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Genotype and phenotype analysis of a family with Waardenburg syndrome type II caused by a de novo mutation in SOX10 gene

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Abstract: *Gather clinical information about children with WS phenotype, including their medical history, pedigree, and imaging and hearing tests, with their informed consent. To find the genes linked to hearing loss, gather peripheral blood, extract genomic DNA, and apply high-throughput sequencing techniques. Conduct a temporal bone CT scan on the proband to assess inner ear development. Test the proband's and their family members' peripheral blood using flow cytometry. The child was diagnosed with inner ear developmental defects and one heterozygous mutation (c.77_104delGGAGCGCGCCTCTAGGGCCCGACGG) in the SOX10 gene, which resulted in a frameshift mutation in amino acids (p.G26Afs * 74). No such mutation was discovered, and the parents' phenotypic was normal. The proband's reduced expression of SOX10, PAX3, and MITF proteins was discovered by flow cytometry detection.Ultimately, we think that this research has found a new case of SOX10 mutation, which is a spontaneous mutation in the patient and preliminarily identified as the cause of the disease. This mutation enriches the mutation spectrum of SOX10.*

Keywords: *Inner ear deformity, SOX10, Hearing impairment, Waardenburg*

1. Introduction

Waardenburg syndrome (WS) is an autosomal dominant disorder discovered in 1951 by Dutch ophthalmologist and geneticist Petrus Johannes Waardenburg[1]. The main clinical features of patients with WS are congenital sensorineural hearing loss, abnormal spacing of the medial canthus, and pigmentary disorders of the hair, skin, and iris[2] .WS is classified into four types based on different clinical phenotypes and genotypes. Type WS1 clinically presents with medial canthus ectasia, frontal hair hypopigmentation, heterochromia of the iris, and a unibrow. Type WS2 is essentially the same as type 1 in terms of clinical phenotypes, except that it does not present with medial canthus ectasia (W<1.95)and a wide nasal root; WS3 is phenotypically similar to WS1 and is notable for its concomitant musculoskeletal developmental abnormalities of the face or upper extremities, WS4 is phenotypically similar to WS2 but with congenital megacolon [3-4]. Seven causative genes for WS have been identified, namely PAX3, MITF, SOX10, SNAI2, EDN3, and EDNRB.Among them, PAX3 leads to WS1 and WS3,WS2 currently reported causative genes include MITF, SOX10, SNAI2, KITLG [5],and WS4 causative genes include SOX10, EDNRB and EDN3[6].

The SOX10 gene (SRY-(sex-determining region Y-)box10) is located on chromosome 22q13.1 and belongs to the SOX (SRY-related HMG-box) family of transcription factors. It contains five exons and encodes a protein consisting of 466 amino acids. Its primary function is to specifically recognize and bind to the promoter DNA of target genes [7]. It is currently believed that the etiology of WS is due to abnormal NCC growth [8]. Hearing loss in WS may be associated with abnormal proliferation, survival, differentiation, or migration of NCC-derived melanocytes [9], and genetic variants affecting melanocyte differentiation and migration may also affect intracochlear potentials, leading to sensorineural deafness [10].SOX10 was first expressed in the dorsal neural tube during the early stages of neural crest cell

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(NCC) migration and is involved in various cellular developmental processes.SOX10 is also a transcription factor for the MITF gene; MITF plays an essential role in melanocyte development. The symptoms of WS caused by different genes are different, but their common manifestation is that they all have different degrees of hearing loss.The clinical manifestation of SOX10-induced WS, inner ear malformation, is more prevalent than WS caused by other genotypes. This paper reports a spontaneous and de novo mutation of SOX10 in a child from the Yunnan region of China. It analyzes the disease's cause, explores its mechanism, and verifies the pathogenicity at the cellular level using flow cytometry.

2. Methods

2.1. Case information

The study was conducted on a child with congenital sensorineural deafness combined with heterochromia of the iris from Yunnan, China, who was admitted to our hospital in May 2021, with a total of 3 members of the family line in 2 generations（figure 2）. Clinical data of the child and the family line were collected, and a comprehensive physical examination including otology, ophthalmology, hair, skin, joints of the limbs, digestive system, and intellectual assessment were systematically performed. The inner canthus distance (A), pupil distance (B), and outer canthus distance (C) were measured in the Propositus. The W value was calculated {X=[2A-(0.2119C+3.909)]/C, Y=[2A-(0.2497B+3.909)]/B, W=X+Y+(A/B)4}, and clinical audiological testing, temporal bone CT, and abdominal ultrasound were carried out to complete the examination After that, cochlear implant surgery was desired. The Medical Ethics Committee of our hospital approved the study, and a genetic diagnosis was performed with the consent of the children's families. The child's guardian signed an informed consent form—the guardian signs in place of the child. In addition, 100 normal controls aged between 7 and 30 years were recruited for this study; this includes 50 males and 50 females without associated genetic disorders. This study obtained written informed consent from all participants.

2.2. Genetic testing methods

2.2.1. DNA library preparation

Genomic DNA was extracted from peripheral blood using a DNA extraction kit (Tiangen Biotechnology Co., Ltd., Beijing, China).DNA was quantified using a Nanodrop 2000 (Thermo Fisher Scientific, Inc. Wilmington, DE, USA). Subsequently, > 3 μg DNA was used for Illumina library construction (Illumina, Inc., San Diego, CA, USA). A total of 3 μg of genomic DNA was fragmented using Covaris-S220 (Covaris, Inc., Woburn, MA, USA). The 3' end of each DNA fragment is ligated by an "A-tail." Attach the Illumina articulator to the fragment. The target sample size was 350-400 base pair (bp) products, and DNA fragments matching the size were selected and amplified by polymerase chain reaction (Applied Biosystems 2720 PCR; Thermo Fisher Scientific, Inc., Waltham, MA, USA), the method is as follows: Initial denaturation at 98°C for 1 min, denaturation at 98°C for 20 s, nine cycles of denaturation, annealing at 65°C for 30 s, extension at 72°C for 30 s, and a final extension to 72°C, held for 5 min. All samples were examined with a Nanodrop 2000 or Qubit 4 fluorometer (Thermo Fisher Scientific, Inc.) to determine if they represented competent capture libraries. DNA fragments between 350-450 bp were selected, and oligonucleotides containing articulator sequences were chosen as DNA libraries.

2.2.2. Target gene capture and sequencing

Whole-exome sequencing was performed using the Gen Cap kit (My Genostics Inc., Beijing, China). Genomic DNA was randomly interrupted into fragments, Linkage to Illumina PE connector oligonucleotide mixtures, DNA libraries were obtained after amplification and purification of the products by linkage-mediated polymerase chain reaction (LM-PCR), and testing them for quality, the above PCR products were hybridized with the target region capture chip to enrich the target region sequences, and Paired-End with the help of Illumina HiSeq 2000 second-generation sequencer, with a read length of 150 bp. The raw data were subjected to preliminary processing, including image recognition and sample differentiation.

2.2.3. Screening

In this experiment, the region captured by the chip included all exons and their flanking sequences (~100bp) in the human genome. Raw data from high-throughput sequencing was generated via the

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Illumina pipeline (version 1.8.2). Low-quality data were removed, and "clean" reads were aligned to the reference sequence of the human genome (UCSC, hg19) by BWA (Burrows-Wheeler aligner). SNPs and INDELs were collected using SOAPsnp and GATK software, respectively. Mutation sites with a frequency of less than 0.05 were selected as suspected pathological mutations by referring to data from the dbSNP database, the 1000 Genomes database, the ESP-da-tabase (NHLBI exome sequencing project), and 100 healthy controls.

2.2.4. Sanger sequencing

Genomic DNA was extracted for Sanger sequencing from venous blood from the parent of the Propositus. Based on the results of high-throughput sequencing, primers were designed: forward primer F416-B1 F sequence: AATCCACCCGAAGCTAGAGG, reverse primer R416-B1 R sequence: GATGACAAGTTCCCC -GTGTG.).PCR amplification steps: initial denaturation for 5 min at 95°C; 34 cycles of denaturation for 30 s at 94°C, 60°C recovery for 30 s, extension at 72°C for 45 s; and finally extension at 72°C for 5 min. PCR products with a length of 420 bp were analyzed by gel electrophoresis and then purified. Sequencing was performed using capillary electrophoresis through an ABI PRISM 3730 sequencer, and mutations were analyzed. Sanger sequencing results were compared with the SOX10 reference sequence (NM_006941) using SeqMan 7.1 software.

2.2.5. Software analysis

Revel software was used for mutation prediction analysis. Conservation of gene sequences near mutation sites located on exons was analyzed using DNAMA software in Homo sapiens, macaca mulatta, canis lupus familiaris, bos taurus, mus musculus,rattus norvegicus,gallus,danio rerio,xenopus tropicalis. The SOX10 gene sequences of each species were obtained from the NCBI website database.

2.3. Flow cytometry validation

Flow cytometry was used to detect the expression of SOX10, PAX3, and MITF proteins in peripheral blood lymphocytes of subjects and family members. Peripheral blood mononuclear cells were isolated from blood samples of family members using the Human Peripheral Blood Lymphocyte Isolation Solution protocol (Shanghai Yousu Biotechnology). The cells were fixed with 4% paraformaldehyde for 15 min at room temperature. Cells were washed with 1×PBS at 1500 rpm for 5 minutes. Cells were suspended by adding 1×10^6 cells to approximately 100 μL of IntraPrep permeabilization reagent (Beckman colter) and then membrane-broken for 15 min at room temperature. Cells were washed with 1×PBS at 1500 rpm for 5 min. 1×10^6 cells were divided into flow tubes, diluted according to the manufacturer's instructions, added with 20 μL of primary antibody, mixed thoroughly, and reacted at room temperature for one hour. Cells were washed thrice with 1×PBS at 1500 rpm, each for 5 min. Add 20μL of diluted fluorescent-labeled secondary antibody to the cells, mix thoroughly, and react at room temperature for 30 min, avoiding light. Wash the cells with 1×PBS at 1500 rpm three times, 5 min each time. 100-200 μL of PBS buffer was added to the cells and then analyzed on a Beckman Coulter DxFLEX flow cytometer, and the resulting data were analyzed using CytExpert software.

3. Results

3.1. Clinical results

The Propositus was an 11-month-old male child who had poor response to sound since birth and had never had a hearing test. The patient was admitted to Kunming Children's Hospital in May 2021. The examination was as follows: the bilateral blue sclera(figure 1), visual acuity examination showed no abnormality, no medial canthus externally shifted (WS index: 1.12<1.95),hair color slightly yellow, no abnormality in limb examination, the bilateral auricular contour was normal, otoscopic examination: external auditory canal was clear, tympanic membrane markings were clear; hearing examination results were as follows: bilateral otoacoustic emissions did not pass, ASSR: both ears at 500Hz, 1000Hz, 2000Hz, and 4000Hz all elicit reactions, with thresholds as shown in the figure3,ABR: bilateral 95dBnHL evoked no wave(figure4),acoustic conductance impedance bilateral A-curve, temporal bone CT showed: bilateral vestibular semicircular canals developmental malformation(figure 5,6). There was no abnormality in the abdominal ultrasound of the Propositus. Combining all the clinical features and examinations, the preterm was diagnosed with WS type 2 according to the clinical diagnostic criteria for WS [11]. The parents did not complain of poor hearing, there was no obvious

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abnormality in phenotype, and pure tone audiometry was standard.

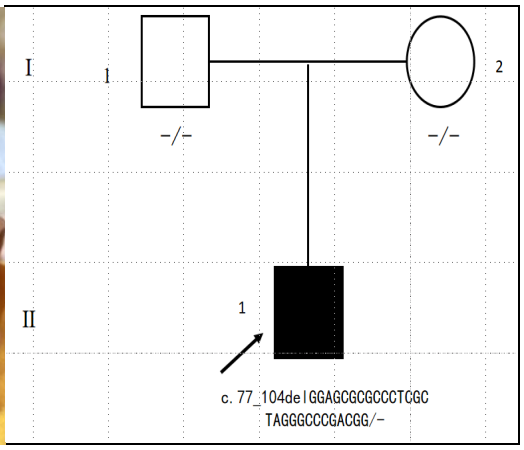
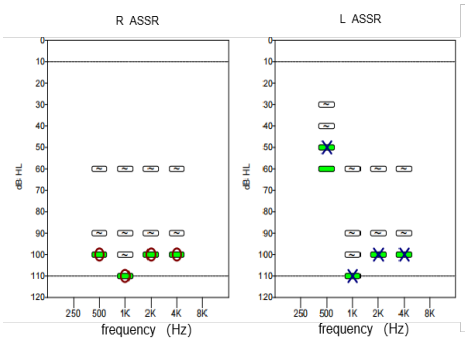


Figure 1: Image of the proband *Figure 2: Family tree*



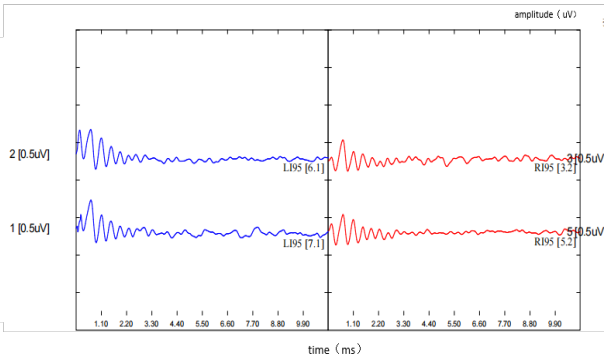
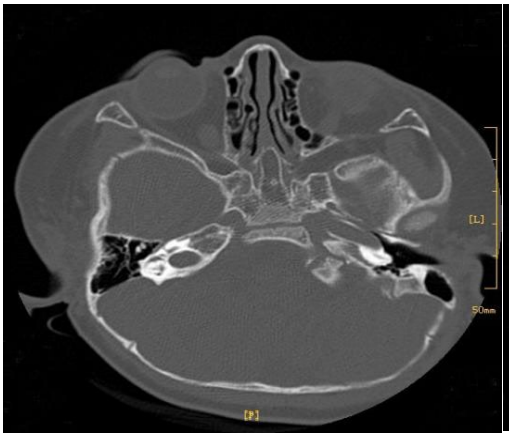


Figure 3: ASSR *Figure 4: ABR*



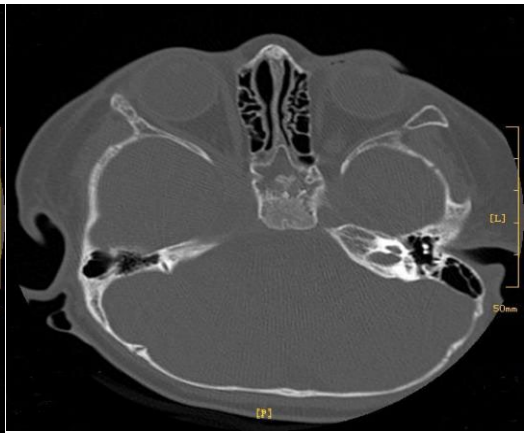


Figure 5: Temporal bone CT 1 *Figure 6: Temporal bone CT 2*

3.2. Genetic test results

The Propositus were subjected to whole-exome sequencing (including WS-related genes) and were analyzed by the dbSNP database, 1000 Genomes Project, and the ESP database to exclude variants with a high prevalence rate in the healthy population, and the variants were categorized according to the ACMG guidelines. One heterozygous mutation was detected in the SOX10 gene of the Propositus: c.77_104delGGAGCGCGCCCTCGCTAGGGCCCGACGG Heterozygous mutation(figure 7), a 28-base deletion after the 77th base of the SOX10 gene, resulting in a shifted amino acid mutation (p.G26Afs*74), which causes the 26th amino acid to be changed from glycine to alanine, and the base encoding amino acid 74 becomes a stop codon, which is expected to produce a truncated protein and lose its normal function (PVS1). The variant (PM2) was not found in the normal control population databases (Exome Sequencing Project EAST, 1000 Genomes Project, gnomAD_genome_ALL, etc.). It

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was verified by Sanger sequencing that the parents did not carry the variant at this site, and the variant was a spontaneous mutation (PS2). The protein function prediction software REVEL predicted as unknown. Amino acid sequences were retrieved by the Ensembl database (http://asia.ensembl.org/index.html), and DNAMA software was used for conservativeness analysis. The results showed that the amino acid site p.G26A corresponding to the SOX10 gene variant in this study was highly conserved among homologous species, which proved that p.G26A is an essential site of SOX10 protein and is very important for the protein to fulfill its normal function(figure 8).

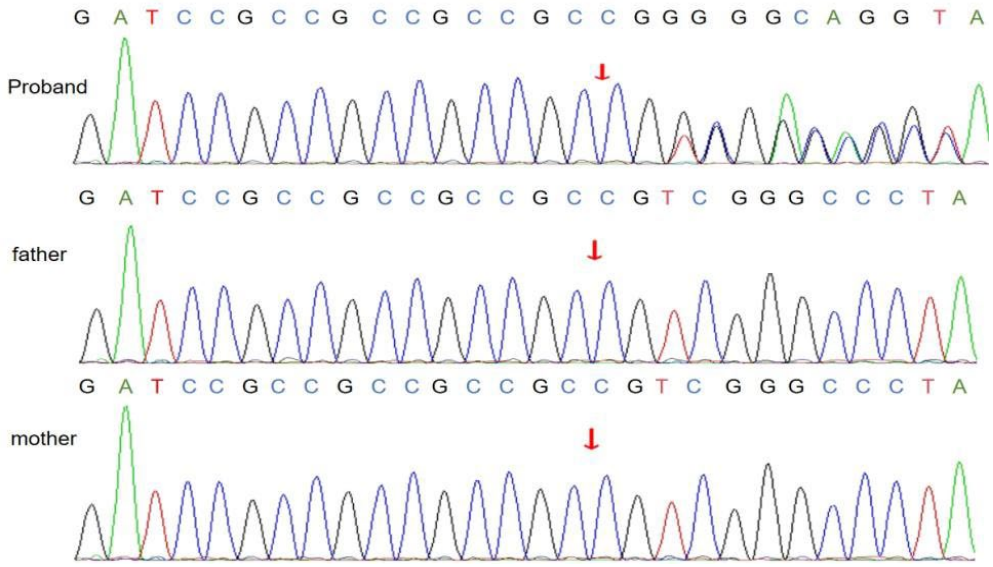

Figure 7: Sanger sequencing

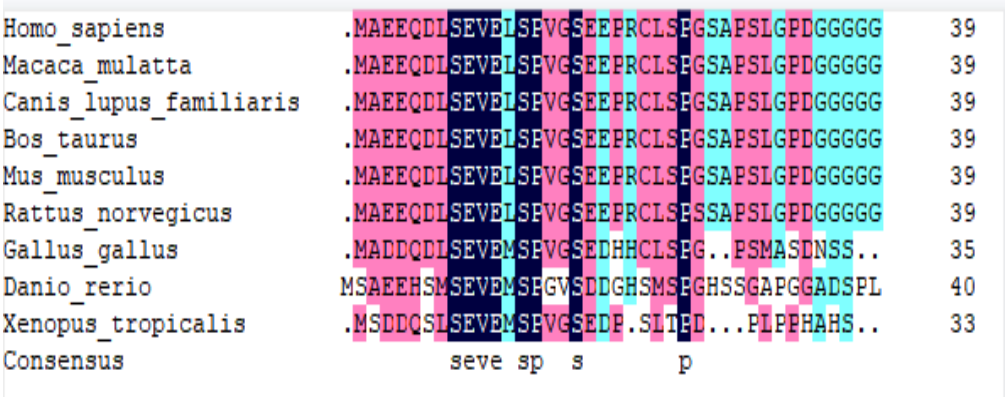

Figure 8: Conservative analysis

3.3. Experimental results

The peripheral blood of the propositus patients and their parents was taken for flow cytometry to evaluate the protein expression levels of SOX10, PAX3, and MITF. As shown in the figure, the green peaks corresponded to the blank control peaks, the red peaks represented the expression of the three proteins in the peripheral blood, and the expression levels of SOX10, PAX3, and MITF proteins were down-regulated in the propositus patients compared with their parents(figure 9).

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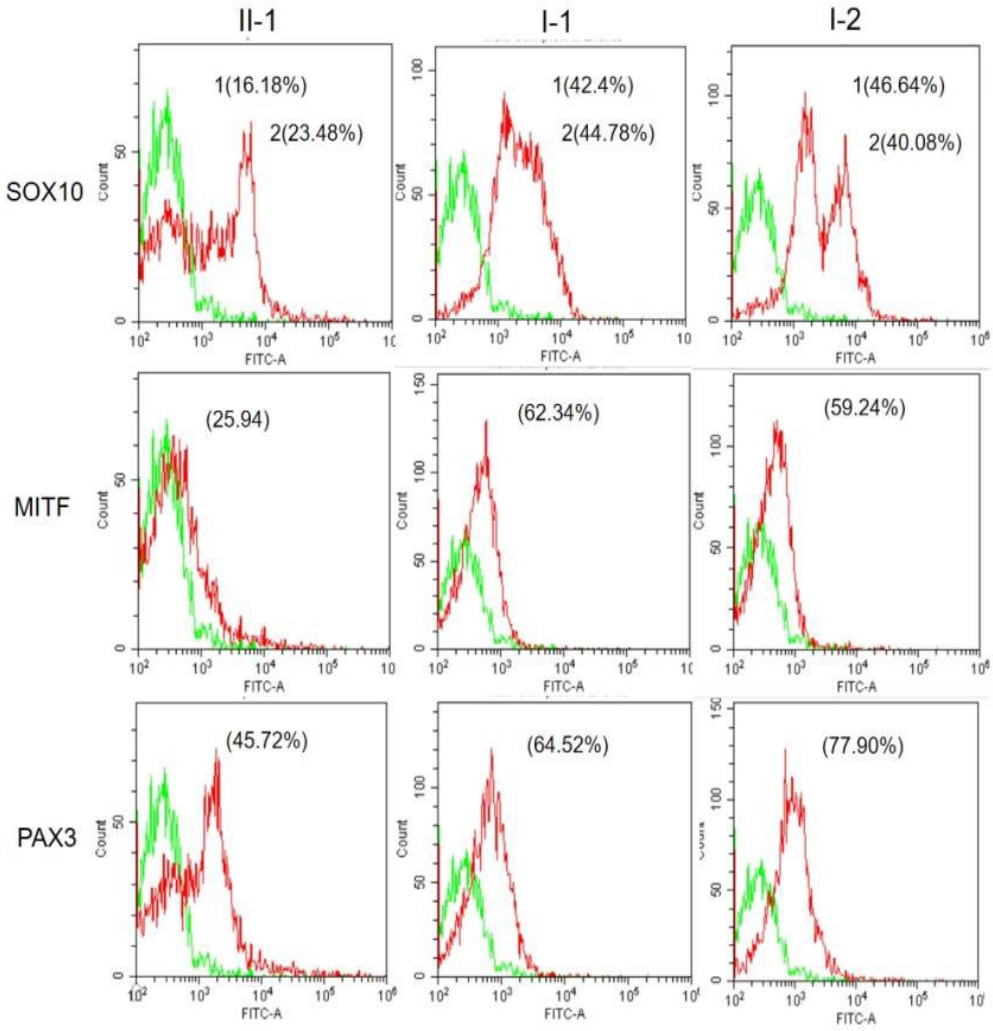

Figure 9: Flow cytometry

4. Discussion

The SOX10 gene encodes a protein that is a transcription factor. The SOX10 gene is located on chromosome 22q13.1 and has five exons, of which exons 3, 4, and 5 are involved in protein-coding. The SOX10 protein consists of 466 amino acids. It contains a DNA-binding HMG (High Mobility Group) structural domain, dimerized region upstream of the HMG structural domain, conserved structural domain at the center, and trans-activating (TA) structural domain at the terminal C-terminus. The HMG structural threshold is homologous to the HMG of the testis determinant SRY; HMG contains 20 transcription factors flanked by nuclear localization signals (NLS) that allow the SOX10 protein to shuttle between the cytoplasm and the nucleus, thus affecting the development of melanocytes or neural crests [12]. SOX10 protein can specifically recognize and bind to target DNA promoters through HMG and further activate DNA transcription through its C-terminal reverse transcription activation domain after binding to target DNA. It can also activate DNA transcription through a specific region before HMG. It can also regulate the activation of DNA recognition by binding to the target DNA through a specific region before HMG forms a dimer. At the same time, SOX10 protein can also synergize with other transcription factors or form complex elements to act on the target DNA to complete the regulation of DNA recognition and activation, and MITF, TYR, TYRP1, DCT, MPZ, GJB1, RET, DCT, and DNRB are the downstream target genes directly regulated by SOX10 protein [13]. The SOX10 gene is involved in the expression of neural crest cell growth. Melanocytes are derived from differentiated neural crest cells and are distributed in the iris and inner ear. Abnormal proliferation, survival, differentiation, or migration of melanocytes may affect hearing and iris color, resulting in WS.

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In this study, we identified a case with one heterozygous mutation in the SOX10 gene: c.77_104delGGAGCGCGCCCTCGCTAGGGCCCGACGG Heterozygous mutation, a deletion of 28 bases after the 77th base in the SOX10 gene, causes frameshift mutations in amino acids (p.G26Afs*74).This preexisting patient had extreme deafness in both ears, heterochromia of the iris, no heterotaxy of the medial canthus, no megacolon, and a diagnosis of WS2. Neither of his parents carried the mutation, which was spontaneous, and the mutation was not included in the population or the gene pool, which is a de novo mutation. The patient also had vestibular and semicircular canal malformations.This mutation results in a truncated SOX10 protein, and the truncated important structural domain, the HMG structural domain, is missing.The HMG structural domain of SOX10 is necessary for binding to MITF, and SOX10 and PAX3 bind to MITF simultaneously to activate the transcriptional activity of MITF.Entry/exit nuclear signaling on the HMG structural domain can drive SOX10 protein to shuttle movement between the nucleus and cytoplasm, and abnormal entry/exit nuclear signaling caused by mutations and deletions can reduce the transcriptional activity of SOX10 [14].In the present study, truncating mutations in SOX10 affected the transcriptional activity of MITF, which resulted in the inner ear vascular stria melanocytes and vestibular and spiral ganglion glial cells being abnormally developed, leading to the Propositus of WS-related phenotypes in the preexisting patients. It is now generally accepted that, at the molecular level, SOX10 may contribute to WS through the following mechanism: after a truncating mutation in SOX10, other wild, unmutated SOX10 proteins may fill in the impaired protein function produced by the mutated SOX10 gene, but in quantities that differ from normal SOX10. The amount of protein required by an individual may vary depending on the amount of residual protein within the individual, thus showing different clinical symptoms; this is the haploinsufficiency effect; in case of a mutation in SOX10, which loses all of its function, the other wild-type SOX10 gene is supposed to retain half of its function, however, in some cases, the mutated SOX10 protein or gene not only loses its normal function but also inhibits the activity of the wild-type protein. This phenomenon of proteins interfering with each other is called the dominant negative effect [15].Mutations in the SOX10 gene, which occur at different sites, have different mechanisms of action and cause different cellular developmental abnormalities and clinical symptoms.Functional redundancy, on the other hand, complements the reasons for the sometimes milder phenotype. The mechanism suggests that SOX10 originates from the SOX-E group of the SOX superfamily, including SOX8, SOX9, and SOX10, which are functionally complementary and similar to SOX10. When a variant of SOX10 results in an abnormal function of the protein it encodes, the other members of the SOX family may fill in or take over the previous function, thus manifesting less severe clinical symptoms [16]. Among the WS caused by different genotypes, the number of inner ear malformations after SOX10 mutations is high [17]. It was found that SOX10 was highly expressed in the ear plate at the beginning of inner ear development, was continuously expressed throughout inner ear development, and maintained the survival and differentiation of cochlear precursor cells. This suggests that in addition to the MITF pathway, which is involved in regulating the development of melanocytes in the inner ear of neural crest origin, there may be other pathways that regulate the development of the inner ear embryo in the mechanism of ear and inner ear malformations caused by mutations in the SOX10 gene. This "bypass pathway" explains why patients with SOX10 mutations in WS are more likely to have inner ear malformations [18-20]. Studies have shown that SOX10 interacts with MITF and PAX3 and that PAX3 and SOX10 activate and up-regulate MITF expression, alone or in concert[21]. SOX10 increases MITF transcription 100-fold by binding to highly conserved sequences in the MITF promoter, and PAX3 enhances this effect[22]. In the present study, flow cytometry was applied, and the down-regulation of MITF and PAX3 protein expression after the SOX10 truncation mutation was initially suggested as the cause of the WS phenotype exhibited by this patient. At present, the clinical diversity and clinical heterogeneity of WS, especially the mechanism of SOX10-causing inner ear malformation, is still not very clear, and it is difficult to explain the proof by some single doctrine; the current in vitro experiments have progressed to the animal experiments, and it is expected that, with the advancement of science and technology, it will be further elaborated in the future to reveal the pathogenic mechanism of WS.

5. Conclusions

This research has found a new case of SOX10 mutation, a spontaneous mutation in the patient that has been preliminarily identified as the cause of the disease. This mutation enriches the mutation spectrum of SOX10.

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