A *De novo* Mutation in the *COL1A1* Gene Leading to Severe Osteogenesis Imperfecta: Case Report and Review of the Literature

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Abstract

Introduction Osteogenesis imperfecta (OI) is the most common monogenic inherited skeletal dysplasia disorder. Mutations in the *COL1A1*/*COL1A2* gene cause ~85 to 90% of OI. Studies of cases have demonstrated that missense mutations are the primary cause of OI, with poor prognosis.

Case Description We report the case of a fetus with skeletal abnormalities and subcutaneous edema. Ultrasound imaging revealed suspected skeletal malformations, including hypoplastic long bones of all four limbs, poorly ossified calvarium, unrevealing nasal bones, and generalized subcutaneous edema. Whole-exome sequencing revealed a heterozygous mutation in *COL1A1* (c.2174G > T/p.(G725V), NM_000088.3). According to the American College of Medical Genetics and Genomics guidelines, it was determined to be a pathogenic variant and identified as a de novo variant (PS2 + PP3_strong + PM2_supporting), which has not been reported in the HGMD, gnomAD, ClinVar, or other databases. This variation causes a glycine-to-valine substitution at position 725, located within the Gly-Xaa-Yaa repeat in the helical domain of the collagen molecule.

Conclusion The *COL1A1* mutation (c.2174G > T/p.(G725V), NM_000088.3) is a novel pathogenic variant of severe OI. Our study expanded the OI *COL1A1* gene variation profiles in the Chinese population and provided a theoretical foundation for prenatal diagnosis, genetic counseling, and obstetric management.

Keywords
- osteogenesis imperfecta
- *COL1A1* gene
- whole-exome sequencing
- prenatal diagnosis

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As one of the most common congenital disorders, fetal skeletal dysplasia is characterized by genetic and phenotypic heterogeneity, making it difficult to differentiate between these diseases on ultrasound.[1] Osteogenesis imperfecta (OI) is the most prevalent monogenic inherited skeletal dysplasia disease. It is predominantly autosomal dominant, but a few autosomal recessive cases have been reported, and it is rarely attributed to X-linked inheritance.[2] The incidence of OI ranges from ~1:15,000 to 1:20,000 births.[3] The main clinical manifestations of OI include short stature, skeletal anomalies, increased skeletal fragility, multiple fractures, other skeletal system pathologies, and extraskeletal manifestations such as dentinogenesis imperfecta, malocclusion, pulmonary dysfunction, and hearing impairment.[4] In 1979, Sillence et al initially categorized OI into four types, I to IV, based on patients' phenotypic characteristics and severity. In 2019, the Chinese guidelines for rare disease diagnosis and treatment further classified it into five types, I to V. Among them, type II OI is fatal, and the phenotype is the most serious, with patients usually succumbing in the perinatal period, and there is no efficacious treatment for live births.[5,6] For fetuses with potential OI suggested by ultrasound, genetic testing to ascertain the etiology and prenatal intervention are optimal prevention and management strategies, respectively. In this study, we conducted whole-exome sequencing (WES) of the fetus, referring to prenatal ultrasound suggestive of OI, with normal copy number variation sequencing (CNV-seq) and classic karyotype. To validate the disease-associated candidate variant sites detected by WES, Sanger sequencing was used to elucidate the fetal genetic etiology and provide a basis for prenatal intervention, genetic counseling, and risk assessment of fertility in the family. Following the CARE reporting checklist, we present the following case.

Case Presentation

A 24-year-old Chinese Han primigravida was found to carry a fetus with suspected skeletal dysplasia, which prompted our attention. No abnormalities were observed in the first trimester, and the couple did not have a history of radiation substance exposure or medication use, as claimed by the couple of primigravida. Additionally, the couple was previously healthy and did not have a family history of skeletal dysplasia or consanguineous marriage. During the routine checkup in the second trimester, other prenatal examinations did not reveal any abnormalities. However, ultrasound imaging at 18 weeks of gestation revealed suspected skeletal malformations, including hypoplastic long bones of all four limbs, poorly ossified calvarium, unrevealing nasal bones, and generalized subcutaneous edema (►**Fig. 1**). Details of the suspected fetuses are shown in ►**Table 1**. Subsequently, diagnostic screening was conducted by collecting amniotic fluid from fetal parents and peripheral blood samples.

After obtaining consent from the couple, we received a 20-mL sample of amniotic fluid via amniocentesis at 18 weeks of gestation. The amniotic fluid sample obtained was aliquoted into two tubes. One tube was utilized for chromosome karyotype analysis, and the other tube (QIAamp DNA Blood Mini Kit produced by German company Qiagen) was used to extract genomic DNA for CNV-seq and Trio-WES; 2-mL samples of each spouse's peripheral blood were collected to extract genomic DNA (Magnetic Blood Genomic DNA Kit from Tiangen Biochemical Technology Company) for Trio-WES.

Karyotype analysis revealed no abnormalities in the chromosome number or structure (►**Fig. 2A**). CNV-seq analysis did not reveal any chromosome aneuploidy or CNVs in the genome, with definite pathogenicity of more than 100 kb (►**Fig. 2B**). We identified a heterozygous mutation of *COL1A1* (c.2174G > T/*p*.(G725V), NM_000088.3), which were not present in either parent. Sanger sequencing corroborated the sequencing results for the whole exon group (►**Fig. 2**), and this variation was confirmed to be a de novo variation through sequencing of the parental samples.

The mutation was deemed pathogenic based on multiple in silico predictions of variant pathogenicity (►**Table 2**), with a Rare Exome Variant Ensemble Learner (REVEL) software prediction score of 0.997. This variation was absent from the ESP6500, ExAC, and 1000 Genome databases. Following the American College of Medical Genetics and Genomics (ACMG) guidelines, the variation was pathogenic (PS2 + PP3_strong + PM2_supporting). This mutation was not present in HGMD, gnomAD, ClinVar, or other databases, indicating that it was a novel mutation site.

Collagen type 1 (Col1) is the principal connective tissue that forms the body's skeleton, sclere, skin, and teeth. Collagen type 1 is a protein composed of α 1 and α 2 chains. We used Uniport (https://www.uniprot.org/) to process protein conservation analysis at the mutation site 725, and the results showed that it is a conservation site for various species (►**Fig. 2D**).

Discussion

OI is a congenital skeletal dysplasia with a genetic classification of 22 types (OI types I–XXII) (https://omim.org). However, there is considerable overlap in the clinical phenotypes of these different types. As of November 11, 2022, the OI and Ehlers–Danlos' syndrome variant databases have included 20 genes associated with OI. Studies have demonstrated that pathogenic mutations cause ~85 to 90% of OI in the type I collagen ligand α1 subunit/α2 subunit (*COL1A1*/*COL1A2*). Despite the identification of thousands of pathogenic mutation types, a precise genotype–phenotype correlation has yet to be established.[7]

In clinical practice, OI is classified into four types (I–IV) based on the clinical phenotype and severity. Type I OI is characterized by the mildest clinical phenotype, typically without skeletal malformations. The clinical phenotype of type II OI is the most grievous, with the most affected individuals dying in the perinatal period due to severe bone deformities. Some severe cases also present with fetal edema.[8] Type III OI is severe, presenting with progressive skeletal malformation and high-frequency fractures as well as abnormal teeth and hearing loss, and has a poor prognosis. Type IV OI is of moderate severity, between types I and III.[5,6]

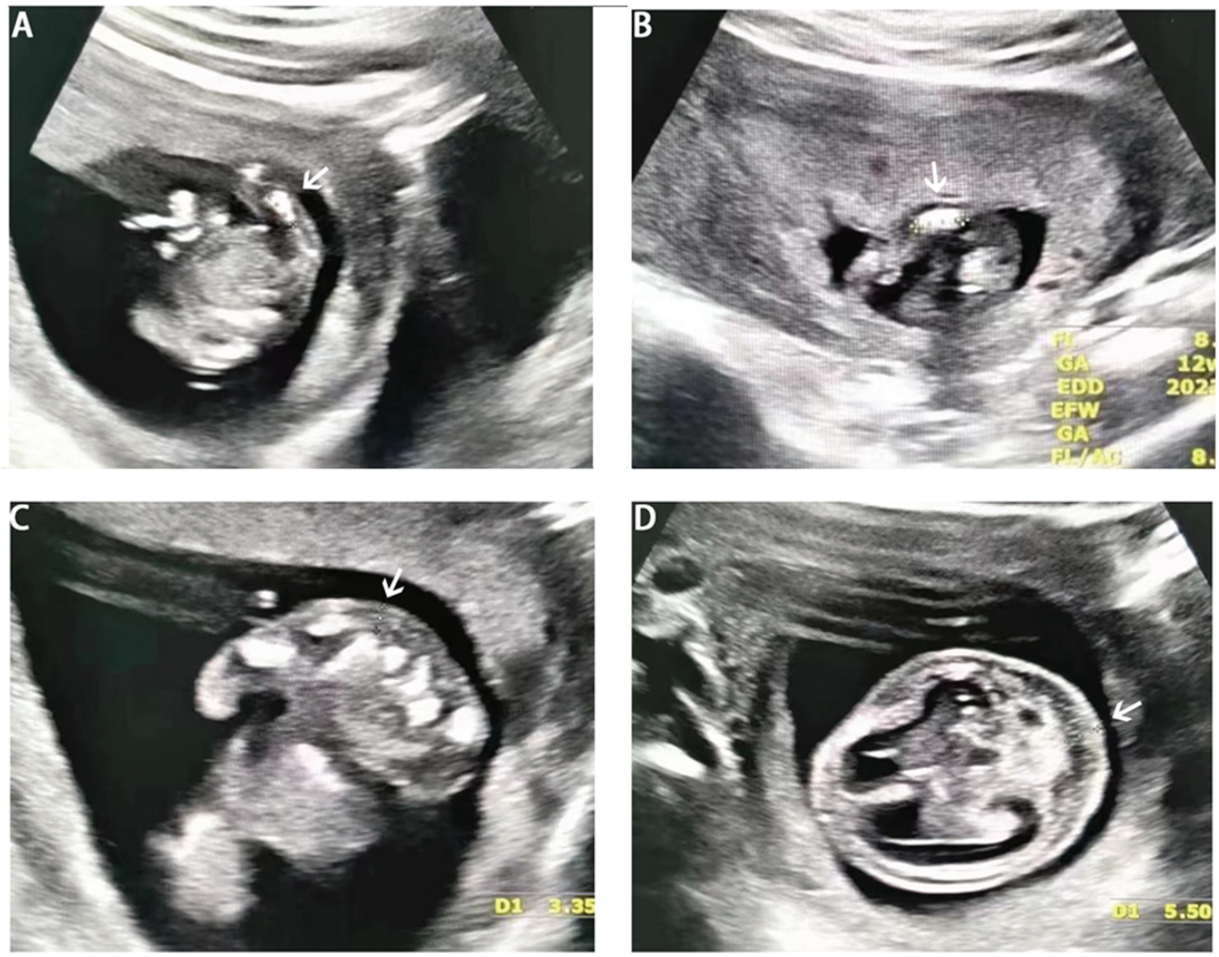

Fig. 1 Ultrasound images of cases. (A) Humeral length: 7 mm. (B) Femur length: 8 mm. (C) The abdomen was ~3.5 mm thick. (D) The scalp was ~5.5 mm thick.

Table 1 Ultrasonographic measurements of suspected fetal skeletal dysplasia

Ultrasonographic measurements	Measured value (mm)	Normal range in 18 weeks' gestation (mm)
Biparietal diameter	42	34–45
Head circumference	59	128–161
Transverse diameter of the cerebellum	16	15.9–20.5
Abdominal circumference	108	110–141
Femoral length	8	21–29
Humeral length	7	22.3–30.1
Fetal weight	118 (g)	184–269 (g)
Fetal skin thickness	Scalp thickness: 5.5 Abdominal skin thickness: 3.5	–
Other	The nasal bone of the fetus was not shown, the lip structure was not clearly displayed, the ossification of the skull ring was not obvious, the cerebellum was visible, the midline of the brain was in the middle, and the width of bilateral ventricles was ~4 mm	–

The *COL1A1* is located at 17q21.33, with a total length of 18 kb and 51 exons. Code-shifting, nonsense, and splicing mutations of *COL1A1* primarily lead to premature termination codons, producing hazardous and degradable truncated gene expression products. OI caused by such mutations typically presents mild clinical manifestations. Missense

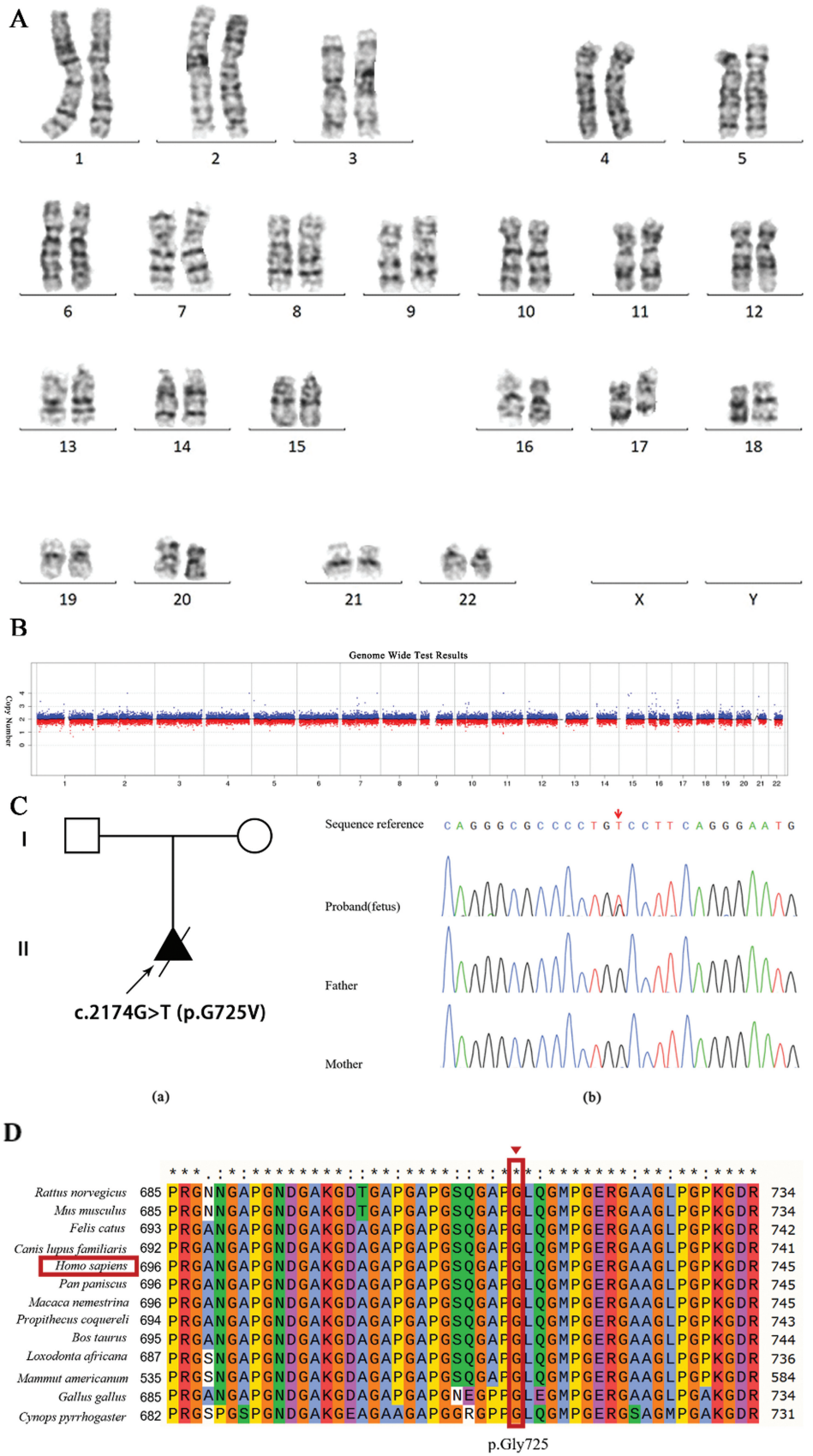

Fig. 2 (A) Karyotype analysis results of cases. (B) CNV-seq results of fetal. (C) (a) Pedigree information in this family. (b) Sanger validation peak plots for the proband (fetus) and family members. The fetal *COL1A1* gene has c.2174G > T / *p*.(G725V) heterozygous variation, which parents do not carry. (D) Protein conservation analysis in the mutation site 725 showed that it is a conservation site for various species (https://www.uniprot.org/). CNV-seq, copy number variation sequencing.

Table 2 Effects of *COL1A1* mutations predicted with in silico tools

Protein prediction algorithm	Score	Interpretation
Scale-Invariant Feature Transform (SIFT)	0	Damaging
Polymorphism Phenotyping Version 2_HDIV (Polyphen2 HDIV)	1	Probably damaging
Polymorphism Phenotyping Version 2_HVAR (Polyphen2 HVAR)	0.999	Probably damaging
Mutation Taster	1	Disease-causing
Protein Variation Effect Analyzer (PROVEAN)	−7.53	Damaging
Rare Exome Variant Ensemble Learner (REVEL)	0.997	Damaging
Combined Annotation-Dependent Deletion (CADD)	34	Damaging
phyloP	7.867	Conserved
phastCons	1	Conserved
SiPhy	18.429	Conserved

mutations in *COL1A1* are associated with the production of proteins with abnormal structures. The mutant subunits participate in and disrupt the triple helix assembly of type I collagen, exacerbating the dominant-negative effect. These mutations typically result in severe phenotypes.[9] Studies in China, Italy, Poland, and other countries have demonstrated that missense mutations are the primary cause of OI with poor prognosis, the majority of which involve the substitution of glycine in the Gly-X-Y (X and Y are random amino acids) repeat sequences of the collagen molecular helix domain with other amino acids.[10–13] The substitution of glycine with branched nonpolar or charged amino acids likely results in a more severe form of OI.[14] Studies conducted in other contexts have corroborated that de novo mutations, which have not been subjected to purifying selection, are associated with a more severe clinical presentation of OI than inherited *COL1A1* mutations.[15,16]

This was the first pregnancy for couples who were not blood-related. No significant skeletal dysplasia or similar clinical manifestations were observed in the family history. Obstetric ultrasonography revealed severe limb shortening, poor skull ossification, absence of nasal bones, and generalized subcutaneous edema. According to research findings, fetuses afflicted with lethal skeletal dysplasia display considerable and premature reduction in the length of their long bones as well as disproportionate growth of the fetal abdomen and cranium. Notably, the ratio of femoral length to abdominal circumference serves as a reliable indicator of skeletal dysplasia lethality. Specifically, 92 to 96% of cases showed a ratio of femoral length to abdominal circumference below 0.16, which is a sign of fatal skeletal dysplasia.[17] The available sonographic parameters indicate the presence of a hypoplastic fetal skeletal system, which is indicative of severe OI. Studies have demonstrated that when a pregnant woman and her spouse have no apparent skeletal system malformations, prenatal ultrasound imaging reveals abnormalities of the fetal skeletal system in conjunction with other system malformations, which are likely caused by chromosomal abnormalities or CNVs. When fetal malformations are mainly observed in the skeletal system, they are usually monogenic in origin.[18] In this study, karyotyping and CNV-seq did not reveal any abnormalities, suggesting that non-chromosomal numerical, structural, and CNVs were associated with skeletal malformations and other ultrasonic manifestations. Trio-WES revealed that the fetus in this case carried the heterozygous c.2174G > T/p.(G725V) variant, which is categorized as a pathogenic variant based on ACMG guidelines. Neither of the parents had this mutation site, which was not present in the database or reported in the literature. Among the candidate genes, the missense variant in *COL1A1* appeared to be the most frequently observed pathogenic variant associated with OI. Therefore, the identified mutation appears to have arisen spontaneously during the early stages of human embryonic development. Based on this and the ultrasound-specific clinical presentation, the fetus was initially diagnosed with perinatal lethal OI. The fetal *COL1A1* gene had a c.2174G > T/p.(G725V) variation, causing a glycine-to-valine substitution at position 725, which is located within the Gly-Xaa-Yaa repeat in the helical domain of the collagen molecule and is a branched nonpolar amino acid, which might be the most responsible for the more severe fetal clinical phenotype. We have summarized the mutated genes of severe fetal OI caused by missense mutations in *COL1A1* and their associated clinical ultrasonic manifestations reported in the literature (►**Table 3**). Ultrasound images exhibit high similarity, primarily displaying a shortened humerus, shortened femur, thoracic stenosis, and a poorly ossified calvarium. This finding was consistent with the ultrasound findings reported in the present study. Consequently, in the absence of a prenatal genetic diagnosis, ultrasound during pregnancy suggests that the aforementioned fetal manifestations could be utilized as the initial diagnostic basis. The patient chose to terminate their pregnancy after genetic confirmation. Regrettably, owing to the lack of aborted tissue, we were unable to definitively ascertain whether it was a perinatal lethal OI.

OI is one of the primary causes of skeletal dysplasia in fetuses for which no adequate therapy exists. Currently, nonlethal patients are managed symptomatically, primarily through lifestyle modification, medications, surgery, and

Table 3 Gene and clinical manifestation of fetal severe OI caused by multiple missense mutations *COL1A1*

References	Gene nucleotide change	Pathogenicity level (evidence)	Fetal gestational age	Radiographic finding	Extraskeletal manifestations in ultrasound examination	Fetal sample for WES
Ji et al[21]	Case 1: c.1634G > A (p.Gly545Asp)	–	Case 1: 17 wk	Case 1: The fetus is characterized by short humeri (10 mm) and short femora (10 mm). Skull ossification is poor with borderline personality disorder (41 mm) and circumference (150 mm)	Case 1: A narrow chest and notch can be seen in the junction of the chest and abdomen, and the maximal pocket of amniotic fluid was 36 mm	Case 1: Amniotic fluid
Tanner et al[22]	Case 1: c.3290G > T (p.Gly1097Val)	–	Case 1: $21^{4/7}$ wk	Case 1: Extremely short limbs corresponding roughly to the gestational age of 12 wk. The thorax was so small; computed tomography showed the fetus was abnormally short and poorly ossified long bones and absent ossification of the skull were evident. The fetus was aborted at 22 wk	–	Case 1: Tissue after fetal abortion
Huang et al[23]	Case 1: c.1822G > A (p.Gly608Ser)	–	Case 1: 20 wk	Case 1: Short and incurved limbs, a small thorax, bowing long bones, and a reduced echogenic ring around the intracranial structures: Fetus was aborted at 17 wk	–	Case 1: Tissue after fetal abortion
Zhang et al[24]	Case 1: c.994G > A (p.Gly332Arg) Case 2: c.2362G > A (p.Gly788Ser) Case 3: c.2444G > C (p.Gly815Ala) Case 4: c.3505G > A (p.Gly1169Ser) Case 5: c.3541G > A (p.Gly1181Ser)	Case 1: P (PS2 + PM1 + PM2 + PP3 + PP4) Case 2: LP (PM1 + PM2 + PP3 + PP4) Case 3: LP (PM1 + PM2 + PP3 + PP4) Case 4: LP (PS2 + PM1 + PM2 + PP3 + PP4) Case 5: LP (PS2 + PM1 + PM2 + PP3 + PP4)	Case 1: $24^{6/7}$ wk Case 2: $31^{3/7}$ wk Case 3: $30^{1/7}$ wk Case 4: 26+ wk Case 5: 21+ wk	Case 1: Fetal whole body bone sonographic changes, clinical suspicion of OI Case 2: The fetal femur and humerus were ~4 wk+ less than the corrected gestational age, and no obvious abnormality was found before 31 wk Case 3: The long bones of limbs are less than gestational age, and bilateral femurs are slightly curved Case 4: Fetal femurs are short and slightly curved on both sides Case 5: The long bones of the fetus limbs are less than 4 standard deviations, and the thoracic cavity is narrow; the nasal bone is absent	Case 3: The diameter of the oval is larger, and the left ventricle has strong light spots Case 5: The eye spacing is widened; the scalp edema, the brain parenchyma is poor, the subdural effusion, and the abdominal fluid is effusion	Unknown
Yang et al[25]	Case 1: c.1678G > A (p.Gly560Ser) Case 2: c.2101G > A	Case 1: P (PP2 + PM2 + PM5 strong + PS4 supporting + PS2 + PP3)	Case 1: $23^{4/7}$ wk Case 2: $22^{6/7}$ wk Case 3: 22 wk; $20^{6/7}$	Case 1: The long bones of the fetus' limbs were short and curved. The fetus was aborted at $24^{1/7}$ wk	Case 4: nuchal translucency thickening (6.0 mm), anasarca	Case 1: Umbilical cord Case 2:

Table 3 (*Continued*)

References	Gene nucleotide change	Pathogenicity level (evidence)	Fetal gestational age	Radiographic finding	Extraskeletal manifestations in ultrasound examination	Fetal sample for WES
	(p.Gly701Ser) Case 3: c.3557C > T (p.Pro1186Leu) Case 4: c.2300G > T (p.Gly767Val)	Case 2: P (PP2 + PM2 + PM5 strong + PS2 + PP3) Case 3: VUS (PP2 + PM2 + PM5) Case 4: LP (PP2 + PM2 + PM5 + PP3)	wk (two pregnancies) Case 4: $13^{4/7}$ wk	Case 2: The fetal femur, tibia, and fibula were initially found to be short and curved; fetus was aborted at $23^{5/7}$ wkCase 3: Two affected pregnancies: (1) The right femur was initially found to be "telephone-like" at 22 wk; both femurs were identified as short and curved at 24 wk; fetus was aborted at 25 wk. (2) Both femurs were identified as short and curved at $20^{6/7}$ wk: fetus was aborted at 32 wk. (3) Still pregnant before submission Case 4: Limb long bones short and curved, abnormal ankle joint and foot posture at $13^{4/7}$ wk; fetus was aborted at 17 wk		Umbilical cord Case 3: Amniotic fluid; umbilical cord Case 4: Amniotic fluid; umbilical cord
Zhuang et al[26]	Case 1: c.1777G > A (p.Gly593Ser)	Case 1: PS2_very strong + PM5 + PM2 supporting + PP3	Case 1: 19 wk	Case 1: Short and curved femurs and humerus in the fetus. (Specially, during her first pregnancy, a c.1777G > A mutation in the *COL1AI* gene was detected in the fetus who exhibited skeletal dysplasia; thus, the family chose to terminate her pregnancy.)	–	Case 1: Amniotic fluid
Cao et al[27]	Case 1: c.644G > A (p.Gly215Asp) Case 2: c.2885G > A (p.Gly962Asp) Case 3: c.994G > A (p.Gly332Arg)	Case 1: PVS1 + PM2 + PM5 + PP2 + PP3 Case 2: PS2 + PM2 + PP3 Case 3: PS2 + PM1 + PM2 + PP3 + PP5	Case 1: 22 wk Case 2: $24^{5/7}$ wk Case 3: $20^{6/7}$ wk	Case 1: Mild bilateral femoral bowing Case 2: Bowing of the long bones, poor ossification of the skull and vertebrae, hypertelorism Case 3: Abnormality of calvarial morphology, short long bone, limb undergrowth, bowing of the long bones, fractures of the long bones	Case 1: Light spot in heart of fetus vertebrae, hypertelorism	Case 1: Aborted fetuses and amniotic fluid samples Case 2: Aborted fetuses and amniotic fluid samples Case 3: Aborted fetuses and amniotic fluid samples
Li et al[28]	Case 1: c.644G > A (p.Gly215Asp) Case 2: c.2885G > A (p.Gly962Asp) Case 3: c.994G > A (p.Gly332Arg)	Case 1: PVS1 + PM2 + PM5 + PP2 + PP3 Case 2: PS2 + PM2 + PP3 Case 3: PS2 + PM1 + PM2 + PP3 + PP5	Case 1: 22 wk Case 2: $24^{5/7}$ wk Case 3: $20^{6/7}$ wk	Case 1: Severe short extremities and severe curvature of the lower limbs Case 2: Severe short and curved extremities	Case 1: Facial dysmorphism (tall forehead, beaked nose, low-set ears, and open triangular-shaped mouth)	Case 1: Amniotic fluid Case 2: Amniotic fluid

(*Continued*)

Table 3 (*Continued*)

References	Gene nucleotide change	Pathogenicity level (evidence)	Fetal gestational age	Radiographic finding	Extraskeletal manifestations in ultrasound examination	Fetal sample for WES
Yang et al[29]	Case 1: c.2605G > T (p.Gly869Cvs Case 2: c.1804G > A (p.Gly602Arg)	–	Case 1: 24 wk Case 2: 25 wk	Case 1: Fetal extremities were short for gestational age. The femurs, humeri, and fibulas were bent, and some of which were telephone receiver-shaped Case 2: Fetal nasal bones were not shown. The thorax was narrow and bell-shaped. Fetal limb bones were short for gestational age, and some were abnormally bending. The fetus was aborted at 25 wk	–	Case 1: Umbilical cord blood Case 2: Aborted fetuses and amniotic fluid samples

Abbreviation: OI, Osteogenesis imperfecta.

rehabilitative training.[19,20] Therefore, regular prenatal checkups, especially prenatal ultrasound examinations, are paramount for such diseases. Prompt prenatal diagnosis is necessary for fetuses with a family history or ultrasound findings suggestive of skeletal dysplasia, for early prenatal intervention and prevention of the birth of affected infants.

Conclusion

In conclusion, we present a case of OI in a fetus with skeletal dysplasia and generalized subcutaneous edema. The c.2174G > T/*p.*(G725V) de novo mutation of *COL1A1* in our patient was a novel pathogenic mutation of OI.

Ethics Approval

The samples used in this study were collected with appropriate informed consent and approval from the Ethics Committee of Shandong Provincial Hospital, affiliated with Shandong First Medical University (LCYJ: NO. 2018-003).

Authors' Contribution

Y.L. and Y.T. wrote the original draft of this manuscript. J.L. and Y.W. visualized the study. X.W. contributed to the conceptualization; methodology; project administration, writing, review, and editing.

Patient Consent

Images and information from individual participants were obtained from the individual's free prior informed consent.

Data Availability

All the data involved in this study are available in the manuscript, tables, and figures.

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Conflict of Interest

None declared.

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