Novel COL1A Gene Mutation Leading to Infantile Osteogenesis Imperfecta Type IV: A Case Report

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Abstract

Introduction: Osteogenesis Imperfecta (OI) is a rare genetic disorder characterized by increased bone fragility and recurrent fractures. OI is classified into types I-IV based on clinical features, with the majority of cases attributed to mutations in the COL1A1 and COL1A2 genes encoding type I collagen. Case Presentation: Here we present the

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Conflicts of interest/Competing interests

There is no conflict of interest among all authors.

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Fei Zhao and Chenglin Luo collect the data and review the patients' images. Xiangyan Chen and Qing Wang analyze and interpret the data. Fei Zhao and Chenglin Luo edit the manuscript. Xiangyan Chen and Qing Wang revise the manuscript. Wang Zeng provides the concept and is a participant in the manuscript editing. All authors read and approve the final manuscript.

Fei Zhao and Chenglin Luo should be considered as the first author equally.

Constent statement:

Written informed consent was obtained from the parents(minor patient) prior to study inclusion according to the local ethical regulations.

Abstract:Introduction: Osteogenesis Imperfecta (OI) is a rare genetic disorder characterized by increased bone fragility and recurrent fractures. OI is classified into types I-IV based on clinical features, with the majority of cases attributed to mutations in the COL1A1 and COL1A2 genes encoding type I collagen.**Case Presentation**: Here we present the case of a newborn with OI who exhibited widened fontanelles and short limbs. Genetic testing of the patient and parents was conducted, with validation by Sanger sequencing. At five months, comprehensive imaging studies were performed to observe skeletal development. A novel missense mutation (c.4097T>A) was identified in the COL1A1 gene of the patient; however, neither the mother nor father carried this mutation. At five months, the child exhibited lower height and weight than normal infants, along with shortened limbs. Radiographic examination revealed slender limb bones and reduced bone density. Based on the clinical presentation and genetic testing, a diagnosis of type IV Osteogenesis Imperfecta (OI) was established. **Conclusion:** Overall, in this case we present a new mutation site (c.4097T>A; p.Ile1366Asn) in COL1A1 in a patient with OI. This mutation suggests a potential link to Type IV OI in the Chinese population, and this case contributes to the diversity of COL1A1 pathogenic mutations.**Keywords** Type IV OI; Type I collagen; COL1A1 gene; novel mutation.

Introduction

Osteogenesis Imperfecta (OI) is a hereditary disorder characterized by fragile and deformed bones, recurrent fractures, blue sclera, incomplete tooth development, short stature, and progressive hearing loss. More than 90% of OI cases result from mutations in the genes COL1A1 and COL1A2, which encode Type I collagen, and the inheritance pattern is typically autosomal dominant. The prevalence of OI is extremely low, estimated to be approximately 1 in 15,000-20,000 individuals[1]. In Europe and the United States, the reported birth prevalence ranges from 3-7/100,000[2-3], whereas in Finland, approximately 0.5/10,000 people are affected[4]. OI is categorized into four types based on the severity of clinical manifestations, as follows: Type I (mild), Type II (lethal), Type III (severe deformities), and Type IV (moderate deformities), with Type I being the most common[5-6]. Statistical data on the prevalence of OI in the Chinese population are currently lacking. However, according to Li et al.[7], among 668 patients with OI from 378 Chinese families, Type I accounted for 39%, and Type IV accounted for 35% of cases. Here we present the case of a newborn diagnosed with OI ultimately confirmed as Type IV, and detail the diagnostic and therapeutic processes based on genetic testing and clinical observations.

Case History and Examination

The patient was a female infant with the chief complaint of premature rupture of the membranes at 26 h, born after 37 min of labor, with a birth weight of 2500 g. Physical examination revealed a head circumference of 32 cm, noticeable widening of the anterior fontanelle, and a sagittal suture with a maximum width of 4.5 cm. Other findings included white sclera, multiple missing teeth in both the upper and lower jaws, outward expansion of the bilateral rib cage, no apparent spinal deformities, short limbs, and wrinkled skin on the palms and soles. Based on the patient's clinical presentation of the newborn, OI was suspected. Targeted high-throughput sequencing was employed to conduct genetic testing on the patient and her parents, identifying a heterozygous, potentially pathogenic variant of the COL1A1 gene, specifically c.4097T>A (p.Ile1366Asn), which correlated strongly with the patient's clinical phenotype (Table 1). The mutation site was verified by Sanger sequencing, while First-generation Sanger sequencing indicated that the parents did not carry the COL1A1 c.4097T>A mutation (Figure 1) . Upon a follow-up visit at 5 months of age, the patient exhibited slower growth than normal infants. Her weight was 3000 g, height was 60 cm, and the sagittal suture of the skull was approximately 4cm wide with a grayish-white sclera. The spine showed no signs of lateral deformity and the limbs were relatively short. Radiographic examination revealed thinning of the bilateral humerus, radius, femur, and tibia-fibula bones; slight curvature of the radius and ulna; and underdeveloped and shallow hips on both sides (Figure2) .

Methods

Differential diagnosis OI needs to be differentiated from Osteopetrosis and Osteoporosis[8-9]. Osteopetrosis: Osteopetrosis is a rare metabolic bone disease characterized by widespread calcification of the entire skeletal system and thickening of bone cortices. Osteoporosis: Osteoporosis is a common metabolic bone disease characterized by decreased bone mass and microstructural damage to bone tissue, leading to bone fragility and susceptibility to fractures. X-rays of osteoporosis patients may show reduced bone mass and blurred trabeculae, which resemble the X-ray features of osteogenesis imperfecta. However, osteoporosis patients typically have a negative family history.

3.2 Investigations and treatment

Currently, there is no cure for osteogenesis imperfecta, but a series of treatments can be employed to alleviate symptoms and improve the quality of life. Treatment modalities include pharmacotherapy, physical therapy, and surgical intervention[10]. Pharmacotherapy involves the use of calcium supplements, vitamin D, and other nutritional supplements to increase bone density and improve skeletal health. Physical therapy includes rehabilitation exercises and orthotic devices to help patients improve posture and mobility. Surgical intervention is primarily reserved for severe spinal curvature and hip joint issues[11]. For this patient, we administered calcium supplements and vitamin D, along with some physical training, as the patient does not exhibit spinal curvature or joint deformities and does not currently require surgical intervention.

Discussion: In 1979, Sillence et al[12]. first proposed a standard classification system for OI based on the severity of clinical manifestations, ranging from Type I to Type IV. The classifications are as follows[13]: Type I is associated with mild clinical features, including blue sclera and no apparent dentinogenesis imperfecta, and typically does not result in disability; Type II is the most severe, characterized by blue sclera, a small chest, rib fractures, pulmonary infections, and often leads to perinatal death due to respiratory failure; Type III, the most severe survivable type of OI, typically presents with progressive bodily deformities such as severe short stature and significant spinal curvature, without blue sclera; and Type IV is a moderate form of the disease characterized by normal sclera and incomplete dentinogenesis, with patients exhibiting more severe clinical features than Type I OI but milder than Type III. In the present case, the patient's stature was slightly smaller than that of a normal newborn, and radiographic examination at 5 months old revealed slender long bones in the limbs and underdeveloped hip joints. There were no obvious deformities of the spine or limbs, and the patient did not have blue sclera. Based on the clinical presentation, the patient was diagnosed with Type IV OI. Osteogenic Imperfecta is primarily caused by abnormalities in the quantity or structure of Type I collagen. Type I collagen is the primary component

of the extracellular matrix of bone cells, is the most common type of collagen in the body, and is found predominantly in tissues such as the bone, cornea, dermis, and tendons. Therefore, its quantity and quality are closely related to bone strength[14-15]. COL1A1 is located at 17q21.33, comprising 52 exons. Mutations in this gene can decrease the quantity or instability of Type I collagen, resulting in increased bone fragility.

In this case report, through genetic sequencing, we identified a heterozygous variant in the coding region of the COL1A1 gene (Chr17:48263290): NM_000088.4:c.4097T>A (p.Ile1366Asn) . This variant was highly correlated with the clinical phenotype of the patient, with a REVEL predicted score of 0.878, and was classified as a likely pathogenic variant according to ACMG classification[16]. Subsequently, the mutation site was verified using Sanger sequencing. The COL1A1 c.4097T>A variant occurs at position 4097 in the coding region of COL1A1, where thymine is replaced by adenine, resulting in the substitution of isoleucine with asparagine at position 1366 of the encoded protein. Owing to this amino acid substitution, the structure of Type I collagen is abnormal,ultimately leading to OI. COL1A1 gene mutations that cause abnormalities in Type I collagen structure most commonly involve the substitution of glycine with other amino acids. Glycine plays a crucial role in the triple helical structure of collagen, and its substitution disrupts this structure[17]. In the present case, genetic testing revealed an amino acid substitution of isoleucine with asparagine, which was classified as a missense mutation. This mutation has not been recorded in the GnomAD, ExAC, or Thousand Genomes Project databases. Furthermore, we found that the patient's parents did not harbor this

mutation (Table 1), indicating that this variant was likely a de novo mutation, although the possibility of parental germ cell mosaicism cannot be ruled out. In conclusion, OI is a rare genetic disorder, and genetic testing is crucial for its diagnosis, in addition to analysis of symptoms and auxiliary examinations. Overall, analysis of the present case revealed a rare variant (COL1A1 exon c.4097T>A) that we believe is linked to Type IV OI in the Chinese population. Overall, the results of the present study contribute to the current knowledge regarding the spectrum of pathogenic COL1A1 gene mutations in a Chinese population with OI.**References:**

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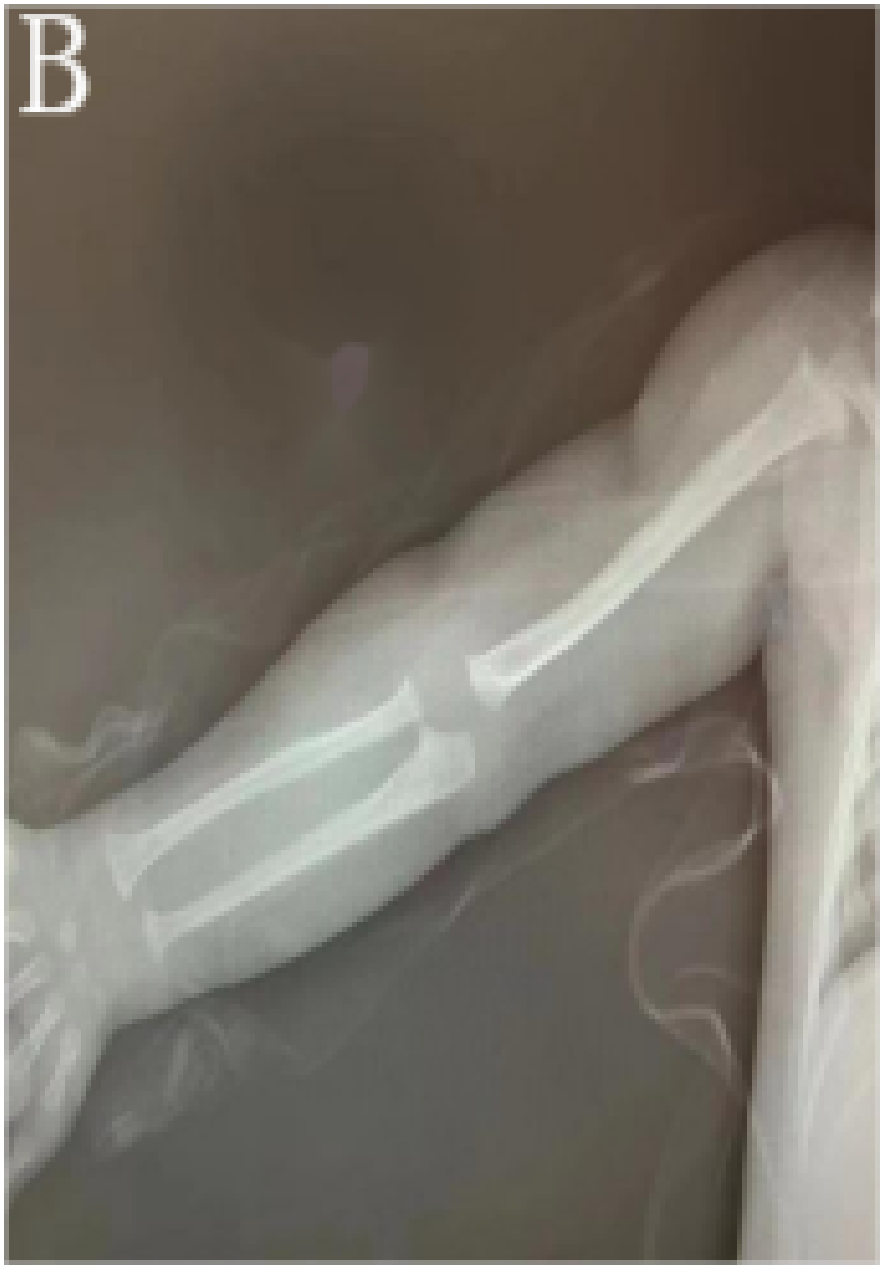
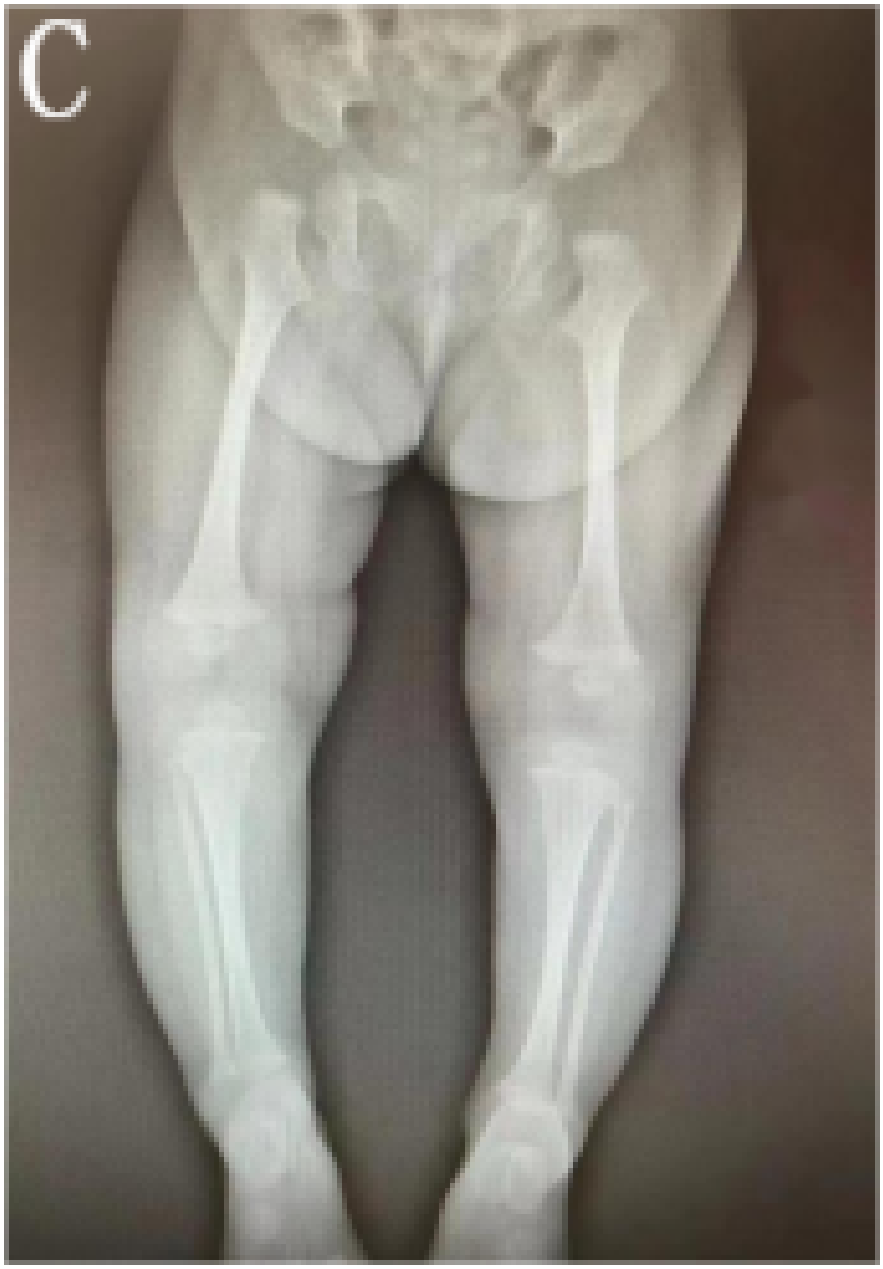
Table 1. Results of genetic testing (SNVs, Indels)

Gene	Chromosomal position (hg19)	HGVS nominate	Gene subregion	Variant type	Zygotic state Proband	Father	Mother	ACMGgrade
COLIA I	chr17: 48263290	NM-000088.4: c.4097T>A p.Ile1366A sn	Exon50	Missensevariatio diseas	Heterozygosis	Wildtype	Wild type	May cause





Figures

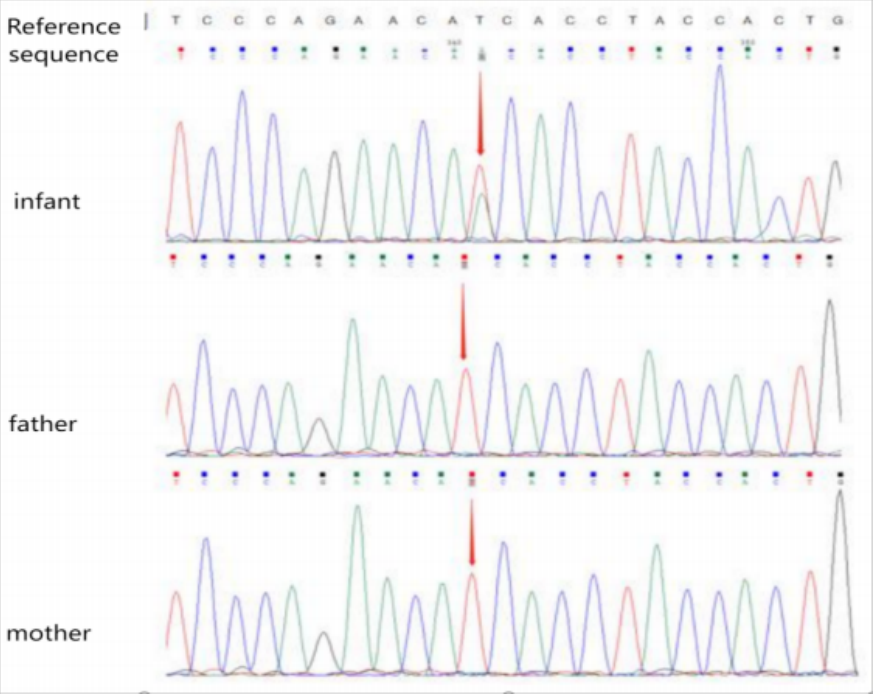


Fig.1 Sanger sequencing results

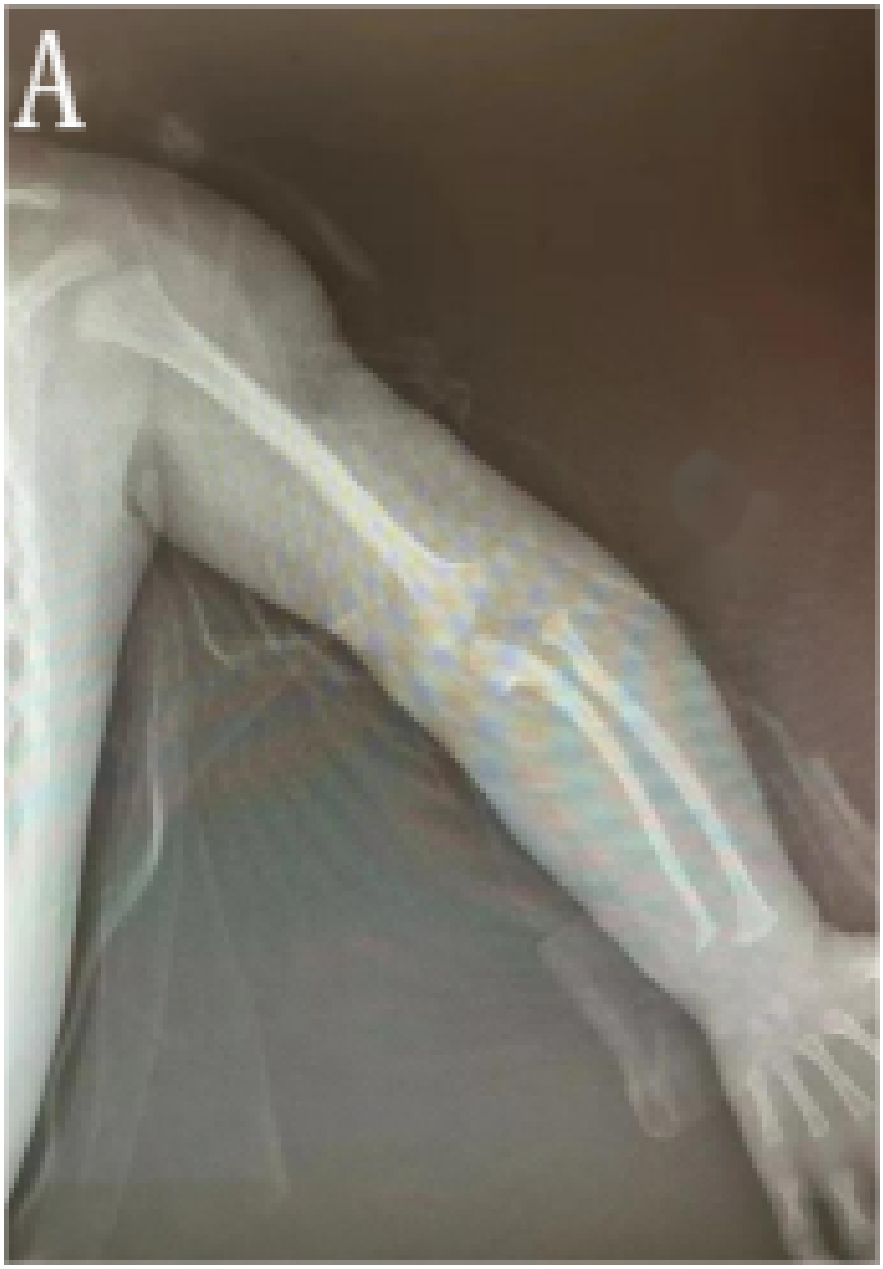
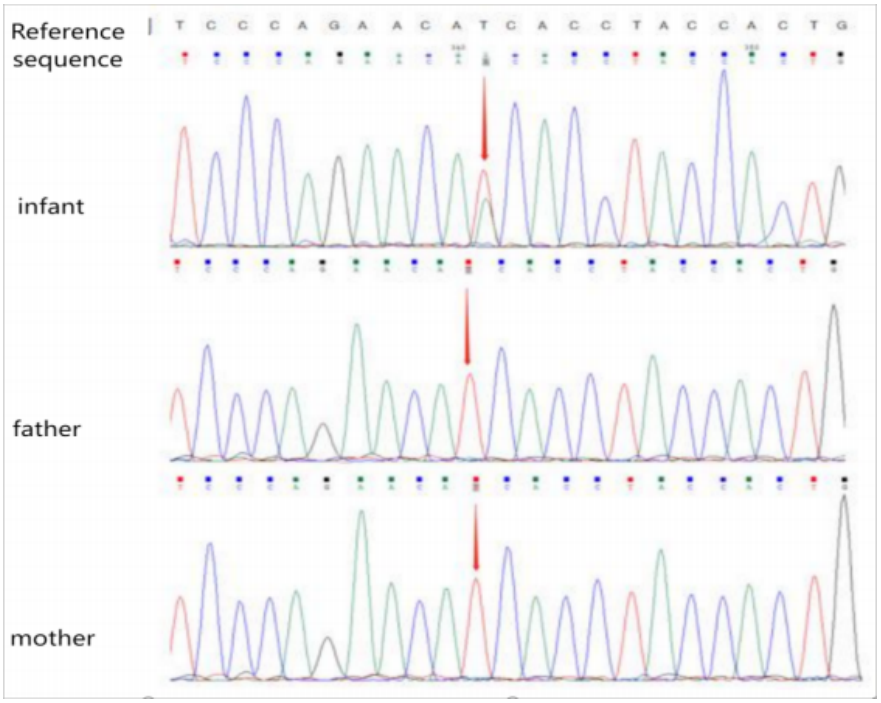
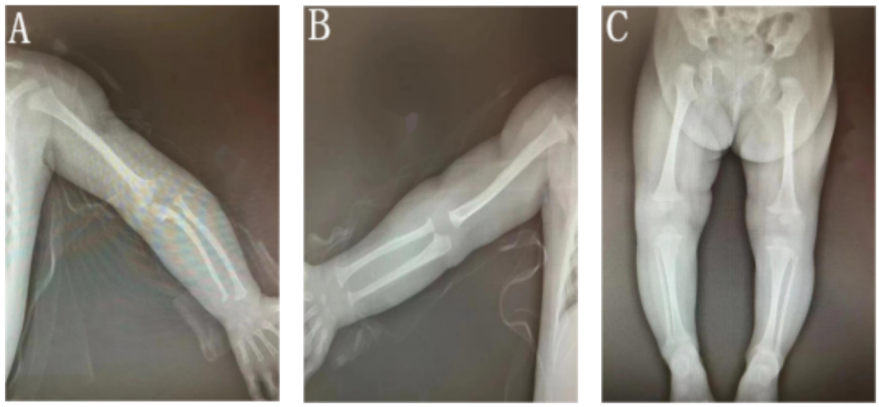


Fig.2 X-ray examination results of the left upper limb(A), right upper limb(B), and both lower limbs(C).





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