A novel dominant mutation in the *SOX10* gene in a Chinese family with Waardenburg syndrome type II

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Abstract. Waardenburg syndrome type 2 (WS2) is a rare genetic disorder, characterized by bright blue eyes, moderate to profound hearing loss and pigmental abnormalities of the hair and skin. Between 10 and 20 mutations in the *SRY-box 10* (*SOX10)* gene were previously identified to be associated with WS2. The present study aimed to identify the genetic causes of WS2 in a Chinese family. Clinical and molecular analyses were performed to genetically characterize a Chinese family with two cases of WS2. The clinical data of the proband were collected using a questionnaire. The genomic DNA was extracted from peripheral blood samples of each individual in the family, and 168 candidate genes associated with hearing loss were sequenced using the Illumina HiSeq 2000 and confirmed by Sanger sequencing. A heterozygous nonsense mutation [substitution; position 127; cytosine to thymine (c.127C>T)] was identified in exon 2 of *SOX10* (transcript ID: NM_006941.3) in the proband and the mother; however, not in other family members or healthy controls. The novel nonsense heterozygous mutation may cause the replacement of codon 43 [arginine (Arg)] with a stop codon (Arg43stop), leading to premature termination of protein translation. The novel nonsense heterozygous mutation c.127C>T in the *SOX10* gene was considered to be the cause of WS2 in the family. This mutation has not been identified in any databases, to the best of the authors' knowledge, including The Single Nucleotide Polymorphism Database, The Human Gene Mutation Database, 1000 Genomes Project and ClinVar and Exome Sequencing Project v. 6500.

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Introduction

Waardenburg syndrome (WS), a type of auditory-pigmentary syndrome, is the most common autosomal dominantly inherited syndrome and is characterized by bright blue eyes, moderate to profound hearing loss (HL), pigmental abnormalities of the hair and skin, and dystopia canthorum (1). This syndrome has been observed in numerous ethnic groups (1,2). WS is responsible for 2-5% of all cases of congenital deafness in children (3). According to the clinical characteristics, WS is divided into four types (4,5). Type I [WS1; Mendelian Inheritance in Man (MIM) no. 193500] and type II (WS2; MIM no. 193510) present common features: Sensorineural HL and pigmental abnormalities. The two types are distinguishable by the presence or absence of dystopia canthorum indicated by the W index (type I: W>1.957; type II: W<1.95). Type III (WS3; Klein-Waardenburg syndrome; MIM no. 148820) is characterized by the presence of musculoskeletal abnormalities, in addition to the typical disorders of WS1. Type IV (WS4; Waardenburg-Hirschprung disease; MIM no. 277580) is characterized by the presence of an aganglionic megacolon or gastrointestinal atresia, in addition to the typical disorders of WS2 (6). WS is phenotypically homogenous; however, it exhibits genetic heterogeneity. *Paired box gene 3*, *melanocyte inducing transcription factor* (*MITF*), *snail family transcriptional repressor 2*, *endothelin 3*, *endothelin receptor type B* (*EDNRB*) and *SRY-box 10* (*SOX10*) have been previously identified to be associated with WS and are located

on chromosomes 2, 3, 8, 13, 20 and 22, respectively (7). *De novo* mutations in the *SOX10* gene, which is one of the genes responsible for WS II, are rarely observed. Between 10 and 20 mutations in the *SOX10* gene have been demonstrated to be associated with WS2 (6). The *SOX10* gene is composed of 3-5 exons, depending on the splice variant, and it is located on the human chromosome 22q13.1 (8). SOX10 is a key transcription factor and serves as a nucleocytoplasmic shuttle in the development of the neural crest and peripheral nervous system (9). Additionally, SOX10 is involved in the regulation of embryonic development and the determination of cell fate (10).

The complete coding regions of 168 candidate genes were amplified and sequenced to identify possible mutations in the Chinese proband. Molecular investigation identified a novel nonsense mutation in the second exon of SOX10.

Materials and methods

Case data. The proband, a deaf boy, received a cochlear implant in Kunming Children's Hospital of Yunnan (Kunming, China). A questionnaire survey was conducted to collect the clinical data of the proband and his parents. A complete physical examination was performed by physicians in the hospital. The inner canthus, outer canthus, pupillary distance and W index were calculated: {X=[2A-(0.2119C+3.909)]/C, Y=[2A-(0.249B+3.909)]/B, W=X+Y+(A/B)}, where A is the inner canthus; B is pupillary distance; C is the outer canthus; and X and Y are indexes. Visual reinforcement audiometry, acoustic immittance, auditory brainstem response, 40 Hz auditory evoked relative potential and hearing aid speech tests were performed to assess the pre-operative hearing speech level. The hearing level of the parents was assessed by pure tone audiometry at frequencies of 250, 500, 1,000, 2,000, 4,000 and 8,000 Hz. The diagnostic criteria were the following: Normal hearing [<20 decibels hearing level (dBHL)], mild (20-40 dBHL), moderate (41-70 dBHL), severe (71-95) and profound (>95 dBHL) deafness. Additionally, temporal bone computed tomography (CT) scans and cranial magnetic resonance imaging (MRI) were performed. Peripheral blood samples (2 ml) from the proband and his parents were collected and informed consent was obtained on February 7th, 2017. The study was performed in accordance with the Declaration of Helsinki and was approved by The Ethics Committee of Kunming Children's Hospital. Additionally, 50 individuals of normal control aged between 7 and 30 years old were enrolled in the present study, including 30 males and 20 females without associated hereditary diseases. Blood samples were collected on February 7th, 2017. Written informed consent was obtained from all participants enrolled in the present study.

DNA library preparation. Genomic DNA was extracted from peripheral blood with a DNA extraction kit (Tiangen Biotech Co., Ltd., Beijing, China), according to the manufacturer's protocol. The DNA was quantified using a Nanodrop 2000 (Thermo Fisher Scientific, Inc., Wilmington, DE, USA). Subsequently, >3 μg DNA was used for the construction of the indexed Illumina libraries (Illumina, Inc., San Diego, CA, USA). A total of 3 μg genomic DNA was fragmented using Covaris-S220 (Covaris, Inc., Woburn, MA, USA). An 'A-tail' was ligated to the 3' end of each DNA fragment. Illumina adapters were ligated to the fragments. The sample size aimed for was a 350-400 base pair (bp) product, and the size-selected product was amplified by polymerase chain reaction (Applied Biosystems 2720 PCR; Thermo Fisher Scientific, Inc., Waltham, MA, USA) as follows: Initial denaturation of 98˚C for 1 min, 9 cycles of denaturation at 98˚C for 20 sec, annealing at 65˚C for 30 sec, extension at 72˚C for 30 sec, and a final extension of 72˚C for 5 min. All samples were checked with a Nanodrop 2000 or Qubit 4 Fluorometer (Thermo Fisher Scientific, Inc.) to determine whether they represented a qualifying captured library. DNA fragments between 350 and 450 bp, and the oligonucleotides containing the adapter sequences were selected for the DNA libraries.

Targeted gene capture and sequencing. The exons and flanking intronic regions of 168 candidate genes associated with hearing impairment diseases were captured and enriched with the GenCap custom enrichment kit (Beijing Kangwei Century Biotechnology Co., Ltd., Beijing, China), according to the manufacturer's protocol. The PCR product was purified with solid phase reversible immobilization beads (Beckman Coulter, Inc., Brea, CA, USA). The enriched libraries were sequenced using the Illumina HiSeq 2500 sequencer (Illumina, Inc.) for paired-end reads of 150 bp.

Bioinformatics analysis of candidate variants. Data analysis and bioinformatics processing were performed as previously described (11). Following the sorting of the raw reads, the low-quality reads and adaptor sequences were filtered using Cutadapt software (v1.16; https://cutadapt.readthedocs.io/en/stable). Subsequently, the selected high-quality reads were aligned to the reference human genome (NCBI database build 37/hg19; https://www.ncbi.nlm.nih.gov/grc) with the Burrows Wheeler Aligner multi-vision software package (12). Single nucleotide polymorphisms (SNPs) and insertion or deletion of bases (indels) were identified using BWA (http://bio-bwa.sourceforge.net) and the Genome Analysis Toolkit Indel Genotyper (http://www.broadinstitute.org/gsa/wiki/index.php), respectively. The SNPs and the indels were filtered if their frequency was >5% in various databases, including dbSNP138 (http://www.ncbi.nlm.nih.gov/projects/SNP/), 1000 Genomes Project (ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp), ClinVar and Exome Sequencing Project v. 6500 (https://esp.gs.washington.edu/drupal), HapMap (ftp://ftp.ncbi.nlm.nih.gov/hapmap/), the Human Gene Mutation Database (HGMD; http://www.ghmd.cf.ac.uk/), SIFT (http://sift.jcvi.org), PolyPhen (http://genetics.bwh.harvard.edu/pph2/) and MutationTaster (www.mutationtaster.org) were used to predict the pathogenic variants of genes.

Validation by Sanger sequencing. The DNA of the parents of the proband was purified in order to perform Sanger sequencing. The polymerase chain reaction (PCR) samples were visualized on agarose gels, purified and sequenced using the ABI PRISM 3730 genetic analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). Following the comparison among DNA sequences, genomic sites exhibiting variations were identified with the corresponding GenBank (www.ncbi.nlm.nih.gov) reference sequences. A primer pair was designed to amplify exon 2 of the *SOX10* (gene ID: 6663;

transcript ID: NM_006941): Exon 2 forward: 5'-CTGAGC CCACACCATGAAG-3' and exon 2 reverse: 5'-GTTGGACTC TTTGCGAGGAC-3'. PCR amplifications were performed using Golden Star T6 Super PCR Mix (1.1X; Qingke Xinye Biotechnology Co., Ltd, Beijing, China) as follows: Initial denaturation of 95˚C for 5 min, 32 cycles of denaturation at 95˚C for 30 sec, annealing at 60.3-59.9˚C for 30 sec, extension at 72˚C for 30 sec, and a final extension of 72˚C for 7 min. The purified PCR products with a size of a 426 bp were sequenced by Sanger sequencing (Biosune, Beijing, China; http://www.biosune.com). The sequencing results were analysed using Mutation Surveyor 5.0.0 (SoftGenetics, Inc., State College, PA, USA).

Figure 1. Clinical features of the proband include iris heterochromia of the right eye.

Results

Clinical features of the patients with WS2. The right iris of the proband has been bright blue since birth (Fig. 1). At 3 months old, he did not exhibit any response to external audio stimuli and at 1 year old he was not capable of speech. Ear injury, otitis media and contact with ototoxic drugs were not detected. Skin depigmentation was observed, eyesight and intelligence were normal, no dystopia cantorum was present, and no abnormalities affecting the digestive system or the skeletal muscles were detected. At birth and at 42 days old, otoacoustic emissions of the two ears were not present. At 10 months old, bilateral congenital profound sensorineural HL was confirmed (Fig. 2). A temporal CT scan, cranial MRI and abdomen B-scan ultrasounds did not identify any abnormalities. The above clinical manifestations fit the criteria of WS2. The proband was diagnosed with WS2, according to the WS diagnostic criteria (13,14).

Left heterochromia iridis and hair hypopigmentation were observed in the mother of the proband (Fig. 3). However, HL was not detected by sound field audiometry. It was identified that the average air-conduction hearing threshold of the right ear at 500, 1,000, 2,000 and 3,000 Hz on the audiogram was 60 dBHL (moderate HL) and the hearing threshold of the left ear was 30 dBHL (mild HL; Fig. 4). The mother of the proband exhibited normal speech ability. Transmission of hearing impairment, as highlighted by the pedigree (Fig. 5), suggested a possible autosomal dominant mode of inheritance with incomplete penetrance. The father of the proband did not exhibit heterochromia iridis, HL or pigmentation abnormality. The parents of the proband state in the interviews that no obvious abnormalities were present in other family members.

Identification of a novel SOX10 termination mutation. The genomic DNA of the proband was extracted, and the coding exons plus ~100 bp of the flanking intronic sequences of 168 deafness-associated genes were sequenced. The raw data comprised of ~805 Mb. The coverage of the target regions was 98.6%. The average sequencing depth of the target coverage area was 346; a total of 539 nucleotide variations were detected, including 48 indels.

A heterozygous mutation cytosine (C) to thymine (T) in position 127 (c.127C>T) was located in the second exon of *SOX10*, leading to a substitution of the 43rd codon: The codon arginine was replaced by a stop codon, causing premature termination of protein translation. According to the standards and the guidelines of The American College of Medical Genetics and Genomics (15), this type of variant is considered to be likely pathogenic and represents a novel variant that was not identified in the following databases: dbSNP, HapMap, 1000 Genomes Project and the HGMD. Additionally, this variant was absent in 50 normal control individuals. The mother exhibited the same variant (*SOX10*, exon 2, c.127C>T). The father exhibited a wild-type genotype (Fig. 6). Furthermore, no additional mutations associated with WS were identified in the proband.

Discussion

Among the congenital genetic diseases, the WS is the most common syndrome involving HL, and this syndrome exhibits a single-gene pathogenic autosomal dominant inheritance with incomplete penetrance (16). WS is divided in four types according to clinical characteristics and various accompanying phenotypes. Children with WS2 exhibit significant phenotypic characteristics, including sensorineural prelingual palsy, unilateral bright blue irises and hypopigmented hair, and a W index of 1.85 (<1.95). Therefore, the clinical diagnosis of the present proband was WS2. *SOXl0* serves an important role in the pathogenesis of WS and melanocyte development, and mutations in this gene may lead to WS2 and WS4 (17). It is estimated that ~15% of the WS2 pathogenesis is associated with mutations in the *SOX10* gene (17), and the genetic data derived from patients with WS2 is increasing in numerous countries; however, the molecular mechanism underlying a large proportion of WS2 cases remains unclear (17). *SOX10* belongs to the SOX gene superfamily (18), that is characterized by a highly conserved and active domain, the high mobility group (HMG) (19), whose principal function is to recognize and bind to the promoters of the target genes.

SOX10 is a key transcription factor involved in the migration and differentiation of neural crest cells and it is able to function alone or in combination with other transcription factors by binding to the promoters or enhancers of target genes (20,21). The downstream target genes of SOX10 are the following: *MITF, tyrosinase, tyrosinase related protein 1, dopachrome tautomerase, myelin protein zero, gap junction protein β 1, ret proto-oncogene* and *EDNRB* (20,21). These target genes are directly or indirectly involved in melanin synthesis, and their expression is regulated by SOX10. The

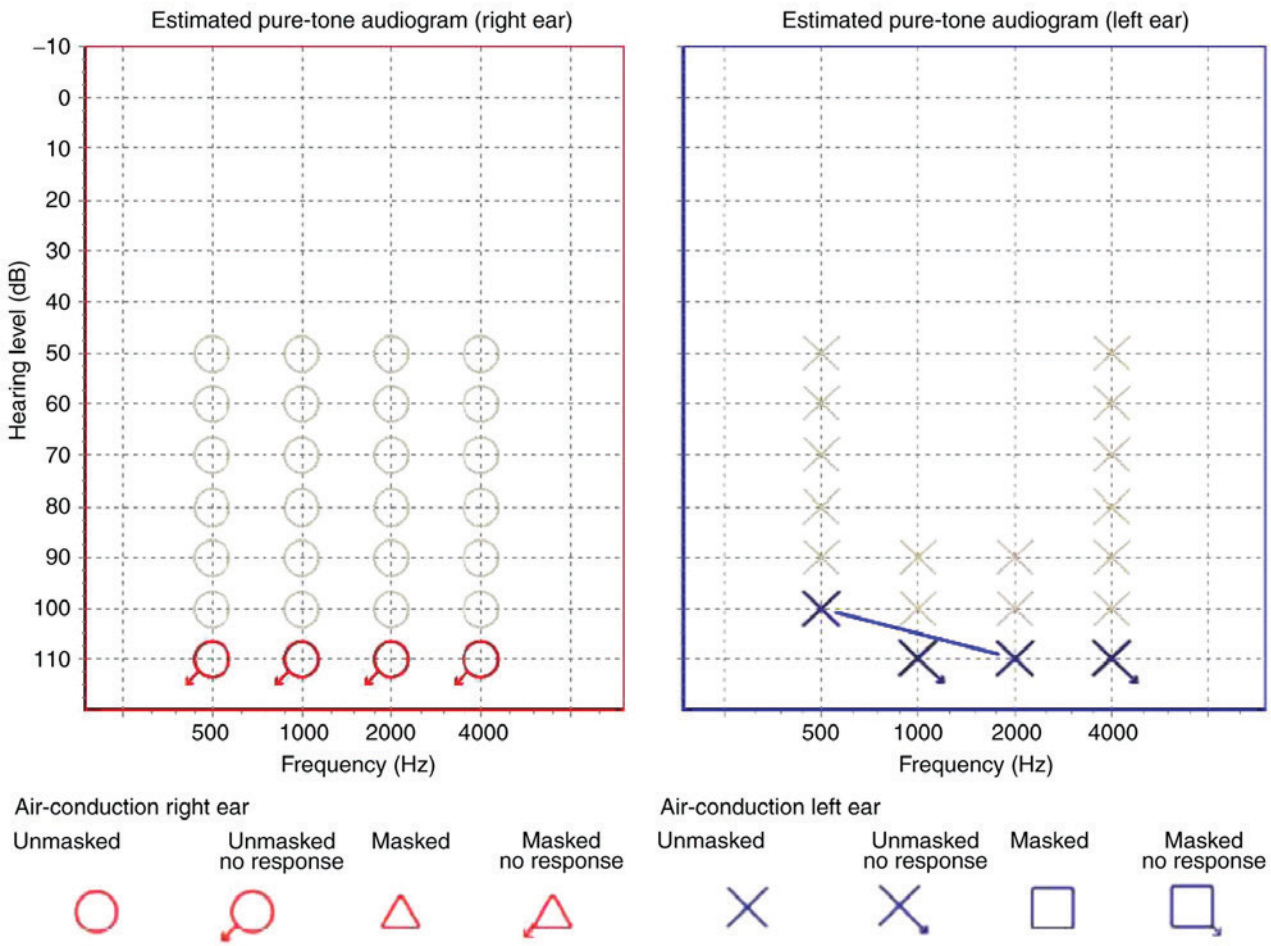

Figure 2. Multi-frequency stimuli based on steady-state evoked potential confirms bilateral congenital profound sensorineural hearing loss (>110 dB hearing level). dB, decibels.

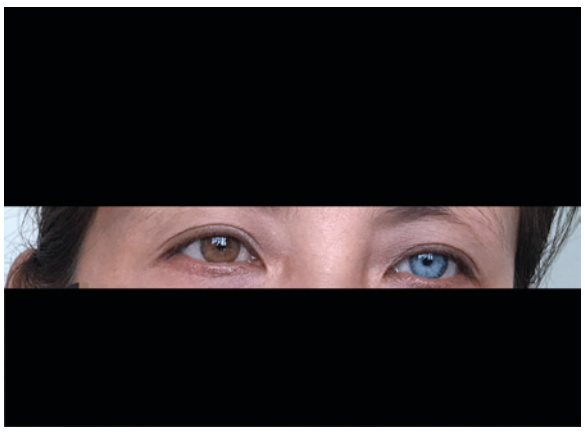

Figure 3. Clinical features of the mother of the proband include iris heterochromia of the left eye.

majority of mutations affecting the *SOX10* gene result in a termination codon that may cause WS4 and WS2. In addition to WS, mutations in the *SOX10* gene may lead to other neural crest-associated diseases (22,23), including peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy and Hirschsprung's disease.

WS is a genetic disorder characterized by numerous and complex genetic mutations that exhibit various clinical manifestations. Individuals with the same type of WS, even in the same family, may exhibit unique phenotypic traits. The present study identified that the proband and his mother carried a c.127C>T heterozygous mutation in exon 2 of the *SOX10* gene. However, the hearing defects between the proband and his mother were phenotypically distinct. The proband exhibited severe bilateral HL, and his mother exhibited moderate HL in the left ear and mild HL in the right ear. Chen *et al* (24) demonstrated that the mutation c.760C>T causing WS2 was located in the seventh exon of *MITF*, leading to a premature termination codon, as Wilcox (25) observed. However, families carrying the same mutation exhibited distinct phenotypes, suggesting that additional genetic variations may be responsible for the partial penetrance and the variability of the clinical manifestations of WS. Notably, this phenomenon was observed among individuals of the same family, carrying the same mutation. In the present study, the proband and his mother exhibited the same pathogenic variation; however, the clinical phenotypes were heterogeneous. The present results suggested that the genetic background serves an important role in the clinical phenotype. The proband presented the typical symptoms of WS, including sensorineural deafness and iris discoloration, in addition to hypochromic hair alterations in the body, which demonstrated the multiple functions of the SOX10 protein. The c.127C>T mutation is a heterozygous mutation in the second exon of *SOX10*, that causes an alteration in the translation

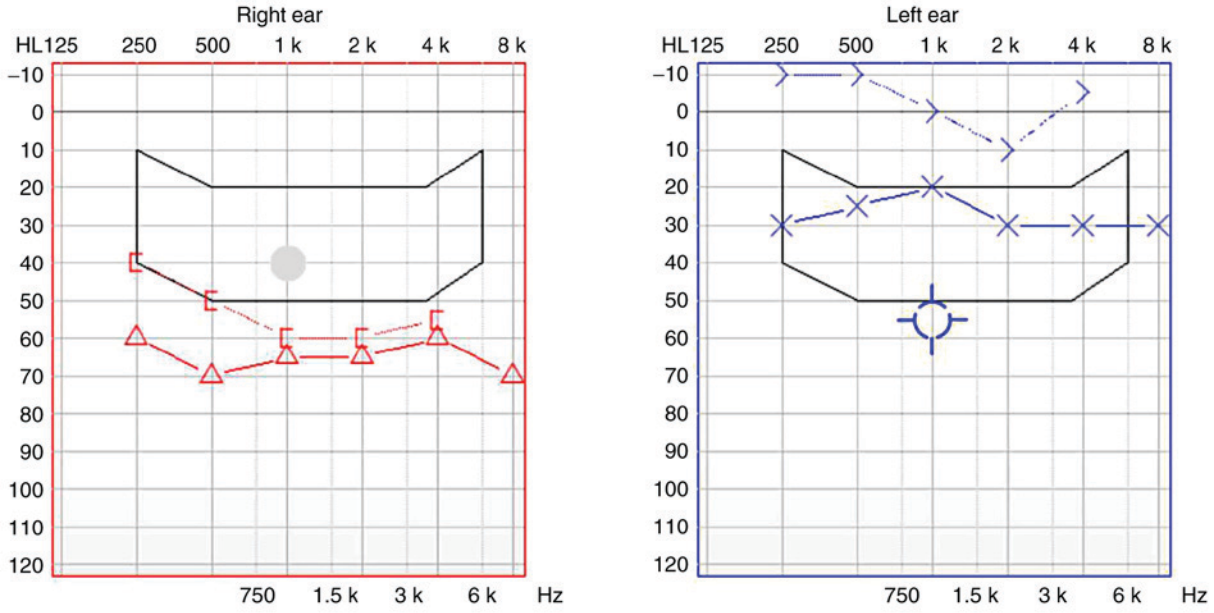

Figure 4. Air conduction hearing threshold of the mother. Right ear, 60 dBHL; left ear, 30 dBHL. dBHL, decibel hearing level.

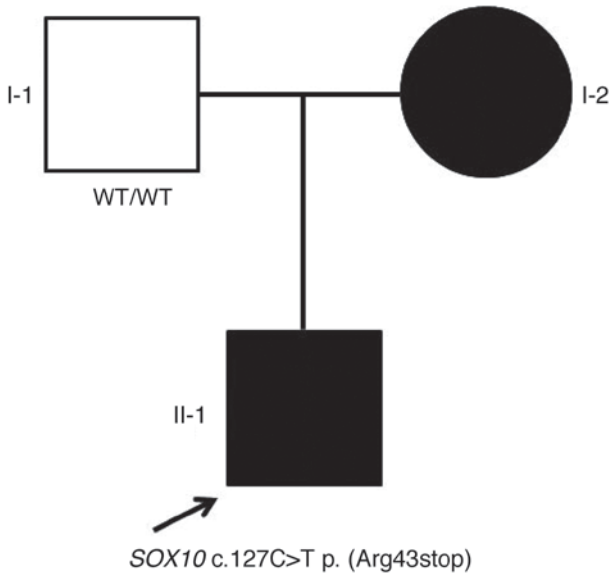

Figure 5. Family pedigree of the proband. WT, wild-type; I-1, father of the proband; I-2, mother of the proband; II-1, proband; *SOX10, SRY-box 10*; Arg, arginine; C, cytosine; T, thymine.

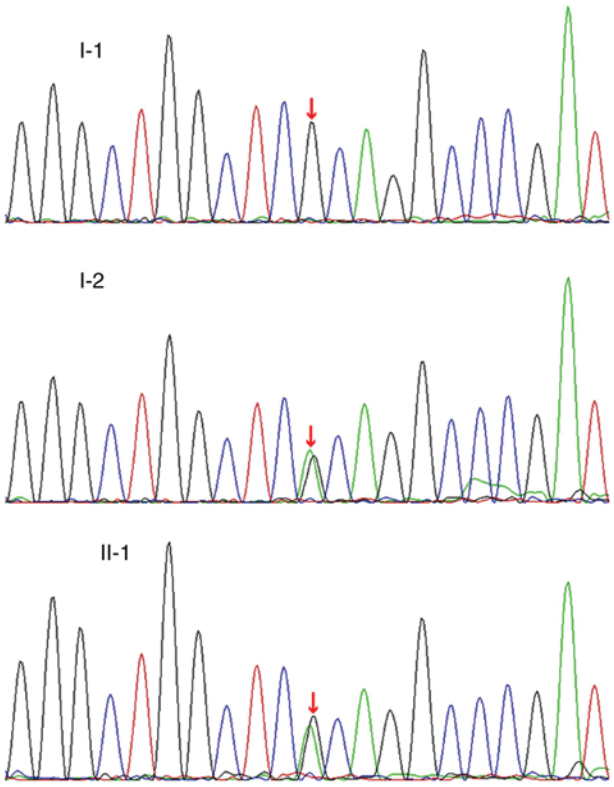

Figure 6. Novel mutation in the *SRY-box 10* gene (transcript ID: NM_006941.3; mutation c.127C>T). I-1, father of the proband; I-2, mother of the proband; II-1, proband.

product; the arginine in the 43rd position is replaced by a stop codon. The early stop codon leads to a premature termination of the protein translation, causing the loss of the majority of the HMG domain. In 50 healthy controls selected randomly, this mutation was not identified. Therefore, the mutation *SOX10* (c.127C> T, Arg43stop) was considered a causative mutation.

In the present study, clinical analyses and diagnoses based on detailed clinical data of patients were performed. In addition, a genetic mutation associated with WS was identified, and the patient received a genetic diagnosis. The novel mutation identified in the *SOX10* gene provides additional insight for the mechanism underlying the disease and refines the human gene mutation database. The experimental data presented may help in examining the associations between various types of WS and in reassessing the current clinical classification of WS. Additionally, the present results provided novel insight to improve the understanding of SOX10 function. The present study may represent an important basis for prenatal genetic diagnosis and provides novel insight for the treatment of patients with WS.

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Availability of data and materials

The analyzed data sets generated during the present study are available in the Figshare repository, https://figshare.com/account/home#/data.

Authors' contributions

JM, ZZ, TSZ and BR were responsible for the conceptualization of the study. ZZ, HCJ, HS and LPZ were responsible for the data curation. JM and ZZ acquired the funding. JM, ZZ, YQG, ZCL, YX and GLW performed the investigation. JM, ZZ, HCJ and CM were responsible for the methodology. TSZ and BR were responsible for project administration. CM, YQG and MHS were responsible for software. TSZ and BR were responsible for supervision. JM, ZZ and HCJ wrote the original draft. JM, TSZ and BR reviewed and edited the manuscript.

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and was approved by The Ethics Committee of Kunming Children's Hospital (Kunming, China). Written informed consent was obtained from all participants enrolled in the present study.

Patient consent for publication

The mother of the proband provided consent for the publication of images of her and the proband.

Competing interests

The authors declare that they have no competing interests.

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