Received: 13 July 2023 | Revised: 6 March 2023 | Accepted: 12 July 2023

DOI: 10.1002/mgg3.2296

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

A novel frameshift mutation in *SOX10* gene induced Waardenburg syndrome type II

Xiuli Ma[1,2] | **Liping Zhao**[1] | **Li Li**[2] | **Xia Li**[1] | **Chaohong Ding**[2] | **Jing Ma**[1]

[1]Department of Otorhinolaryngology Head and Neck Surgery, Kunming Children's Hospital, Kunming, Yunnan, China

[2]Yunnan Institute of Pediatrics, Kunming Children's Hospital, Kunming, Yunnan, China

Correspondence
Jing Ma, Department of Otorhinolaryngology Head and Neck Surgery, Kunming Children's Hospital, 288 Qianxing Road, Xishan, Kunming, Yunnan 650228, China.
Email: majing@etyy.cn

Funding information
National Natural Science Foundation of China, Grant/Award Number: 82060192; Digitalization, Development and Application of Biotic Resource, Grant/Award Number: 202002AA100007; Reserve Talents for Young and Middle-aged Academic and Technical Leaders in Yunnan Province, Grant/Award Number: 2019HB102; Haibo Wang Expert Workstation in Yunnan Province, Grant/Award Number: 202105AF150056; Yunnan Province Clinical Research Center for Children's Health and Disease, Grant/Award Number: N08901146

Abstract

Objective: To explore the molecular etiology of Waardenburg syndrome type II (WS2) in a family from Yunnan province, China.

Methods: A total of 406 genes related to hereditary hearing loss were sequenced using next-generation sequencing. DNA samples were isolated from the peripheral blood DNA of probands. Those pathogenic mutations detected by next-generation sequencing in probands and their parents were validated by Sanger sequencing. The conservatism of variation sites in genes was also analyzed. The protein expression was detected by flow cytometry.

Results: A heterozygous mutation c.178delG (p.D60fs*49) in the *SOX10* gene was identified in the proband, which is a frameshift mutation and may cause protein loss of function and considered to be a pathogenic mutation. This was determined to be a de novo mutation because her family were demonstrated to be wild-type and symptom free. SOX10, FGFR3, SOX2, and PAX3 protein levels were reduced as determined by flow cytometry.

Conclusion: A novel frameshift mutation in *SOX10* gene was identified in this study, which may be the cause of WS2 in proband. In addition, *FGFR3*, *SOX2*, and *PAX3* might also participate in promoting the progression of WS2.

KEYWORDS
hearing loss, *SOX10* gene, Waardenburg syndrome

1 | INTRODUCTION

Waardenburg syndrome (WS) mainly manifested as hearing loss combined with heterochromia iridum, which accounts for about 2%–5% of congenital deafness cases (Read & Valerie, 1997). There are four subtypes of WS (WS1-4) (Pingault et al., 2010): The clinical manifestations of type II WS (WS2, OMIM #193510) are basically the same as type I WS (WS1, OMIM #193500), but without dystopia of the canthus (Ma, Lin, et al., 2019; Zardadi et al., 2021). The clinical manifestations of type III WS (WS3, OMIM #148820) are the same as type I but combined with upper

Xiuli Ma and Liping Zhao are contributed equally to this work.

limb deformity (Hoth et al., 1993), while type IV WS (WS4, OMIM #277580) exhibits basically the same symptoms as type II, but is combined with Hirschsprung disease or gastrointestinal atresia and other gastrointestinal symptoms (Bondurand et al., 2007).

Six gene mutations were found to be associated with WS, including four transcription factors *SOX10*, *PAX3*, *MITF*, and *SNAI2*, and two signaling molecules *EDNRB* and *EDN3* (Issa et al., 2017; Pingault et al., 2014). *SOX10* gene encodes the SRY-BOX 10 transcription factor and is a member of the SOX transcription factor family. Previous studies have shown that *SOX10* heterozygous mutations can lead to WS2 and WS4 (Bondurand et al., 2007), and approximately 15% of WS2 and 45%–55% of WS4 were caused by *SOX10* variants (Elmaleh-Berges et al., 2013; Suzuki et al., 2018).

In this study, a novel frameshift mutation c.178delG (p.D60fs*49) in *SOX10* was identified by next generation sequencing. The p.D60fs*49 mutations resulted in truncation of the mutant SOX10 protein. In addition, *FGFR3*, *SOX2*, and *PAX3* might also participate in promoting the progression of WS2 in this family.

2 | MATERIALS AND METHODS

2.1 | Subjects

The present study was approved by the Medical Ethics Committee of Kunming Children's Hospital. Study participants were collected from the Otology Clinic at Kunming Children's Hospital in June 2022. Four subjects were enrolled in the present study, including the parents and two children (I-1, I-2, II-1, and II-2) of two generations in one family. A comprehensive medical history was collected, and clinical evaluations including otology, ophthalmology, and abdominal examination were conducted. The W index was calculated by the following formula: $X=[2A-(0.2119C+3.909)]/C$; $Y=[2A-(0.249B+3.909)]/B$; $W=X+Y+(A/B)$, where A is the inner canthal distance, B is the interpupillary distance, and C is the outer canthal distance. Clinical information and DNA samples of all subjects were obtained with informed consent and in accordance with Chinese law for genetic testing.

2.2 | Sequencing

Peripheral blood samples were collected from all members of this family and healthy controls. Genomic DNA was extracted with the TIANamp Blood DNA Kit (TianGen, Beijing, China). The target DNA regions of subjects were enriched by the GenCap custom enrichment kit (MyGenostics Inc., Beijing, China). Then, NGS was conducted, of which the resultant raw image files were processed for bioinformatics analysis. Through the filtering of variants, the (c.178delG, p.D60fs*49) mutation in *SOX10* gene (NM_006941.4) was filtered out. It should be the 'pathogenic' mutation based on the criteria in ACMG guidelines (Richards et al., 2015). Genomic DNA from all family members was obtained, *SOX10* PCR product was sequenced by Sanger Sequencing (Biosune).

2.3 | Flow cytometry

Previously, flow cytometry has been utilized for protein expression detection and the findings and outcomes of these studies suggest that flow cytometry is a feasible method for detecting protein expression (Bachelet et al., 1998; Kim et al., 2012; Wasik et al., 2015). The expression of SOX10, SOX2, FGFR3, and PAX3 proteins in peripheral blood lymphocytes of the subjects and family members were detected by flow cytometry. Peripheral blood mononuclear cells were isolated from blood samples of family members using a human peripheral blood lymphocyte isolation solution protocol (Shanghai Yes Service Biotech). The cells were fixed at room temperature with 4% paraformaldehyde for 15 min. Cells were washed with 1× PBS at 1500 rpm for 5 min. 1×10^6 cells were added with about 100 μL IntraPrep Permeabilization Reagent (Beckmancoulter), the cells were suspended, and the membrane was broken at room temperature for 15 min. Cells were washed with 1× PBS at 1500 rpm for 5 min. 1×10^6 cells were divided into flow tubes, and 20 μL of primary antibody was added after dilution according to the manufacturer's instructions, thoroughly mixed, reaction at room temperature for 1 h. Cells were washed three times with 1× PBS at 1500 rpm for 5 min each. A volume of 20 μL dilute fluorescently labeled secondary antibody was added to the cells, thoroughly mixed, reaction at room temperature and away from light for 30 min. Cells were washed three times with 1× PBS at 1500 rpm for 5 min each. A volume of 100–200 μL PBS buffer was added to the cells, followed by analysis on a Beckman Coulter DxFLEX flow cytometer, resulting data were analyzed using CytExpert software.

3 | RESULTS

3.1 | Clinical features of the patients with WS2

The family in this study has four members of two generations (Figure 1). The proband (II-2) was a female, 2 years old, of Han nationality, had a poor response to voice after

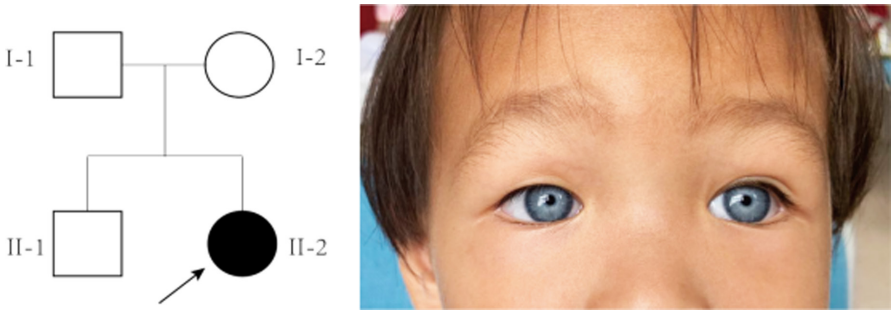

FIGURE 1 Family pedigree and main clinical features of the proband. Heterochromia iridis and hair hypopigmentation were observed in the proband (II-2), her father (I-1), mother (I-2), and brother (II-1) have normal phenotypes.

birth, failed with the hearing screening, had bright blue irises on both sides and yellowish hair (Figure 1). The proband was diagnosed with severe bilateral sensorineural hearing loss. Clinical audiological examination showed failed bilateral otoacoustic emission, auditory steady-state response threshold >95 dB hearing level (HL) under 500–4000 Hz and with bilateral ABR threshold >85 dB HL (Figure 2). Clinical audiological examination showed failed bilateral otoacoustic emission. Binaural tympanic impedance diagram for A-type, the temporal bone CT (Figure S1), cranial MRI, and abdominal ultrasound showed no obvious abnormalities. The semicircular canals of the child were normal (Figure S2), and he had normal balance. The interpupillary distance was 5.2 cm, the inner canthal distance was 3.0 cm, and the outer canthal distance was 7.6 cm ($W = 1.85 < 1.95$). The proband was diagnosed with WS2 according to the WS diagnostic criteria.

3.2 | The heterozygous mutation (c.178delG) in *SOX10* is the pathogenic mutation in patients of the WS2 family

A heterozygous mutation of c.178delG on exon 2 of *SOX10* gene (NM 006941) was found in the peripheral blood genomic DNA of the proband. Sanger sequencing of the *SOX10* gene in the genome of her parents and sister verified that there was no mutation at this locus, *SOX10* c.178delG of the proband was a de novo mutation (Figure 3a). The mutation was found at the site c.178delG of *SOX10* and caused a frameshift for 49 codons, as well as alteration of the subsequent amino acids (p.D60Tfs*49), which is located in the HMG domain (102–181 amino acids). The stop codon in the 109th amino acid appeared early so that it almost completely deleted all HMG domains, resulting in the large fragment of the SOX10 protein truncation (Figure 3b). This variant was preliminarily assessed as pathogenicity (PVS1 + PS1 + PS2 + PM2) in accordance with the American Society of Medical Genetics and Genomics (ACMG) guidelines. Since the mutation is a frameshift mutation, which often results in protein truncation and may lead to the loss of function of SOX10 protein (PVS1). The novel variants identified in this study have the same amino acid change as a previously established pathogenic variant regardless of nucleotide change (PS1). This is considered a de novo mutation as there is no mutation in the proband's family at this specific site (PS2). We used the second-generation sequencing method with a sequencing depth of more than 1000× to detect the chimerism ratio of *SOX10* c.178delG (p.D60fs*49) mutation in the peripheral blood DNA of the children and their parents. The following results were obtained: A total of 70,164 reads were detected from peripheral blood DNA samples collected from children in this cohort. Among these, 33,660 reads showed the presence of *SOX10* c.178delG (p.D60fs*49) mutation with a mutation rate of 47.97% (Figure S3). And the locus of the parents was wild type, indicating that the detected mutation in the child is de novo. The mutation is of low frequency and not present in the normal population database (PM2). Furthermore, there are no reports related to this locus in the literature database. The ClinVar database lacks pathogenicity analysis results for this locus. In order to detect the mutation sites of the *SOX10* gene, 200 healthy controls were randomly selected from the central DNA library. The results showed that the above mutations were not detected in any of the healthy controls, which excluded the possibility of polymorphic sites.

3.3 | Expression of SOX10, SOX2, FGFR3, and PAX3 in peripheral blood of the family

To confirm alterations in protein expression resulting from gene mutations, flow cytometry was employed to assess protein expression levels. As shown in Figure 4, the red peak corresponded to the blank control peak, and the green peak represented the expression of four proteins in the peripheral blood. The peak values are shown in Figure 4. Compared with the three family members (I-1, I-2, and II-1), the flow cytometry results of the proband (II-2) shown two peaks and the expression of SOX10, FGFR3, and PAX3 protein were down-regulated in this family, while the flow cytometry results of SOX2 protein showed only one peak. In addition, the expression of the proband (II-2) was also slightly lower than that of her three family

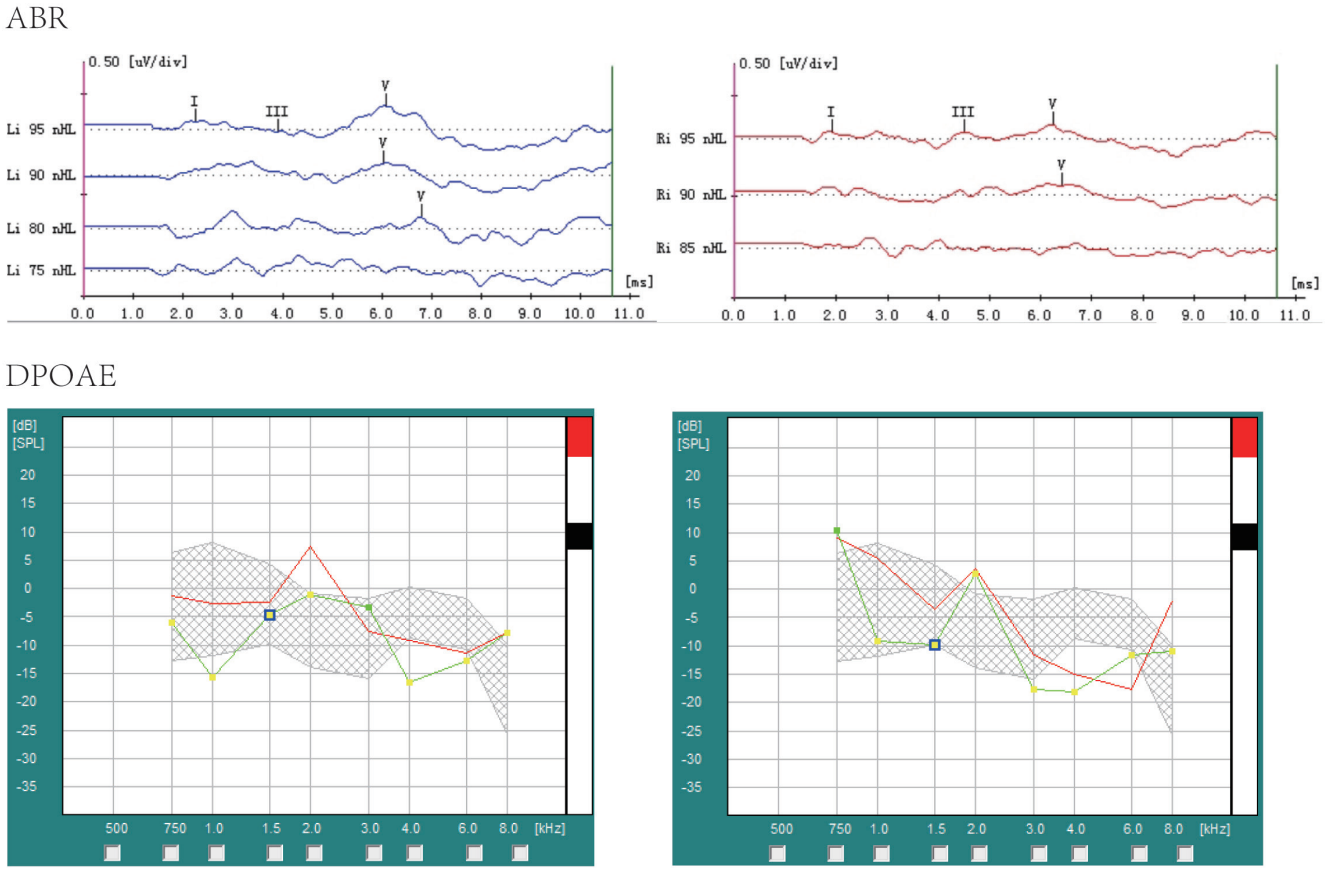

FIGURE 2 Audiological examination of the proband. Results of auditory brainstem evoked potential examination and distortion product otoacoustic emission indicated severe hearing impairment.

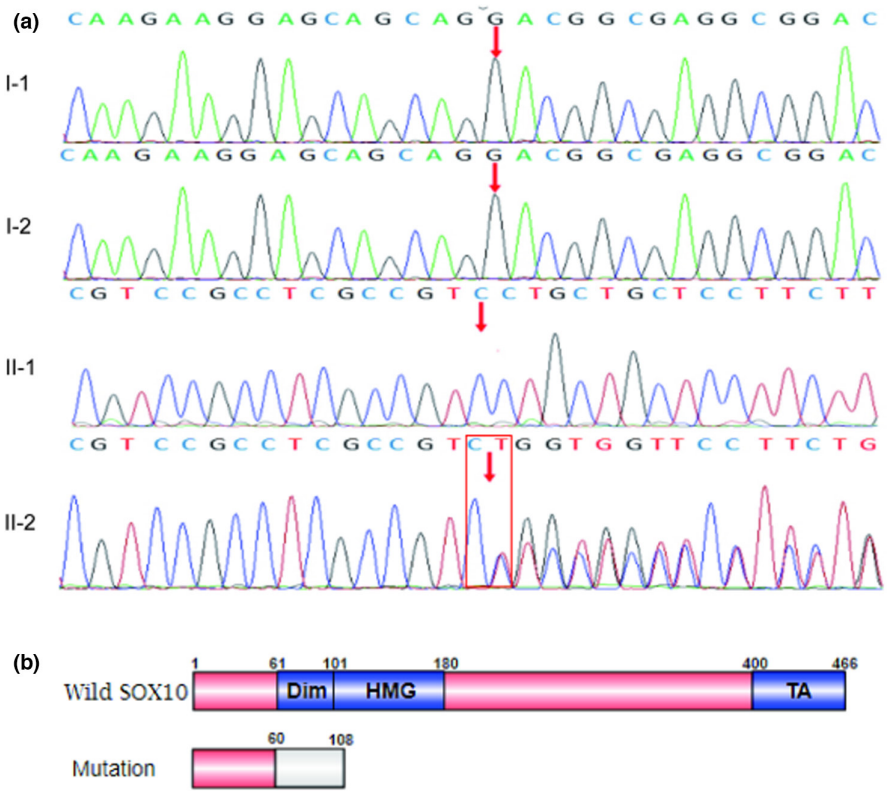

FIGURE 3 Mutation on *SOX10* in WS2 family and the Schematic representation of *SOX10* gene. (a) Genetic sequencing results of the proband and her parents. The red arrow indicates the site of the base deletion at c.178delG in *SOX10*. (b) The mutation caused early termination of the coding sequence.

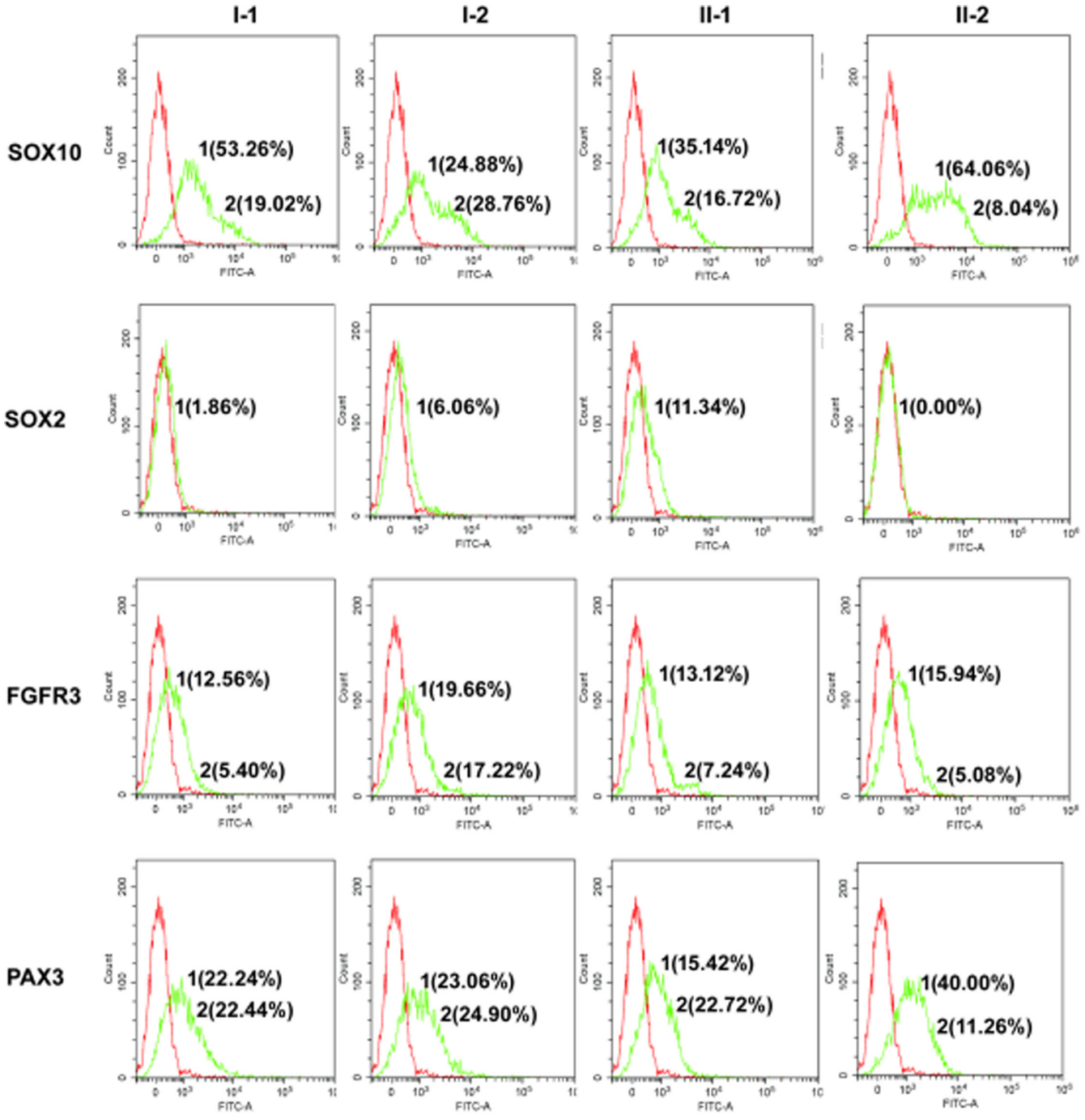

FIGURE 4 Expression of SOX10, SOX2, FGFR3, and PAX3 in peripheral blood lymphocytes of the family. The red peak corresponded to the blank control peak. The green peak represents the expression of four proteins in peripheral blood of the families (from left to right: I-1, I-2, II-1, II-2).

members. The most obvious alteration among the four proteins was the expression of SOX10 protein.

4 | DISCUSSION

Sex determining region-related transcription factor 10 (SRY-BOX 10, *SOX10*), 22q13.1, a member of the *SOX* gene superfamily, plays a key regulatory role in neural crest development and is widely expressed in multiple tissues and organs of the human body, including the inner ear (Pingault et al., 2022). In 1993, Wright et al. (1993) made the initial discovery and subsequent report of the *SOX10* gene in mouse tissue RNA from embryos at 11.5 days gestation and beyond. The cDNA has a full length of 1.4 kb and contains five exons, of which only the third, fourth, and fifth exons encode a total of 466 amino acids proteins. The SOX10 protein contains four domains: high-mobility

group (HMG), nuclear localization signal (NLS), Group E domain and a C-terminal transcriptional activation (TA) domain (Arnheiter, 2010; Pingault et al., 2010). The HMG domain is composed of 80 amino acids at the position of 102–181 and is highly conserved. It contains three 'L'-shaped curved α-helix regions, which are necessary for the SOX10 protein to mediate downstream target protein interactions (Yu et al., 2020). The HMG active domain can recognize and regulate downstream target genes (*MITF*, *MPZ*, *GJB1*, *TYR*, *TYRP1*, *DCT*, *RET*, *DCT*, and *EDNRB*), and combine them with enhancers or promoters to exert their transcriptional regulatory functions, resulting in DNA degradation. The conformational change of SOX10 protein can directly or indirectly affect the synthesis of melanin (Song et al., 2016).

Conventionally, it is postulated that a *SOX10* gene mutation exclusively results in WS4 or PCWH. Bondurand et al. (2007) for the first time found a *SOX10* mutation can cause WS2. With the advancement of sequencing technology, it has been discovered that approximately 15% of cases with WS2 are attributed to mutations in the SOX10 gene. In addition, Sun et al. (2016) found that the incidence of *SOX10* gene mutations in the Chinese Han population with WS2 was as high as 45% (13/29). In recent years, there were three deafness patients with *SOX10* gene mutations identified by our team, those all diagnosed with WS2 (Li et al., 2021; Ma et al., 2016; Ma, Zhang, et al., 2019). As of December 2021, there are a total of 184 *SOX10* gene mutations in the HGMD professional database, of which 47 *SOX10* mutations cause WS2. In this family, only the proband with a heterozygous mutation in the *SOX10* gene c.178delG, which is considered to be a de novo mutation because neither his parents nor sisters have the corresponding mutation. If the proband has a de novo pathogenic variant and the parents cannot rule out germ cell mosaicism, prenatal diagnosis is recommended in future pregnancies to determine whether the fetus carries this variant. The *SOX10* gene variation of the proband is a frameshift mutation and truncates the protein in advance, the truncation position is located in the HMG domain (102–181 amino acids), which may cause an insufficient haploid dose after SOX10 mutation. On the other hand, HMG is a DNA binding domain that can directly or indirectly bind to the cis-acting element of the target gene's promoter to regulate the expression of the target gene (Pingault et al., 2022). The SOX10 mutant protein lacking the HMG domain cannot bind to DNA, resulting in a decrease in the transcription level of the downstream target gene, which promotes the occurrence of disease.

Whenever a complex disease occurs, it is not only due to a mutation caused by a single pathogenic gene. Often, a gene or protein may interact with other genes or proteins in addition to performing its own role in the body. When one gene is mutated, its protein function is affected, and the expression and function of other interacting proteins are also prone to change, resulting in the emergence of syndrome. In the present study, deficient expression of the SOX10, SOX2, FGFR3, and PAX3 proteins were detected in this family. The diseases caused by *FGFR3* and *PAX3* mutations were autosomal dominant lacrima-otodont-finger syndrome (LADD) and WS, respectively (Talebi et al., 2017; Wollnik et al., 2003). *SOX2* is a crucial transcription factor in the development of hearing, predominantly expressed in cochlear glial cells and playing a pivotal role in hair cell differentiation (Chen et al., 2021; Dabdoub et al., 2008). The FGFR3 protein plays a central role in pillar cells and supporting cell differentiation, with its mutation resulting in an autosomal dominant disorder characterized by sensorineural hearing loss, accompanied by the typical facial and skeletal manifestations (Hayashi et al., 2007). In addition, defects in PAX3 proteins have also been detected. *PAX3* plays a vital role in the development and differentiation of melanocytes derived from embryonic neural crest cells (NCC) (Elmaleh-Berges et al., 2013). The melanocyte originates from the NCC, which exists in the human cochlea, eyes, and skin. Melanocytes in the iris and stria vascularis contribute to eye color variation and hearing, respectively (Shields et al., 2013; Tachibana, 2001).

In conclusion, as a crucial transcription factor in migration and differentiation of NCC, *SOX10* can act independently or in concert with other target genes. The research conducted on the pathogenesis of this family can help us find more pathogenic molecular mechanisms associated with deafness and abnormal pigmentation, as well as facilitate the diagnosis and discovery of new mutations in WS-related genes. Furthermore, the follow-up mechanism and more case-based research will be continued to provide more valuable supporting data to elucidate the development mechanism of WS pathogenesis.

AUTHOR CONTRIBUTIONS

Xiuli Ma: Project administration, experiment design, experiments performed and data collection and processing, resources, writing (original draft preparation), writing (review and editing), and final approval of the article. *Liping Zhao*: Project administration, experiment design, experiment performed and data collection and processing, resources, writing (original draft preparation), writing (review and editing), and final approval of the article. *Li Li*: Experiment performed and data collection and processing. *Xia Li*: Experiment performed and data collection and processing. *Chaohong Ding*: Experiment performed and data collection and processing. *Jing Ma*: Project administration, experiment design, resources, supervision, and final approval of the article.

ACKNOWLEDGMENTS

We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

FUNDING INFORMATION

National Natural Science Foundation of China (82060192); Digitalization, Development and Application of Biotic Resource (202002AA100007); Reserve Talents for Young and Middle-aged Academic and Technical Leaders in Yunnan Province (2019HB102); Haibo Wang Expert Workstation in Yunnan Province (202105AF150056).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of the present study are included within the article.

ETHICS STATEMENT AND CONSENT TO PARTICIPATE

The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants enrolled in the present study. The mother of the proband provided consent for the publication of images of the proband.

REFERENCES

Arnheiter, H. (2010). The discovery of the microphthalmia locus and its gene, Mitf. *Pigment Cell & Melanoma Research*, *23*(6), 729–735.

Bachelet, M., Mariethoz, E., Banzet, N., Souil, E., Pinot, F., Polla, C. Z., Durand, P., Bouchaert, I., & Polla, B. S. (1998). Flow cytometry is a rapid and reliable method for evaluating heat shock protein 70 expression in human monocytes. *Cell Stress & Chaperones*, *3*(3), 168–176.

Bondurand, N., Dastot-Le Moal, F., Stanchina, L., Collot, N., Baral, V., Marlin, S., Attie-Bitach, T., Giurgea, I., Skopinski, L., Reardon, W., Toutain, A., Sarda, P., Echaieb, A., Lackmy-Port-Lis, M., Touraine, R., Amiel, J., Goossens, M., & Pingault, V. (2007). Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. *American Journal of Human Genetics*, *81*(6), 1169–1185.

Chen, Z., Huang, Y., Yu, C., Liu, Q., Qiu, C., & Wan, G. (2021). Cochlear Sox2(+) glial cells are potent progenitors for spiral ganglion neuron reprogramming induced by small molecules. *Frontiers in Cell and Development Biology*, *9*, 728352.

Dabdoub, A., Puligilla, C., Jones, J. M., Fritzsch, B., Cheah, K. S. E., Pevny, L. H., & Kelley, M. W. (2008). Sox2 signaling in prosensory domain specification and subsequent hair cell differentiation in the developing cochlea. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(47), 18396–18401.

Elmaleh-Berges, M., Baumann, C., Noël-Pétroff, N., Sekkal, A., Couloigner, V., Devriendt, K., Wilson, M., Marlin, S., Sebag, G., & Pingault, V. (2013). Spectrum of temporal bone abnormalities in patients with Waardenburg syndrome and SOX10 mutations. *AJNR. American Journal of Neuroradiology*, *34*(6), 1257–1263.

Hayashi, T., Cunningham, D., & Bermingham-Mcdonogh, O. (2007). Loss of Fgfr3 leads to excess hair cell development in the mouse organ of Corti. *Developmental Dynamics*, *236*(2), 525–533.

Hoth, C. F., Milunsky, A., Lipsky, N., et al. (1993). Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). *American Journal of Human Genetics*, *52*(3), 455–462.

Issa, S., Bondurand, N., Faubert, E., Poisson, S., Lecerf, L., Nitschke, P., Deggouj, N., Loundon, N., Jonard, L., David, A., Sznajer, Y., Blanchet, P., Marlin, S., & Pingault, V. (2017). EDNRB mutations cause Waardenburg syndrome type II in the heterozygous state. *Human Mutation*, *38*(5), 581–593.

Kim, J., Jimenez-Mallebrera, C., Foley, A. R., Fernandez-Fuente, M., Brown, S. C., Torelli, S., Feng, L., Sewry, C. A., & Muntoni, F. (2012). Flow cytometry analysis: A quantitative method for collagen VI deficiency screening. *Neuromuscular Disorders*, *22*(2), 139–148.

Li, L., Ma, J., He, X. L., Zhou, Y.-t., Zhang, Y., Chen, Q.-d., Zhang, L., Ruan, B., & Zhang, T.-S. (2021). Waardenburg syndrome type II in a Chinese pedigree caused by frameshift mutation in the SOX10 gene. *Bioscience Reports*, *41*(6), 1–12.

Ma, J., Lin, K., Jiang, H. C., et al. (2019). A novel mutation of the PAX3 gene in a Chinese family with Waardenburg syndrome type I. *Molecular Genetics & Genomic Medicine*, *7*(7), e00798.

Ma, J., Zhang, T. S., Lin, K., Sun, H., Jiang, H.-C., Yang, Y.-L., Low, F., Gao, Y.-Q., & Ruan, B. (2016). Waardenburg syndrome type II in a Chinese patient caused by a novel nonsense mutation in the SOX10 gene. *International Journal of Pediatric Otorhinolaryngology*, *85*, 56–61.

Ma, J., Zhang, Z., Jiang, H. C., Sun, H., Ming, C., Zhao, L.-P., Gao, Y.-Q., Li, Z.-C., Sun, M.-H., Xiao, Y., Wu, G.-L., Zhang, T.-S., & Ruan, B. (2019). A novel dominant mutation in the SOX10 gene in a Chinese family with Waardenburg syndrome type II. *Molecular Medicine Reports*, *19*(3), 1775–1780.

Pingault, V., Ente, D., Dastot-Le Moal, F., Goossens, M., Marlin, S., & Bondurand, N. (2010). Review and update of mutations causing Waardenburg syndrome. *Human Mutation*, *31*(4), 391–406.

Pingault, V., Pierre-Louis, L., Chaoui, A., Verloes, A., Sarrazin, E., Brandberg, G., Bondurand, N., Uldall, P., & Manouvrier-Hanu, S. (2014). Phenotypic similarities and differences in patients with a p.Met112Ile mutation in SOX10. *American Journal of Medical Genetics. Part A*, *164A*(9), 2344–2350.

Pingault, V., Zerad, L., Bertani-Torres, W., & Bondurand, N. (2022). SOX10: 20 years of phenotypic plurality and current understanding of its developmental function. *Journal of Medical Genetics*, *59*(2), 105–114.

Read, A. P., & Valerie, E. N. (1997). Waardenburg syndrome. *Journal of Medical Genetics*, *34*(8), 656–665.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & ACMG Laboratory Quality Assurance Committee. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, *17*(5), 405–424.

Shields, C. L., Nickerson, S. J., Al-Dahmash, S., & Shields, J. A. (2013). Waardenburg syndrome: Iris and choroidal hypopigmentation: Findings on anterior and posterior segment imaging. *JAMA Ophthalmology*, *131*(9), 1167–1173.

Song, J., Feng, Y., Acke, F. R., Coucke, P., Vleminckx, K., & Dhooge, I. J. (2016). Hearing loss in Waardenburg syndrome: A systematic review. *Clinical Genetics*, *89*(4), 416–425.

Sun, L., Li, X., Shi, J., Pang, X., Hu, Y., Wang, X., Wu, H., & Yang, T. (2016). Molecular etiology and genotype-phenotype correlation of Chinese Han deaf patients with type I and type II Waardenburg syndrome. *Scientific Reports*, *6*, 35498.

Suzuki, N., Mutai, H., Miya, F., Tsunoda, T., Terashima, H., Morimoto, N., & Matsunaga, T. (2018). A case report of reversible generalized seizures in a patient with Waardenburg syndrome associated with a novel nonsense mutation in the penultimate exon of SOX10. *BMC Pediatrics*, *18*(1), 171.

Tachibana, M. (2001). Cochlear melanocytes and MITF signaling. *The Journal of Investigative Dermatology. Symposium Proceedings*, *6*(1), 95–98.

Talebi, F., Mardasi, F. G., Asl, J. M., Bavarsad, A. H., & Tizno, S. (2017). Identification of a novel missence mutation in FGFR3 gene in an Iranian family with LADD syndrome by next-generation sequencing. *International Journal of Pediatric Otorhinolaryngology*, *97*, 192–196.

Wasik, A. M., Priebe, V., Lord, M., Jeppsson-Ahlberg, Å., Christensson, B., & Sander, B. (2015). Flow cytometric analysis of SOX11: A new diagnostic method for distinguishing B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma from mantle cell lymphoma. *Leukemia & Lymphoma*, *56*(5), 1425–1431.

Wollnik, B., Tukel, T., Uyguner, O., Ghanbari, A., Kayserili, H., Emiroglu, M., & Yuksel-Apak, M. (2003). Homozygous and heterozygous inheritance of PAX3 mutations causes different types of Waardenburg syndrome. *American Journal of Medical Genetics. Part A*, *122A*(1), 42–45.

Wright, E. M., Snopek, B., & Koopman, P. (1993). Seven new members of the Sox gene family expressed during mouse development. *Nucleic Acids Research*, *21*(3), 744.

Yu, Y., Liu, W., Chen, M., Yang, Y., Yang, Y., Hong, E., Lu, J., Zheng, J., Ni, X., Guo, Y., & Zhang, J. (2020). Two novel mutations of PAX3 and SOX10 were characterized as genetic causes of Waardenburg syndrome. *Molecular Genetics & Genomic Medicine*, *8*(5), e1217.

Zardadi, S., Rayat, S., Doabsari, M. H., Alishiri, A., Keramatipour, M., Shahri, Z. J., & Morovvati, S. (2021). Four mutations in MITF, SOX10 and PAX3 genes were identified as genetic causes of waardenburg syndrome in four unrelated Iranian patients: Case report. *BMC Pediatrics*, *21*(1), 70.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ma, X., Zhao, L., Li, L., Li, X., Ding, C., & Ma, J. (2023). A novel frameshift mutation in *SOX10* gene induced Waardenburg syndrome type II. *Molecular Genetics & Genomic Medicine*, *12*, e2296. https://doi.org/10.1002/mgg3.2296