elastic intramedullary nailing, but nonunion with progressive bowing developed. An outside institution subsequently performed plate fixation, which achieved temporary union, however, refracture occurred at the distal screw sites, necessitating additional surgical interventions. In the absence of bisphosphonate therapy and adequate rehabilitation, repeated fracture events and surgical trauma ultimately led to marked cortical thinning and severe atrophy of the right femur. Operative management in osteogenesis imperfecta differs from standard pediatric fracture care: plates and screws should be avoided as they predictably fail and predispose to recurrent fractures at the plate ends [11]. Currently, telescoping intramedullary Fassier-Duval rods represent the optimal implant—they are minimally invasive, accommodate growth-related elongation, reduce revision rates, and yield the best documented functional outcomes to date [12].

Bisphosphonates, which act by inhibiting osteoclast activity and bone resorption, are the mainstay of pharmacologic treatment in pediatric patients with OI[13]. Bisphosphonates have been shown to consistently improve bone mineral density in patients with OI and, to some extent, reduce fracture incidence[14,15]. Consensus on the optimal therapeutic window for bisphosphonates has not been reached[16]. Generally, in childhood osteoporosis, the presence of either vertebral fractures (VF), independent of LS BMD z-score, or at least two low-trauma long-bone fractures by age 10 years or at least three by age 18 years, together with LS BMD z-score ≤ -2, especially in cases with heritable forms, may be considered indications for therapy[17]. In view of the poor prognosis after the proband's first fracture and the high fracture risk in the proband's younger sister (femoral neck z-score −2.9), zoledronic acid was administered. It is of particular interest that, compared with the proband's modest bone mineral density gain after three treatment cycles, the sister achieved a significant increase after only one cycle, along with improved height, indicating that early diagnosis and treatment in *CCDC134*-related OI may improve prognosis. Studies have shown that early bisphosphonate therapy may prevent scoliosis and basilar impression[18,19].

Functional studies reveal that *CCDC134* deficiency releases its inhibitory constraint on the ERK-MAPK cascade, increasing ERK phosphorylation and down-regulating COL1A1 expression and mineralization in patient-derived osteoblasts[5]. A comparable biochemical signature has been documented in the skeletal tissue of NF1 patients, where neurofibromin loss drives constitutive Ras/MAPK signaling and impaired fracture repair[20]. In murine models of neurofibromatosis type 1, selective MEK blockade rescued osteoblast differentiation and improved tibial fracture healing[21]. These observations suggest that MEK inhibition might be explored as a potential therapeutic strategy for *CCDC134*-associated osteogenesis imperfecta, pending further investigation.

Conclusion

We confirm that the synonymous CCDC134 variant c.492G>C causes osteogenesis imperfecta type XXII by inducing complete skipping of exon 5. Our report of two affected siblings expands the clinical features of this condition to include individuals with low bone mineral density but no fractures at diagnosis, and shows that disease severity can vary even among family members with the same genotype. Both patients showed improved bone mineral density after zoledronic acid treatment, but the proband's established femoral non-union did not heal despite therapy. This

suggests that although bisphosphonates can increase bone mineral density in CCDC134-related OI, such treatment may not result in the healing of established non-unions.

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Availability of data and materials: The data that supports the findings of this study are available on request from the corresponding author.
Ethics approval and consent to participate: This study was reviewed and approved by the Ethics Committee of Guangdong Women and Children's Hospital (Approval No. 20251094). Strict measures were taken to protect the patient's privacy. Any potentially identifiable images or data were anonymized, and written informed consent was obtained from the patient's legal guardian. All procedures were performed in accordance with the principles of the Declaration of Helsinki.
Competing interests: The authors declare that they have no competing interests.

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