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Case Report

Simultaneous MT-RNR1 and MYO15A Mutations in a Family with Non-Syndromic Hearing Loss

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Congenital hearing loss is one of the prevalent birth defects, with approximately 60% of cases attributed to genetic factors. Genetic hearing loss is broadly classified into syndromic and non-syndromic forms, with non-syndromic hearing loss accounting for 70% of cases. *MYO15A* mutations are known to cause autosomal recessive non-syndromic hearing loss (ARNSHL), while *MT-RNR1* mutations follow a maternal inheritance pattern and are linked to aminoglycoside-induced hearing loss. In this study, a family with diverse manifestations of non-syndromic hearing loss was investigated, including aminoglycoside-induced, congenital profound, and post-lingual profound hearing loss. Through whole exome sequencing, distinct genetic etiologies responsible for hearing loss in affected family members were identified. This is the first report to document the co-occurrence of a compound heterozygous *MYO15A* mutation alongside an *MT-RNR1* mutation within a pedigree. Additionally, it is the first observation of both a homozygous *MYO15A* c.6956+9C>G mutation and compound heterozygous *MYO15A* mutations (c.[6956+9C>G]+[4898T>C]) in ARNSHL. These findings broaden the genotype-phenotype spectrum of *MYO15A* and highlight the critical role of genetic diagnosis in managing hearing loss.

KEYWORDS: Genetic deafness, hearing loss, *MT-RNR1*, *MYO15A*, otogenetics, sensorineural hearing loss

INTRODUCTION

Congenital hearing loss is one of the prevalent birth defects[1] with a global prevalence of 0.1% to 0.2% in live births.[2] Genetic mutations are responsible for up to 60% of congenital hearing loss cases.[2] Based on the presence of additional phenotypes, genetic hearing loss is classified into syndromic hearing loss and non-syndromic hearing loss (NSHL), with NSHL accounting for 70% of all cases.[3] The inheritance pattern of 80% NSHL is autosomal recessive.[3]

More than 70 genes have been identified in association with autosomal recessive non-syndromic hearing loss (ARNSHL) (http://hereditaryhearingloss.com), with *MYO15A* being one of the most implicated.[3] The *MYO15A* gene encodes the myosin-XV protein, which is crucial for the mechanosensory function of cochlear hair cells and over 600 mutations have been reported (www.hgmd.org).[4]

In addition to mutations in nuclear genes, mutations in the mitochondrial genome, such as *MT-RNR1*, contribute to aminoglycoside-induced hearing loss.[5] *MT-RNR1* m.1555A>G mutation is particularly prevalent, with a prevalence of approximately 1.8% in global hearing loss patients and rising to 2.48% in Asia.[6]

In the otolaryngology clinic, a family with varying manifestations of NSHL was encountered, and diverse etiologies among affected family members were identified. Based on these findings, recommendations were provided for hearing treatment, reproductive planning, and drug-use management for the family.

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CASE PRESENTATION

A Han Chinese family with varying manifestations of NSHL was diagnosed (Figure 1a). Written informed consent was obtained from all patients. This study was approved by Ethics Committee of Eye & ENT Hospital of Fudan University (Approval No. 2020069; Date: July 8, 2024). The proband (III-1), a 5-year-old girl, presented with a gradual onset of hearing loss during 3 months without accompanying symptoms. Audiometric tests including pure-tone audiometry, multiple auditory steady-state response, and auditory brainstem response testing, confirmed bilateral profound sensorineural hearing loss (Figure 1b-d). Imaging studies, such as computed tomography and cranial magnetic resonance imaging, revealed normal outer and middle ear structures (Figure 1e), and excluded abnormalities of the internal auditory canals, auditory nerve dysplasia, or space-occupying lesions in cerebellopontine angle (Figure 1f). The proband had no siblings, and her father (II-4) had congenital profound hearing loss, while her mother (II-3) developed profound hearing loss due to kanamycin exposure. Additionally, her maternal aunt (II-1) who had no children experienced hearing loss following streptomycin use and her grandmother (I-2) maintained normal hearing without exposure of aminoglycoside antibiotic.

Whole exome sequencing (WES) and Sanger sequencing revealed that the proband (III-1) carried compound heterozygous mutations in the *MYO15A* gene (NM_016239.4) (c.[6956+9C>G] +[4898T>C]) and a mitochondrial mutation, *MT-RNR1* (NC_012920.1) m.1555A>G. The proband's father (II-4) was homozygous for the *MYO15A* c.6956+9C>G mutation. Her mother (II-3) was heterozygous for the *MYO15A* c.4898T>C mutation and carried the *MT-RNR1* m.1555A>G mutation, which was also identified in the unaffected grandmother(I-2) (Figure 2a).

The *MYO15A* c.4898T>C (p.Ile1633Thr) mutation is a missense mutation, causing an isoleucine-to-threonine substitution at a highly conserved site within the motor protein coding region (Figure 2b and c). This mutation has been reported in 6 NSHL patients[7-10] and is classified as pathogenic based on American College of Medical Genetics and Genomics (ACMG) guidelines (Figure 2d). The *MYO15A* c.6956+9C>G (p.Val2320Ter) mutation is located in intron 33 and affects splicing, resulting in the retention of 4 nucleotides (GTAG) between exon 33 and 34,[10] leading to a premature stop codon and a shortened protein lacking several domains (Figure 2b). This mutation has been reported in 7 NSHL patients[7,10,11] and is classified as pathogenic by ACMG criteria (Figure 2d). In addition, the *MT-RNR1* m.1555A>G mutation was consistent with maternal inheritance and classified as pathogenic by ACMG criteria (Figure 2d).

DISCUSSION

Based on the clinical presentation and mutation identifications, *MYO15A* compound heterozygous mutations (c.[6956+9C>G] + [4898T>C]) were determined to be the cause of hearing loss in the proband, who had no history of aminoglycoside use, despite carrying the *MT-RNR1* m.1555A>G mutation. Furthermore, homozygous *MYO15A* c.6956+9C>G mutations were identified as the cause of congenital profound hearing loss in the proband's father, while the *MT-RNR1* m.1555A>G was identified as the cause of aminoglycoside-induced hearing loss in the proband's mother, as she carries only heterozygous *MYO15A* c.4898T>C mutation. Although the proband's aunt did not undergo genetic testing, her phenotype and the maternal inheritance of mitochondrial genes suggest that she carries the *MT-RNR1* m.1555A>G mutation.

The *MYO15A* gene mutations identified in this study contribute to hearing loss through distinct molecular mechanisms. The c.4898T>C (p.Ile1633Thr) mutation, located within the highly conserved motor domain, replaces isoleucine (a nonpolar, hydrophobic, branched-chain amino acid) with threonine (a polar, hydrophilic amino acid with a hydroxyl group). This alteration in amino acid properties and spatial configuration within the motor domain possibly disrupts the precise adenosine triphosphate-binding (ATP-binding) and actin-interaction sites, which are essential for force production and movement.[12] The c.6956+9C>G (p.Val2320Ter) mutation results in a truncated protein incapable of adopting its correct conformation. Collectively, the impaired motor function and the severe protein truncation compromise the critical role of MYO15A in inner ear hair cell stereocilia formation and maintenance, leading to the hearing loss observed in affected family member.[4]

Although both *MYO15A* c.6956+9C>G and c.4898T>C mutations have been previously reported, this is the first report of homozygous c.6956+9C>G mutations and compound heterozygous mutations (c.[6956+9C>G] + [4898T>C]), expanding the genotype-phenotype spectrum of *MYO15A* mutations.

Here, a pedigree with NSHL associated with *MYO15A* mutations and the *MT-RNR1* mutation was reported for the first time. This case underscores the value of genetic testing in the management of NSHL. The comprehensive genetic testing strategies, such as WES, are often financially challenging. It was proposed that WES was a viable option for patients with phenotypes highly consistent with a specific hereditary disorder or with a clear family history. Following candidate pathogenic mutation identification via WES, Sanger sequencing in relevant family members can confirm inheritance patterns and co-segregation. This tiered approach balances comprehensive diagnosis with economic feasibility, enhancing the utility and accessibility of genetic testing.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by Ethics Committee of Eye & ENT Hospital of Fudan University (Approval No. 2020069; Date: July 8, 2024).

Informed Consent: Written informed consent was obtained from all the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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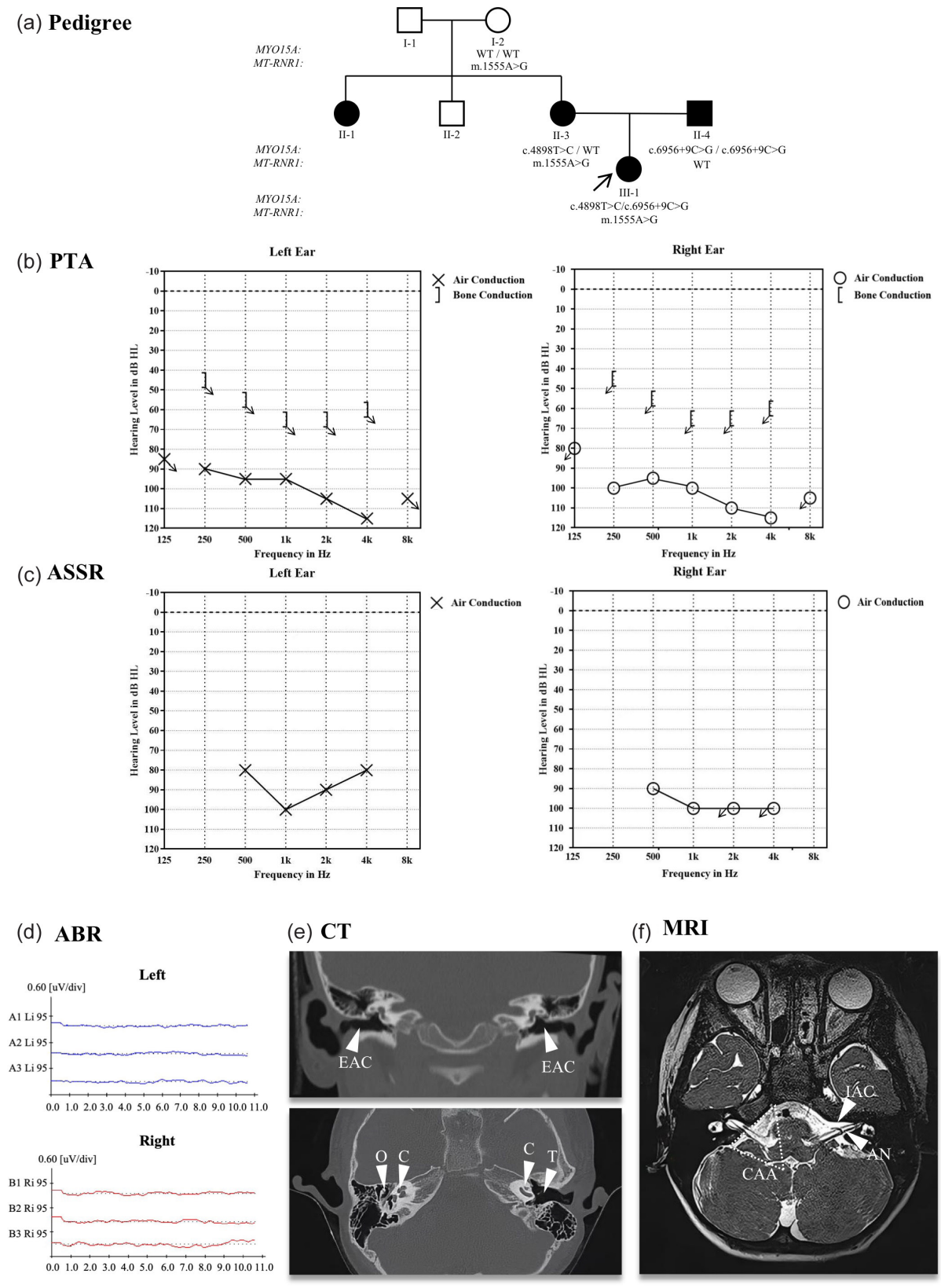
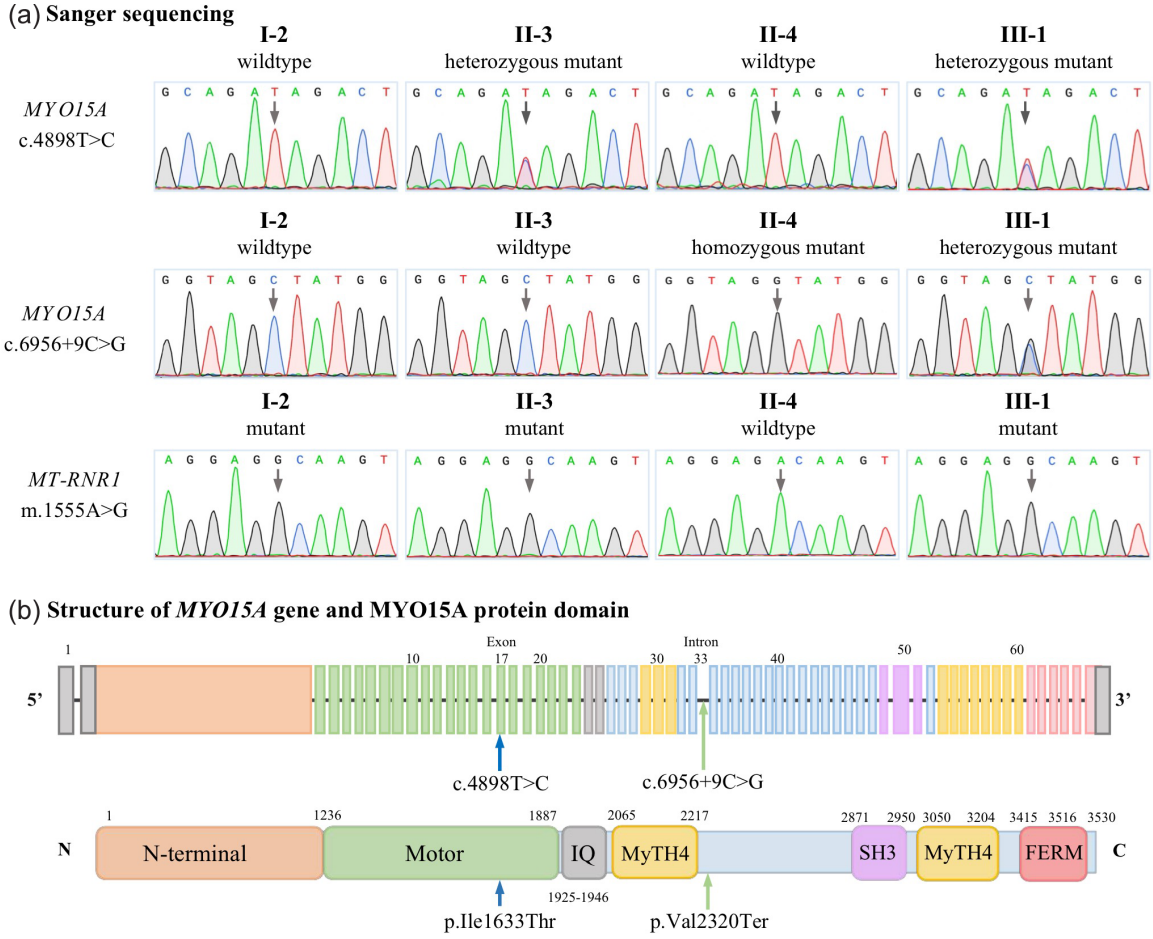


Figure 1. The pedigree and clinical manifestation of the proband. (a) Pedigree: males are represented by squares and females by circles, with filled symbols indicating individuals affected by hearing loss. The arrow points to the proband. (b) pure-tone audiometry results: the hearing threshold of the left ear was 98 dB, and the right ear was 101 dB. (c) Auditory steady-state response results (air-conduction): profound hearing loss was observed across all tested frequencies in both ears. (d) Auditory brainstem response results: all waves disappeared at a threshold of 95 dB HL. (e) Computed tomography results: the external auditory canals were unobstructed, and the middle ear structures were normal. (f) Magnetic resonance imaging results: the internal auditory canals were of normal diameter, and the auditory nerves were well developed. No space-occupying lesions were found in the cerebellopontine angle.



(d) **Summary of the pathogenic mutations identified**

Patient	Mutation	Highest allele frequency	Mutation taster	Polyphen2_HDIV	Clinvar	ACMG	Reference
II-3 III-1	*MYO15A* c.4898T>C p.Ile1633Thr	0.001661	disease-causing (0.99)	likely damaging (0.99)	Likely Pathogenic	Pathogenic PM2_Supporting +PM3_VeryStrong + PP3_Moderate	Fu et al.(2022) Rehman et al.(2016) Gu et al.(2015)
II-4 III-1	*MYO15A* c.6956+9C>G p.Val2320Ter	0.000071	disease-causing (0.99)	-	Pathogenic	Pathogenic: PVS1+PM2_Supporting +PM3	Fu et al.(2022) Wu et al.(2022) Yang et al.(2013)
I-2 II-3 III-1	*MT-RNR1* m.1555A>G	0.00112	-	-	Drug response; Pathogenic	Pathogenic: PS3+PS4+PM1	Prezant et al.(1993)

Figure 2. Sanger sequencing and pathogenic mutations information in the family. (a) Sanger sequencing results for the *MYO15A* (c.4898T>C, c.6956+9C>G) and *MT-RNR1* (m.1555A>G) mutations in family members I-2, II-3, II-4, and III-1. The arrows indicate the mutation sites. (b) Structure of the *MYO15A* gene (top panel), with exons shown as boxes. Arrows mark the mutation sites. The MYO15A protein domain structure (bottom panel) with colored boxes corresponding to the exon-encoding regions and arrows indicating mutation locations. (c) Analysis of the conserved region surrounding the MYO15A p.Ile1633Thr mutation. (d) Summary of the pathogenic mutations identified. Values from Mutation Taster and PolyPhen2_HDIV indicate the pathogenicity predictions, with a maximum score of 1.

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