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Type XV osteogenesis imperfecta: A novel mutation in the *WNT1* gene, c.620G >A (p.R207H), is associated with an inner ear deformity

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SUMMARY The Wnt signaling pathway is vital in encouraging bone growth. *WNT1* gene mutations have been identified as the major cause of type XV osteogenesis imperfecta (OI). Described here is a case of complex heterozygous *WNT1* c.620G>A (p.R207H) and c.677C >T (p.S226L) OI caused by a novel mutation at locus c.620G >A (p.R207H). The female patient had type XV OI, distinguished by poor bone density, frequent fractures, a small stature, skull softening, lack of dentine hypoplasia, a brain malformation, and obvious blue sclera. A CT scan of the temporal bone revealed abnormalities of the inner ear, necessitating a hearing aid 8 months after birth. There was no family history of such disorders in the proband's parents. The proband inherited complex heterozygous *WNT1* gene variants c.677C>T (p.S226L) and c.620G>A (p.R207H) from her father and mother, respectively. Presented here is a case of OI with inner ear deformation caused by c.620G>A (p.R207H), which is a novel *WNT1* site mutation. This case broadens the genetic spectrum of OI and it provides a rationale for genetic testing of mothers and a medical consultation to estimate the risk of fetal illness.

Keywords type XV osteogenesis imperfecta, heterozygous mutation, *WNT1*, inner ear dysplasia

Osteogenesis imperfecta (OI) is a condition with various morphologies caused by insufficient type I collagen production (*1*). It is distinguished by brittle bones and frequent fractures, which may result in bone abnormalities (*2*). Mutations in the *WNT1* gene generate type XV OI, which is responsible for severe (gradually deformed) recessive OI (*3*). Classic *WNT1* signaling is essential for optimal bone growth and maintenance of bone homeostasis. Patients with *WNT1* mutations have lower bone mineral density, more fractures, a shorter stature, and blue sclera (*4-9*), and some also had cognitive difficulties, developmental delays, and central nervous system problems. Over the past few years, congenital ptosis has been described in a few cases (*8,10,11*). No congenital hearing impairment (inner ear hypoplasia) or encephalomalacia has been reported in children heterozygous for the *WNT1* mutation. Described here is a female patient with type XV OI and impaired hearing, cranial softening, frequent fractures, and no family history. The female toddler had a complex heterozygous mutation of the *WNT1* gene. The location of c.677C >T (p.S226L) has been reported, but c.620G >A (p.R207H) is novel.

1. Clinical manifestations in a rare case

The proband (Figure 1A, B) was 8.5 years old and born to her mother, G1P1, after 39 weeks of pregnancy at the age of 22. She was born *via* cesarean section at Kunming Children's Hospital, weighed 2.6 kg, and measured 50 cm. There was no history of asphyxia or family history of asphyxia. A general medical examination of the proband revealed a height of 93 cm (-3SD), a weight of 14 kg (-3SD), a brain circumference of 50 cm, and physical asymmetry (left side length: 94 cm, right side length: 97.5 cm, left lower limb: 47.5 cm, right lower limb: 49 cm). Hearing loss was apparent, necessitating hearing aids, and both lower limbs have sustained several fractures. The proband was able to walk after one year of age, but she is still unable to walk alone.

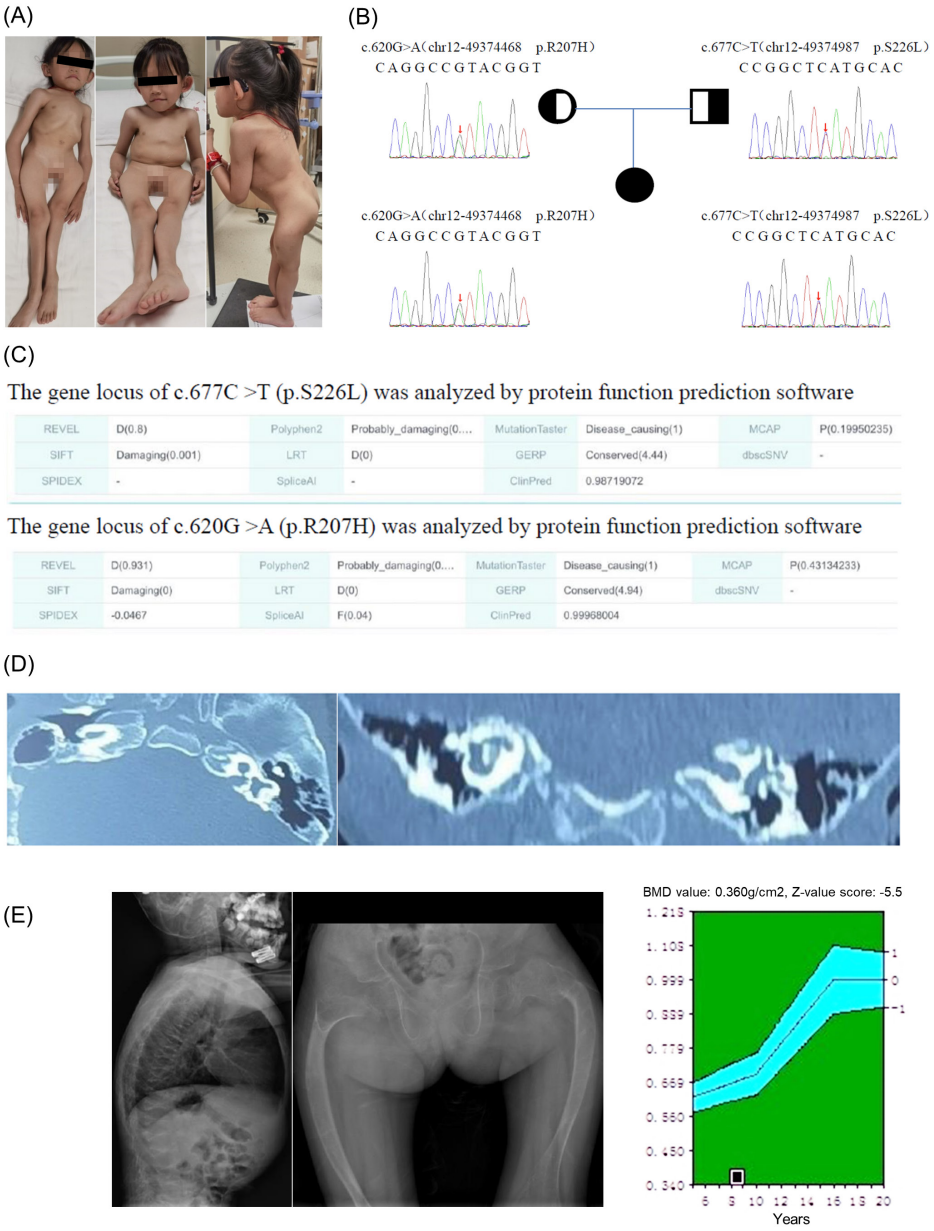

Figure 1. Clinical phenotype and Sanger sequencing results for the proband. **(A)** The proband was 8.5 years old, had a weight of 8.5 kg, a height of 75 cm, a brain circumference of 50 cm, and physical asymmetry (left side length: 94 cm, right side length: 97.5 cm, left lower limb: 47.5 cm, right lower limb: 49 cm). **(B)** The proband had a complex heterozygous variation of *WNT1* gene c.677C>T (p.S226L) and c.620G>A (p.R207H) from her father and mother respectively. **(C)** The two sites were predicted to be harmful according to REVEL, which is a bioinformatics program that compiles scores from multiple tools to predict the pathogenicity of missense variants. The mutations were predicted to be harmful according to SIFT, possibly harmful according to PolyPhen_2, harmful according to MutationTaster, and the sites were predicted to be conserved according to GERP+. **(D)** A plain CT scan of the temporal bone revealed bilateral inner ear dysplasia. **(E)** An X-ray bone density meter revealed a significant decrease in bone mineral density (BMD: 0.360 g/cm^2, Z-value score: -5.5). The X-ray revealed flattening of thoracic 4 to lumbar 5 vertebrae in a double concave shape, enlargement of the bilateral upper femur, deformity of the diaphysis, decreased bone density, sparse trabecular bone, thin bone cortex, and sequelae.

A temporal bone CT scan indicated bilateral inner ear dysplasia (Figure 1D). An X-ray bone density meter revealed a considerable reduction in bone mineral density (BMD: 0.360 g/cm^2, Z-value score: -5.5). The X-ray revealed a twofold concave flattening of the thoracic 4 to lumbar 5 vertebrae, expansion of the bilateral upper femur, deformity of the diaphysis, reduced bone density, scant trabecular bone, thin bone cortex, and sequelae (Figure 1E).

An eye examination revealed no substantial abnormalities, and a brain MRI revealed no significant abnormalities in the parenchyma.

Calcium serum levels were normal at 2.50 mmol/L, phosphorus levels were normal at 1.47 mmol/L, alkaline phosphatase levels were normal at 220 U/L, vitamin D levels were normal at 30.2 ng/mL, calcitonin levels were normal at 2.95 pg/mL, and parathyroid hormone levels were normal at 31.30 pg/mL.

The proband in this case inherited a complex heterozygous mutation of the *WNT1* gene from both parents, c.677C>T (p.S226L) and c.620G>A (p.R207H). REVEL, which is a comprehensive bioinformatics program that compiles scores from multiple tools to predict the pathogenicity of missense variants, predicted that these two mutations were detrimental, while SIFT predicted that they were harmful, PolyPhen 2 predicted that they were probably harmful, MutationTaster predicted that they were dangerous, and GERP+ predicted that the sites were conserved (Figure 1C). Her mother had a heterozygous *WNT1* mutation (c.620G >A (p.R207H)) while her father had a *WNT1* mutation (c.677C >T) (p.S226L). Her father is 33 years old (height: 171 cm, weight: 75 kg), and her mother is 30 years old (height:144 cm, weight: 45.5 kg), and neither has clinical symptoms of OI.

This study was approved by the ethics committee of the First People's Hospital of Yunnan Province, and written informed consent was obtained from a parent prior to this study.

2. Experience and insights

Type XV OI is uncommon; as the number of patients increases, new phenotypes will appear, and the phenotype-genotype relationship will be explored in greater depth. Type XV OI is an autosomal-recessive disorder in which individuals have either a *WNT1* homozygous mutation or a complex heterozygous mutation. The most prevalent mutation in the *WNT1* gene is c.677C >T (p.S226L). The clinical features of a type XV OI patient from a non-related family with a compound heterozygous missense *WNT1* mutation, c.620G>A(p.R207H) and c.677C >T, have been described here. The pathogenic variant c.677C >T (p.S226L), which changes amino acid 226 from serine to leucine, is a missense variant. According to the Human Gene Mutation Database (HGMD), it may result in the development of type XV OI (*8,12*). Another known missense mutation is c.620G>A (p.R207H), which results from a change in amino acid 207 from arginine to histidine. This missense mutation is sporadic in the population and has not been documented in the HGMD. REVEL, a sophisticated bioinformatics program that compiles scores from multiple tools to predict the pathogenicity of missense variants, indicated that these two mutations were detrimental. However, the proband's parents did not exhibit symptoms, indicating recessive inheritance. The pathogenicity of the c.677C>T (p.S226L) mutation has been well established in previous studies, but the pathogenicity of the c.620G>A (p.R207H) mutation has not been documented. The proband had apparent clinical signs of OI, and the gene mutation satisfied the genetic co-separation requirement. c.620G>A (p.R207H) is a unique *WNT1* gene mutation with new clinical signs. However, its precise mechanism needs to be investigated further in additional patients.

Described here is a patient with type XV OI with heterozygous mutations in *WNT1* genes (c.620G >A (p.R207H) and c.677C >T (p.S226L) from her father and mother, respectively. The child's symptoms include hearing loss, cranial softness, and repeated fractures. The most notable clinical feature of the case is inner ear dysplasia. It is uncommon in people with this type of OI. Gradual hearing loss has been described in some individuals with classic OI caused by the *COL1A1* or *COL1A2* genes. The processes, onset, and severity of these two types of hearing impairment vary. There are no reports of hearing loss in people with the c.677C >T (p.S226L) homozygous mutation. More research is required to determine if the proband's hearing impairment was caused by c.620G>A(p.R207H) alone or by interaction of c.620G>A(p.R207H) and c.677C>T(p.S226L). At the age of two months, the proband was diagnosed with inner ear dysplasia. Following treatment with a calcium supplement, there was no substantial progress until she received a hearing aid at 8 months. Thus, her language development is delayed for her age.

In conclusion, novel mutations in *WNT1* locus c.620G>A (p.R207H) or the interaction of c.620G>A (p.R207H) and c.677C>T (p.S226L) may be responsible for the new clinical symptoms of type XV OI described here, and early intervention is required to prevent and manage language and intellectual disabilities. Addition of the *WNT1* locus c.620G>A (p.R207H) broadens the genetic spectrum of OI and offers grounds for genetic testing of mothers and a medical consultation to estimate the risk of fetal illness.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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