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CASE REPORT

Autosomal dominant non-syndromic hearing loss caused by a novel mutation in *MYO7A*: A case report and review of the literature

Cai-Feng Xia, Rong Yan, Wen-Wen Su, Yu-He Liu

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Abstract

BACKGROUND

Variants in the *MYO7A* gene commonly result in Usher syndrome, and in rare cases lead to autosomal dominant non-syndromic deafness (DFNA11). Currently, only nine variants have been reported to be responsible for DFNA11 and their clinical phenotypes are not identical. Here we present a novel variant causing DFNA11 identified in a three-generation Chinese family.

CASE SUMMARY

The proband was a 53-year-old Han male who presented with post-lingual bilateral symmetrical moderate sensorineural hearing loss. We learned from the patient's medical history collection that multiple family members also had similar hearing loss, generally occurring around the age of 40. Subsequent investigation by high-throughput sequencing identified a novel *MYO7A* variant. To provide evidence supporting that this variant is responsible for the hearing loss in the studied family, we performed Sanger sequencing on 11 family members and found that the variant co-segregated with the deafness phenotype. In addition, the clinical manifestation of the 11 affected family members was found to be late-onset bilateral slowly progressive hearing loss, inherited in this family in an autosomal dominant manner. None of the affected family members had visual impairment or vestibular symptoms; therefore, we believe that this novel *MYO7A* variant is responsible for the rare DFNA11 in this family.

CONCLUSION

We report a novel variant leading to DFNA11 which further enriches the collection of *MYO7A* variants, and our review of the nine previous variants that have been identified to cause DFNA11 provides a reference for clinical genetic counseling.

Key Words: Autosomal dominant hearing loss; *MYO7A* gene; Non-syndromic hearing loss; Variant; Hereditary hearing loss; Case report

Core Tip: Autosomal dominant non-syndromic hearing loss caused by the *MYO7A* variant (DFNA11) is rare and characterized by post-lingual sensorineural hearing loss with no or mild vestibular dysfunction. To date, only nine variants have been identified to be responsible for DFNA11. Here we present a novel variant (c.1531G>A) causing DFNA11 identified in a three-generation Chinese family. Progressive hearing loss is the only clinical manifestation in this family, and the onset age of affected members is later and more concentrated than that of other DFNA11 families. Our findings further enrich the collection of *MYO7A* mutations, and our review of the nine reported DFNA11 families can provide a reference for clinical genetic counseling.

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INTRODUCTION

Hearing loss is the most common clinical manifestation in otology, with both genetic and environmental etiologies. Genetic factors account for approximately 60% of cases[1,2]. To date, more than 150 genes have been linked to hearing loss (https://hereditaryhearingloss.org), including *GJB2, GJB3, SLC26A4*, and *MYO7A*. *MYO7A* is located at 11q13.5, has 49 exons encoding 2215 amino acids, and is mainly expressed in the inner ear, retina, testis, lungs, and kidneys[3]. Variants in *MYO7A* can cause both syndromic (Usher syndrome)[4-6] and non-syndromic deafness, with the latter including autosomal dominant (DFNA11) and autosomal recessive (DFNB2) inheritance patterns[7-9].

Usher syndrome is the most common consequence of *MYO7A* variants, in which patients experience congenital sensorineural hearing loss, progressive retinitis pigmentosa, and vestibular dysfunction. Furthermore, severe cases can lead to deaf-mutism, total blindness, intellectual disability, and other disorders[10,11]. In contrast, the clinical symptoms of DFNB2 caused by the *MYO7A* gene variant are milder than those of Usher syndrome and are mainly characterized by congenital sensorineural hearing loss and vestibular dysfunction. A study by Astuto *et al*[12] found late-onset mild visual impairment in members of a family with DFNB2. Hence, the authors determined that DFNB2 and Usher syndrome are different stages of the same disease. However, this conclusion remains controversial, and visual impairment is still commonly used as the primary criterion to distinguish syndromic from non-syndromic hearing loss caused by *MYO7A*. Moreover, DFNA11 is the rarest consequence of the *MYO7A* gene variant and mainly manifests as delayed post-lingual sensorineural hearing loss. Most patients with DFNA11 present with mild or no vestibular dysfunction, but all cases exhibit normal vision[13,14]. To date, no specific association between clinical manifestations and variant location has been found, and only nine variants have been identified as causing DFNA11. The rarity of DFNA11 combined with its occult and atypical clinical manifestations makes the diagnosis of DFNA11 more challenging.

Here, we describe a novel variant in the *MYO7A* gene (c.1531G>A) that caused DFNA11 in a three-generation Chinese family. All affected members of this family presented with bilateral progressive sensorineural hearing loss beginning in adulthood. Additionally, we provide a summary of the clinical and genetic features observed in previously reported families with DFNA11.

CASE PRESENTATION

Chief complaints

The proband was a 53-year-old Han male who sought treatment at the outpatient clinic of Peking University First Hospital for progressive hearing loss in both ears, manifested for more than 10 years.

History of present illness

The patient presented with bilateral hearing loss that began around the age of 40 and gradually affected daily listening and communication. There were no vestibular disorders such as vertigo or unsteady walking.

History of past illness

The patient had no history of past illness.

Personal and family history
The patient had no history of noise exposure, otitis media, or ototoxic drug use. However, it was understood that several of the patient's family members had similar symptoms, with slowly progressive bilateral hearing loss, also beginning around the age of 40. Therefore, we contacted 11 additional members of the patient's family (including four members experiencing hearing loss) and obtained their consent to participate in our study (Figure 1). The first member of the third generation (III:1) had a history of noise exposure for about 20 years because of his work. The remaining 11 family members had no history of noise exposure, otitis media, or ototoxic drug use.

Physical examination
No abnormality was found in the ear examination of the 12 family members.

Laboratory examinations
The proband's routine blood, liver function, renal function, and coagulation function tests showed no obvious abnormalities.

Imaging examinations
Five family members with deafness were examined by high-resolution computed tomography of the temporal bone, and no obvious abnormality was found.

Hearing, vestibular function, and eye examinations
We found that all five affected members had bilateral symmetrical moderate to profound sensorineural hearing loss (Figure 2). The audiograms of the affected family members were flat or slightly sloping, and high-frequency hearing loss was particularly severe. And none of them had vestibular dysfunction or visual impairment.

Genetic analysis
After written informed consent was obtained from all participants or their guardians, peripheral blood samples were collected for genetic analysis. High-throughput sequencing was used for the proband, including the exons of 415 genes, and partial deep intron regions of 147 genes reported by the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/) were also detected. The coverage density of the probe (GenCap deafness gene capture probe V4.0, https://www.mygeno.cn/) was increased in 29 common deafness pathogenic genes, among which *GJB2*, *SLC26A4*, and *POU3F4* were covered in full length. Deafness-related genes in the mitochondrial circular DNA were also detected using GenCap Mitochondrial Loop Gene Capture Probe V1.0 (MyGenostics, Beijing, China). Then five candidate variants were identified in the proband: *MYO7A* (c.1531G>A), *TRIOBP* (c.3689C>T), *WHRN* (c.2090C>T), *USH1C* (1534G>A), and *PDZD7* (c.1529G>A). These variants were annotated using ANNOVAR (v20200607)[15] and compared with the Exome Aggregation Consortium (ExAC, v0.3.1, Broad Institute, United States), 1000 Genomes (http://www.1000genomes.org/), and Genome Aggregation Database (gnomAD, http://www.gnomad-sg.org/) databases. The pathogenicity of the variants was predicted using Rare Exome Variant Ensemble Learner (REVEL, https://sites.google.com/site/revelgenomics/), Mutation Taster (https://www.mutationtaster.org/), and PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/) programs. At the same time, we obtained the spatial structure of the MYO7A protein with AlphaFold2 (https://alphafold.ebi.ac.uk), and then used PyMOL (v2.5.4, Schrodinge, United States) to map and analyze the effect of the mutation on the structure of MYO7A protein. Finally, Sanger sequencing of the remaining 11 family members showed that only *MYO7A* (c.1531G>A) co-segregated with the deafness phenotype. This variant resulted in the conversion of Asp to Asn at position 511 of the MYO7A protein (Figure 3A), an amino acid highly conserved among species (Figure 3B). This variant was not detected in the control group consisting of 200 Chinese Han individuals with normal hearing, or in the ExAC, 1000 Genomes, or gnomAD database. The pathogenicity of this variant was predicted to be "probably damaging" (0.994) by PolyPhen-2, "damaging" (0.853) by REVEL, and "disease-causing" (1.000) by Mutation Taster. As shown in Figure 3C, the Asp at position 511 of wild-type MYO7A protein is located in the motor domain, has three hydrogen bonds with surrounding amino acids, and has electrostatic interaction with Lys at position 515. However, the p.Asp511Asn variant loses one hydrogen bond and the only electrostatic interaction.

FINAL DIAGNOSIS
The phenotype of deafness in this family was typical of late onset and progressive sensorineural hearing loss, which is consistent with that reported in other families with DFNA11. The *MYO7A* (c.1531G>A, p.D511N) variant co-segregated with the deafness phenotype in an autosomal dominant pattern in this family. The variant was not detected in 200 normal hearing controls, or in the ExAC, 1000 Genomes, or gnomAD database. Finally, the variant was predicted to be generally damaging by REVEL, Mutation Taster, and PolyPhen2. The p.511D is highly conserved among species, and PyMOL analysis suggests that the structural stability of the MYO7A protein was destroyed after Asp was replaced by Asn in the variant. Based on the above evidence and following the criteria of the American College of Medical Genetics and Genomics, we diagnosed the affected members of this family with autosomal dominant hearing loss caused by the *MYO7A* (c.1531G>A, p.D511N) variant.

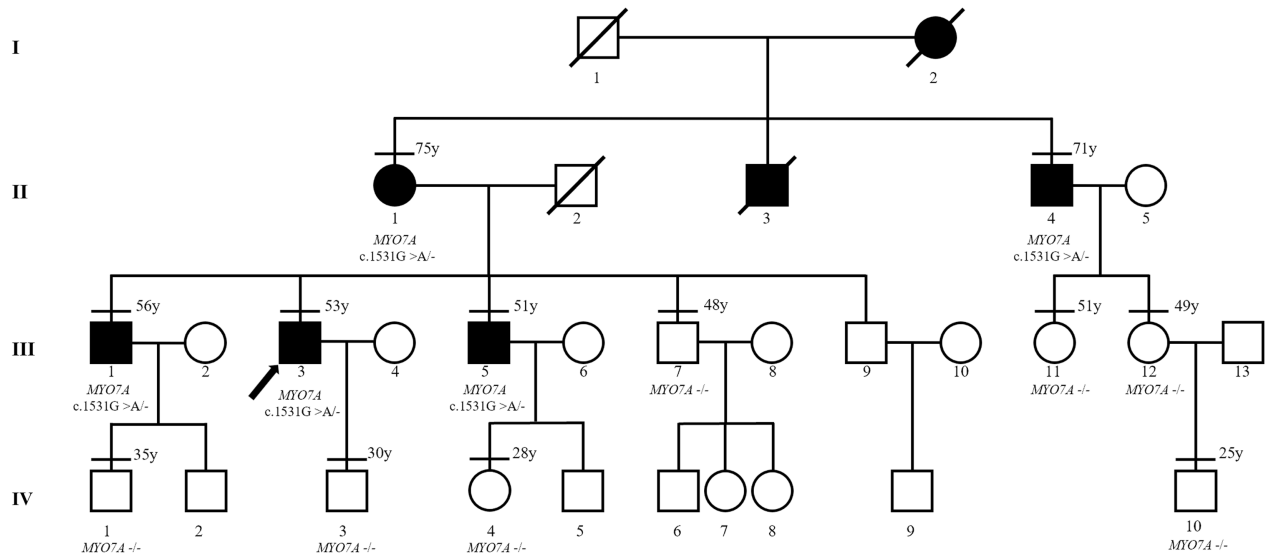

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Figure 1 Pedigree of the DFNA11 family. The arrow indicates the proband. Horizontal lines above the individuals indicate that genetic testing was performed. The age of each subject at the time of genetic testing is listed on the top-right region of each symbol. The genotype of *MYO7A* for each individual is indicated below the symbol, heterozygous mutant: c.1531G>A/- or wild type: -/-.

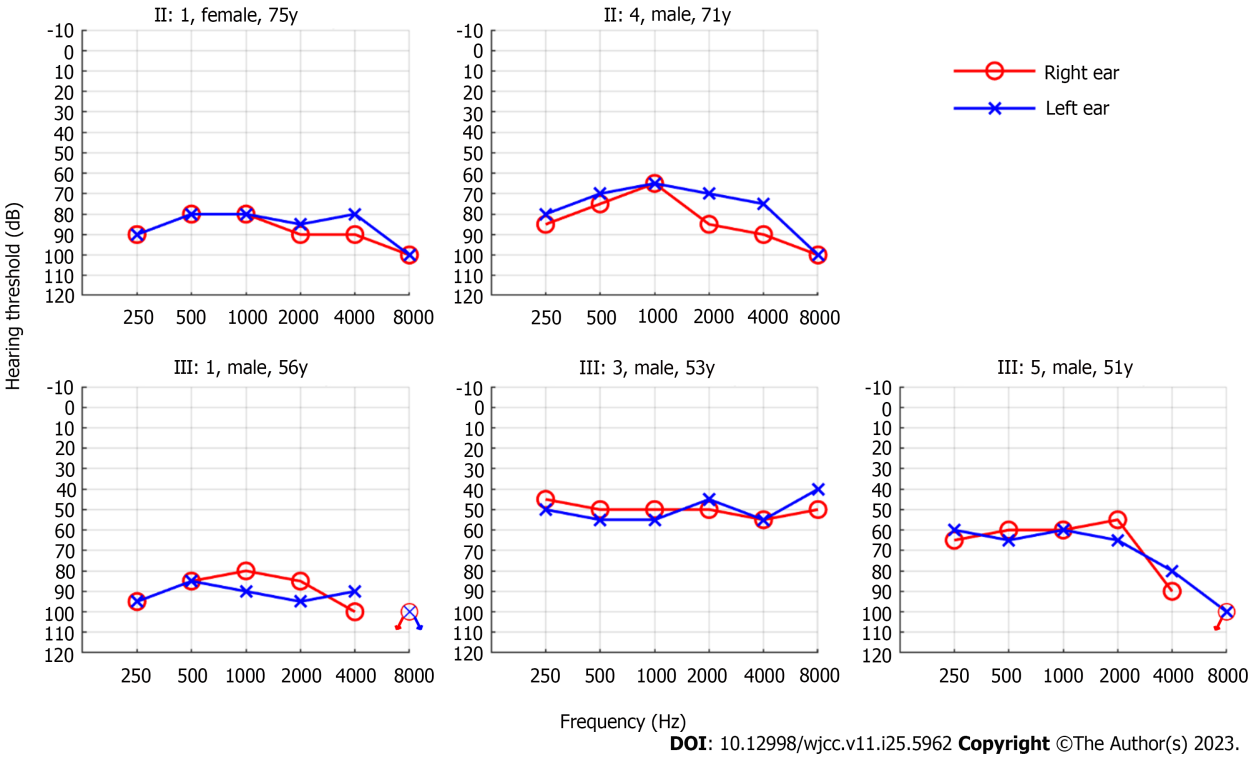

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Figure 2 Pure-tone audiogram of the five affected members in this family. Each person presented bilateral symmetrical moderate-to-profound sensorineural hearing loss, with audiograms that were either flat or slightly downward-sloping at high frequencies. Specifically, III:1 had particularly profound hearing loss owing to occupational noise exposure.

TREATMENT

We advised the five hearing-impaired members to protect their residual hearing by avoiding exposure to noise and ototoxic drugs. In addition, the family members were advised to wear hearing aids to improve hearing and daily communication.

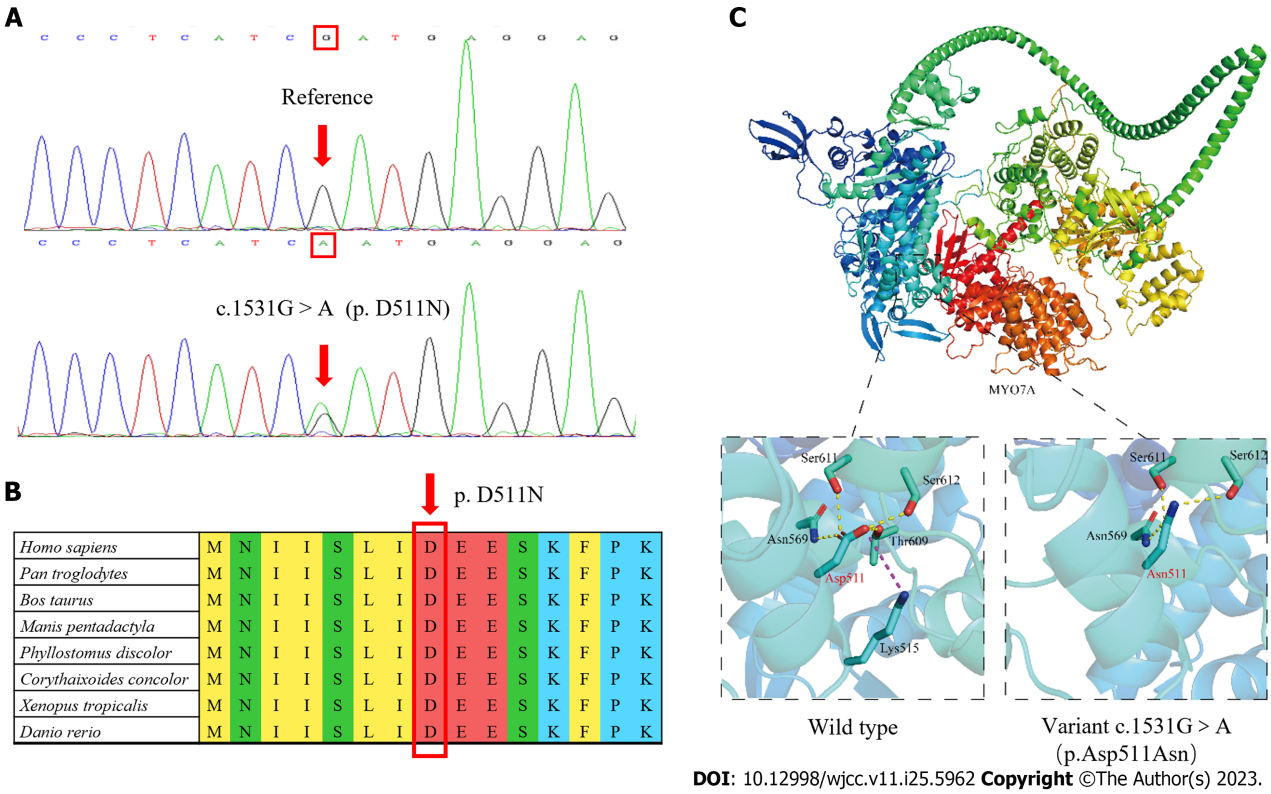

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Figure 3 Location of nucleotide changes and functional analysis of the variant. A: DNA sequence chromatograms. Arrows indicate the site of the mutation, which results in the p.D511N variant; B: Evolutionary conservation of Asp at position 511 (indicated by the arrow) on the MYO7A protein; C: The wild-type and variant (p.D511N) of the MYO7A protein. Yellow dashed lines represent hydrogen bonds between amino acids, and the purple dashed line represent electrostatic interaction between amino acids.

OUTCOME AND FOLLOW-UP

Hearing aids greatly improved the hearing and quality of life for the affected family members, as we learned in our telephone follow-ups 3 mo later. Considering that all participants' hearing loss will progress with age, they were encouraged to make regular follow-up visits and facilitate timely adjustment of hearing aid parameters.

Review of the literature

We searched for articles in the PubMed database published up to December 2022 using the keywords "DFNA11", "*MYO7A*", "autosomal dominant inheritance", and "hearing loss". A total of 11 families with DFNA11, including nine *MYO7A* mutation sites, were identified by genetic analysis. The genotype, hearing status, age of onset, and other information of these families are shown in Table 1[8,13,14,16-22].

DISCUSSION

Since the first family with DFNA11 was reported by Liu *et al* in 1997[8], nine variants from 11 families have been identified to be responsible for DFNA11. The clinical phenotypes of deafness in members of these families with DFNA11 varied; however, most presented with post-lingual progressive sensorineural hearing loss[16,20]. In the family of this study, the affected members presented bilateral symmetrical sensorineural hearing loss. The audiograms of the affected family members were flat or slightly sloping, and high-frequency hearing loss was particularly severe, which is consistent with the symptoms previously reported in families with DFNA11[13,14,20]. In the family of this study, the onset age of hearing loss among affected members was relatively late and concentrated, occurring at around 40 years old. This differs from most reported families with DFNA11, where the age span of onset is larger and hearing loss occurred before adulthood in many cases[14,17,22]. The hearing loss of the second-generation members was generally more severe than that of the third-generation members, which also horizontally reflects that hearing loss progresses with age. However, differences were observed between III:1, III:3, and III:5, who were in the same age group. Although the presence of genetic modifications cannot be excluded[23], environmental effects on the phenotype, such as chronic exposure to noise (*i.e.*, III:1), should also be considered. Therefore, the preservation of residual hearing is one of the important therapeutic measures. Moreover, it is essential to select hearing aid devices according to the hearing threshold and actual needs of each patient, to minimize the impact of DFNA11 on their daily life.

Table 1 Summary of the identified DFNA11 variants

Mutation	Exon	Structure	Patient number	Age of onset (yr)	Audiogram	Vestibular symptoms	Family origin	Ref.
c.2656-2664del/A886-K888Del	22	Coiled coil	8/19	12-16	Flat/sloping	Absent	Japan	[8]
c.652G>A/p.D218N	7	Motor domain	11/29	20-47	Flat/sloping	Absent	China	[13]
c.689C>T/p.A230V	7	Motor domain	1 (sporadic case)	4	U-shaped	Absent	Japan	[16]
c.689C>T/p.A230V	7	Motor domain	9/18	Mean 6-7	Flat/sloping	Bilateral areflexia	Italy	[17]
c.1373A>T/p.N458I	13	Motor domain	11/26	4-43	Ascending-flat-sloping	Vertigo and unsteady walking	Netherlands	[18]
c.2003G>A/p.R668H	17	Motor domain	9/15	17-45	Ascending-flat-sloping	-	China	[19]
c.2011G>A/p.G671S	17	Motor domain	9/23	10-39	Ascending-flat-sloping	Absent	China	[13]
c.2011G>A/p.G671S	17	Motor domain	11/29	13-40	Flat/sloping	Absent	China	[20]
c.2164G>C/p.G722R	17	Motor domain	13/43	20-30	Ascending-flat-sloping	Absent	United States	[21]
c.2557C>T/p.R853C	21	IQ 5	5/12	1 mo to puberty	-	Mild dysfunction	Germany	[22]
c.2558G>A/p.A853H	21	IQ 5	12/23	1-33	Flat/sloping	Absent	Japan	[14]
c.1531G>A/p.D511N	13	Motor domain	5/12	35-42	Flat/sloping	Absent	China	This report

In the inner ear, *MYO7A* is expressed in hair cells, utricles, and semicircular canals and is involved in the transmembrane transport of proteins and functional maintenance of hair cells[24,25]. In the eyes, *MYO7A* is mainly expressed in photoreceptors and pigment epithelial cells and its main function is to transport visual proteins together with connecting cilia[26,27]. Therefore, in most cases, variants in *MYO7A* cause dysfunction in the encoded protein, leading to both sensorineural hearing loss and visual impairment. In the eye, the dysfunctional protein may be compensated by other proteins in the retina[18]; nonetheless, its function in the inner ear is unique[25,28]. Therefore, patients with variants in *MYO7A* can present only hearing loss and mild or no vestibular dysfunction with no ocular symptoms[17,18,22], resulting in rare non-syndromic hearing loss. In the family of this study, the phenotype of hearing loss of the study participants is consistent with an autosomal dominant inheritance pattern, and clinical examination revealed no visual impairment or vestibular symptoms in the affected members. This is consistent with the symptoms reported in families with DFNA11. The only symptom of the studied family was slowly progressive hearing loss, which may also have contributed to the delay in seeking medical attention.

The protein encoded by *MYO7A* belongs to the myosin family, which is composed of three regions: the N-terminal head (motor domain), IQ5 neck, and C-terminal tail, the last of which begins with a single α-helix domain[29,30]. The motor domain contains the binding domains of adenosine triphosphate and actin, which are the core functional areas of the molecule[31]. The variant identified in this study leads to the loss of hydrogen bond and electrostatic interaction in the motor domain, which is predicted to cause a decrease in the stability of the local structure and subsequently affect the function of the MYO7A protein.

In a clinical setting, a diagnosis of this type of post-lingual hereditary hearing loss requires ruling out many lesions of the middle and inner ear, as well as nerve damage caused by noise, drugs, autoimmunity, or other factors. The key points of differential diagnosis are to inquire about the characteristics of hearing changes carefully, collect details on the patient's personal and family medical history, and complete various clinical examinations. For rare variants, extensive clinical and genetic data collection from family members is a prerequisite for diagnosis. Based on the results presented above, we made the diagnosis and provided effective treatment recommendations and genetic counseling for all family members. However, owing to the limited experimental conditions, we did not conduct further verification of the pathogenic mechanism of this variant.

CONCLUSION

In this study, we report a new family with DFNA11 caused by a *MYO7A* variant, which provides a new screening site for hereditary deafness. At the same time, the late onset age of hearing loss in the studied family also provides new insights

into the clinical phenotype of DFNA11.

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FOOTNOTES

Author contributions: Xia CF and Yan R contributed equally to this work. Xia CF and Yan R conducted the clinical investigations of the patients and drafted the manuscript; Su WW participated in the collection of clinical data; Liu YH supervised the study and revised the manuscript; and all authors have contributed to the manuscript and approved the submitted version.

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