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ORIGINAL RESEARCH

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A novel *MPZL2* c.68delC variant is associated with progressive hearing loss in Chinese population and literature review

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Abstract

Objective: The aim of this study was to identify genetic etiology in two unrelated Chinese probands with progressive sensorineural hearing loss.

Methods: Two unrelated Chinese families were recruited. Genetic etiology was identified by targeted next-generation sequencing (NGS) and verified by Sanger sequencing. Hearing evaluations included pure tone audiometry, auditory brainstem response to clicks, and otoscopic examination. Medical history and computerized tomography scan of temporal bone were also collected. In addition, linear regression was used to summarize all of the reported cases and estimate the progression of hearing loss.

Results: A 28-year-old man with variant c.68delC had progressive, moderately severe hearing loss and a suspicious history of renal impairment. His hearing result was 63.75 dB HL. The other proband was the youngest patient with MPZL2-related hearing loss reported so far in the literature (genotype: c.220C>T homozygote). Her hearing result by click-ABR was 25 dB nHL at 3 months of age, and deteriorated to 40 dB nHL at 15 months. Behavioral audiometry identified a hearing loss of 26.25 dB HL. In summarizing all of the reported cases, using linear regression, MPZL2-related hearing loss may deteriorate by 0.59 dB HL per year, and different MPZL2 variants may lead to different rates of progression.

Conclusion: In this study, we first identified two unrelated patients with *MPZL2*-related hearing loss in Chinese population, and a novel variant c.68delC. Our results expanded the mutation spectrum of deafness genes. Further studies are required to clarify the genotype–phenotype correlation and the progression of *MPZL2*-related hearing loss.

KEYWORDS

genetic, *MPZL2*, novel variant, progressive hearing loss

Zhili Wang and Mengda Jiang contributed equally in this work.

1 | INTRODUCTION

The etiology of hearing loss can generally be divided into genetic and environmental factors. To date, 124 genes associated with non-syndromic hearing loss, and more than 40 genes associated with the most common 11 types of syndromic hearing loss have been identified according to the Hereditary Hearing Loss Homepage (https://hereditaryhearingloss.org/, accessed on April 3, 2022). And genetic factors are the primary cause for over 50% of congenital hearing loss.[1] The inheritability of age-related hearing loss was estimated to be 35%–55%.[2,3] However, in 15%–44% of children (>1 year old) with hearing loss, the etiology still could not be determined.[4,5] The contribution of genetic factors to disease etiology remains unclear.

The *MPZL2* gene is located on chromosome 11q23.3. It has 6 exons and a coding sequence of 648 bp, encoding the myelin protein zero like 2 (MPZL2, OMIM: 604873, http://www.omim.org), a member of the immunoglobulin (Ig) superfamily. This protein was originally known as epithelial V-like antigen (EVA or EVA1)[6] as it has a characteristic V-type domain, and has been observed in fetal thymus and most thymic epithelial cell lines.[7] In 2018, *MPZL2* was first reported to be associated with hearing loss,[8] and its product was also expressed in tissue including the inner ear.[9] In the inner ear of mice, Mpzl2 localized in the organ of Corti, inner and outer hair cells, and the stria vascularis.[8,9] In the *Mpzl2* knockout model, alterations in cell organization and cell loss were identified in the organ of Corti implying that the gene plays a crucial role in maintaining the inner ear cell structure.[9]

So far, only three *MPZL2* variants (c.72delA, c.220C>T and c.463delG) in 27 patients with hearing loss have been identified (Table 1). These patients are from Turkey,[8,9] the Netherlands,[9] Korea,[10] Iran,[8] and Morocco.[11] Nonsyndromic, slowly progressive, mild to severe hearing loss was observed in these patients, but evidence from large-scale targeted investigations remains absent. In this study, we report the first two unrelated patients with *MPZL2*-related hearing loss in the Chinese population, identify a novel variant c.68delC, and summarize the relevant cases in the literature.

2 | MATERIALS AND METHODS

2.1 | Patients and Ethics Statement

This study was approved by the Ethics Committees of Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine (No.SH9H-2019-T245-1). Two Chinese probands and their family

TABLE 1 Clinical data for all of the patients in the literature having *MPZL2* variants

				Latest hearing result			Initial hearing result			
No.	Sex	Origin	Genotype	Age (years)	PTA (dB HL)	Grade[a]	Age (years)	PTA (dB HL)	Grade[a]	Literature
1	M	Dutch	c.72delA/c.72delA	37	61.25	MS	16	50.00	MS	Wesdorp et al. 2018 [12]
2	M			42	68.75	S	22	47.50	M	
3	M			9	40.00	M	4	40.00	M	
4	M	Turkish	c.72delA/c.72delA	8	42.50	M	5	37.50	M	
5	F	Turkish	c.72delA/c.220C>T	44	50.00	MS	34	42.50	M	
6	F		c.72delA/c.220C>T	13	36.25	M	6	37.50	M	
7	M		c.72delA/c.72delA	16	42.50	M	5	26.25	Mild	
8	F		c.72delA/c.220C>T	7	37.50	M	6	40.00	M	
9	M	Turkish	c.72delA/c.72delA	21	48.75	M	Not presented			Bademci et al. 2018 [11]
10	F			14	50.00	MS				
11	F	Turkish	c.72delA/c.72delA	8	48.75	M				
12	M			4	50.00	MS				
13	F	Iranian	c.72delA/c.72delA	36	71.25	S				
14	M			13	42.50	M				
15	F			8	35.00	M				
16	F			5	70.00	S				
17	/	Korean	c.220C>T/c.463delG	12.4 (4.2)[b]	43.8 (8.1)[b]	M	Not presented			Kim et al. 2020 [13]
18–25			c.220C>T/c.220C>T							
26	M	Moroccan	c.72delA/c.72delA	Childhood	53.75[c]	MS	Not presented			Amalou et al. 2021 [14]
27	F				61.25[c]	MS				
28	M	Chinese	c.220C>T/c.68delC	28	63.75	MS	15	28.75	Mild	This study
29	F		c.220C>T/c.220C>T	1.25	26.25	Mild	0.25	25 dB nHL (click-ABR)	N/A	

[a]M = moderate, MS = moderately severe, S = severe, N/A = not applicable.
[b]Age and hearing results for the 9 patients were not presented individually in the literature, thus the data are shown as mean (SD).
[c]These hearing results are from the poorer hearing ear, as PTAs for the other ear were not provided.

members were recruited; all of them were Chinese Han ethnicity. All participants or their guardians gave written informed consent.

2.2 | Clinical assessment

For each proband, a complete medical history was obtained, including the onset and progression of hearing loss, family history, history of drug and noise exposure, and other clinical manifestations. Physical and otoscopic examinations were performed by experienced doctors. To identify abnormal ear structures, high-resolution computed tomography (HRCT) scans of temporal bone were performed by using a 128-slice spiral CT scanner (Siemens, SOMATOM Definition Flash, Germany). The scanning baseline was parallel to the orbital line, and the scanning range was from the upper margin of petrous portion to the lowest point of the mastoid process. The collimation width (also the slice thickness) was 0.6 mm, and other scanning parameters were as follows: 120 keV, 120 mAs, pitch of 0.8, bone reconstruction algorithm, reconstruction of oblique sagittal and coronal planes, 4000 Hu of window width, and 700 Hu of window level. For the 15-months-old child, chloral hydrate was orally given prior to the CT scan (50 mg/kg).

For each patient, wideband tympanometry (WBT) including 226 and 1000 Hz was routinely done before the measurement of hearing threshold. Hearing was assessed by auditory brainstem response to clicks (click-ABR, Interacoustics, Denmark) and the behavioral audiometry test (Otometrics, Denmark) at frequencies of 0.5, 1, 2, and 4 kHz. The latter test was only used for children over 1 year of age. The hearing of other participants, including parents of the two probands, was also assessed by air and bone conductive pure tone audiometry (Otometrics, Denmark) at frequencies of 0.25, 0.5, 1, 2, 4, and 8 kHz. For comparison, the hearing results were defined as the pure-tone average (PTA) of the better hearing ear, calculated by the average hearing threshold over frequencies of 0.5, 1, 2, and 4 kHz. They were graded as mild (20 to <35 dB HL), moderate (35 to <50 dB HL), moderately severe (50 to <65 dB HL), severe (65 to <80 dB HL), profound (80 to <95 dB HL) and complete (95 dB HL or greater) hearing loss, following the 2021 WHO Guidelines.[12]

2.3 | Genetic analyses

Genomic DNA was extracted from peripheral blood samples of the two probands and their parents. For the participants with hearing loss (two probands and patient II-5 in Family 1), a targeted NGS of all 415 genes known to be associated with hearing loss was performed(Supplemental Table S1). The amplified DNA of the two probands was captured using the GenCap deafness capture kit (MyGenostics, Beijing, China). The probes were designed to tile along all exons, splice sites, and immediate flanking intron sequences of the candidate genes. Captured DNA fragments were sequenced on an Illumina HiSeq2000 Analyzer (Illumina Inc., San Diego, CA). Data analysis and bioinformatics processing were performed following the standard Illumina procedure. Potential pathogenic variants were filtered using the minor allele frequency (MAF) threshold of <0.01 for dominant inheritance (determined from databases including NCBI dbSNP, NHLBI Exome Sequencing Project and 1000Genomes). Sanger sequencing was used to validate parental origin of the candidate variants.

2.4 | Data and statistical analysis

Scatter diagrams and linear regression were used to present the hearing level of the patients in this study and in the literature. For patients who had a follow-up visit, the progression of hearing was plotted separately and then integrated with earlier plots. Statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). Statistically significance was defined as P <0.05.

3 | RESULTS

3.1 | Clinical and genetic findings in Family 1

In Family 1, proband III-1 (Figure 1A) is a 28-year-old man with bilateral progressive hearing loss. He self-reported a right-sided hearing loss at the age of 13, but the initial hearing report was not provided. Bilateral hearing aids (HAs) were fitted at about 15 years old. The audiometry result at that time showed a PTA of 28.75 dB HL in left and 57.50 dB HL in right. The patient had no difficulties in schooling or communication owing to regular use of HAs. Otoscopic examination and WBT result of the proband was normal, and an HRCT scan of his temporal bone showed no structural abnormalities in the inner ear (Figure 1B). His latest PTA at the age of 28 was 63.75 dB HL in the left ear and 68.75 dB HL in the right ear (Figure 1C), indicating a progressive hearing loss deteriorating by an average of 2.69 dB HL per year in his better hearing ear. No balance complaints reported during the course.

In addition, at about 14 years of age, a single bout of fever and joint pain was reported, accompanied by a high level of uric acid (UA) and creatinine (Cr). The proband was advised by a rheumatologist, and used Benzbromarone routinely at the first year to help lowering the UA and Cr level. After a whole year of treatment, the drug was not used, and by the change of diet and proper physical exercises, the level of UA and Cr became normal. In his recent health examination, both his blood UA and Cr level were in normal range (UA: 155–357 μmol/L, Cr: 44–106 μmol/L). A family history of metabolic disease or immune system disorder was also excluded. The proband's father, II-5, reported a 6-year history of occupational noise exposure in his twenties. He started having hearing difficulty at the age of 37, and was diagnosed as asymmetric bilateral sensorineural hearing loss since the age of 40. His recent PTA was 38.75 dB HL in his right ear and 55 dB HL in his left ear at the age of 55 years (Figure 1C).

Using targeted NGS, the compound heterozygous variant in *MPZL2* gene (NM_005797.4) c.220C>T (p.Gln74Ter)/c.68delC (p.Pro23LeufsTer2) was identified in proband III-1. Genotypes of his parents were present in the pedigree (Figure 1A), and were validated by Sanger sequencing

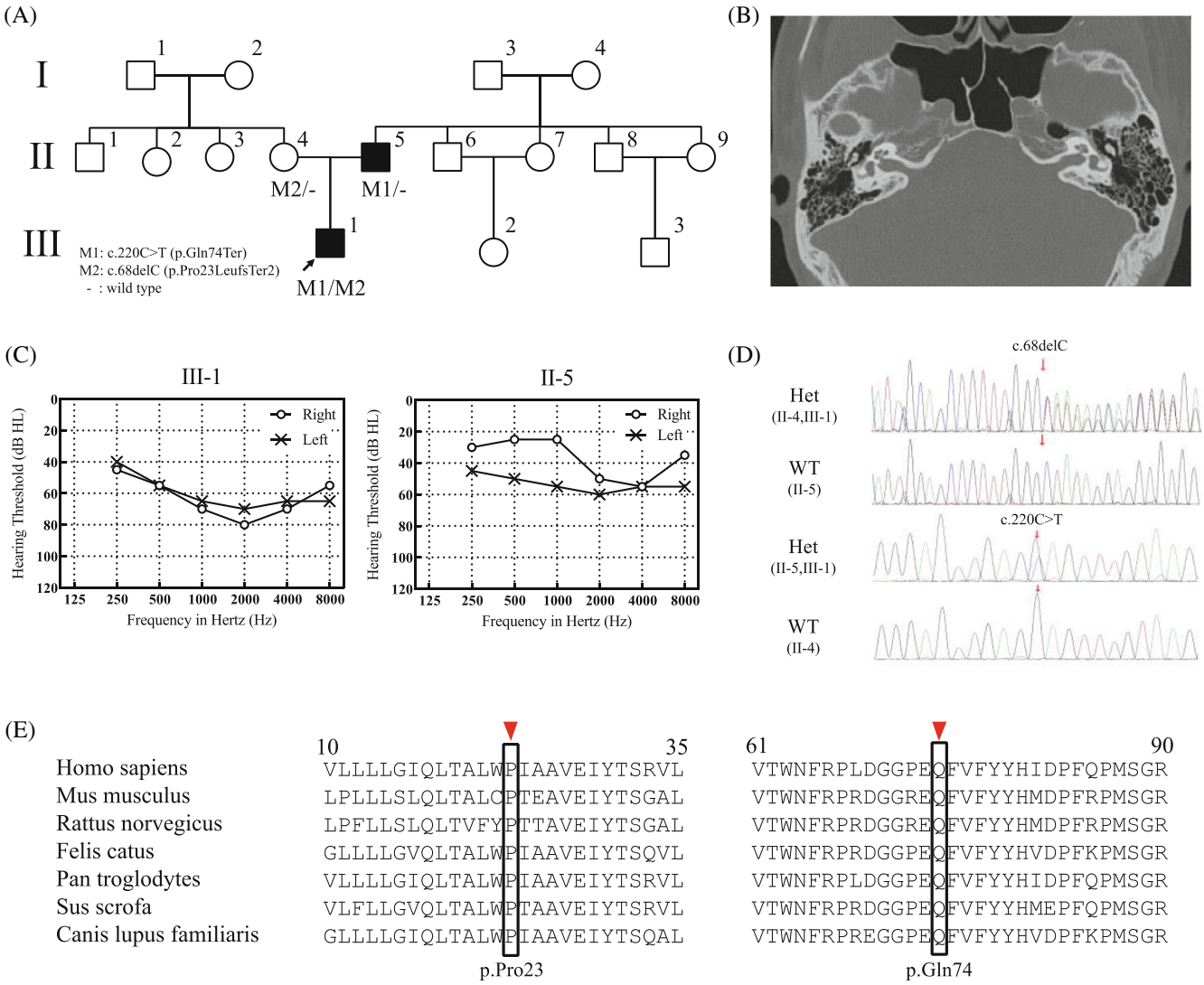

FIGURE 1 Clinical and genetic findings in Family 1. (A) The pedigree. (B) HRCT image from III-1. (C) Latest audiogram. (D) Sequence chromatogram. (E) Pro23 and Gln74 residues are highly conserved in six different species

(Figure 1D). Both variants could result in the early termination of protein synthesis, and were defined as "Pathogenic" according to the American College of Medical Genetics (ACMG) guideline[13] (c.220C>T variant met PVS1 + PM3_Strong criterion, and the novel c.68delC variant met PVS1 + PM2 + PM3 criterion). The other variants are shown in Supplemental Table 2. The Gln74 and Pro23 residues were highly conserved in multiple species (Figure 1E). Since his father II-5 also had a hearing loss, the same targeted NGS was done, and none of the obvious pathogenic variants were identified.

3.2 | Clinical and genetic findings in Family 2

Proband III-2 in Family 2 (Figure 2A) is a 15-month-old girl who had failed the initial and repeated screening in the universal newborn hearing screening (UNHS) program. Her parents reported no family history or relevant systemic diseases, and both of them had normal hearing by audiometry. The otoscopic examination, WBT result and CT images (Figure 2B) were also normal. At 3 months of age, a click-ABR was performed, and the result was 35 dB nHL in the left ear and 25 dB nHL in the right ear. At the age of 15 months, she was tested again by click-ABR, and the result was 45 dB nHL in the left ear and 40 dB nHL in the right ear indicating progressive hearing loss. The behavioral audiometry test showed a PTA of 33.75 dB HL in the left ear and 26.25 dB HL in the right ear, graded as mild hearing loss (Figure 2C). Also, her parents had observed no equilibrium problems, staggering or unusual vomiting in the proband.

Genotype of the proband and her parents were also shown in the pedigree (Figure 2A) and validated (Figure 2D). She was homozygous for *MPZL2* (NM_005797.4) c.220C>T, and her parents were heterozygous for this variant. She was also heterozygous for *MYO15A* gene c.4207-9A>G and c.7547C>T (Table S2), but both of the two variants were inherited only from her father, who had a normal hearing, and neither of them have been reported in the literature about the

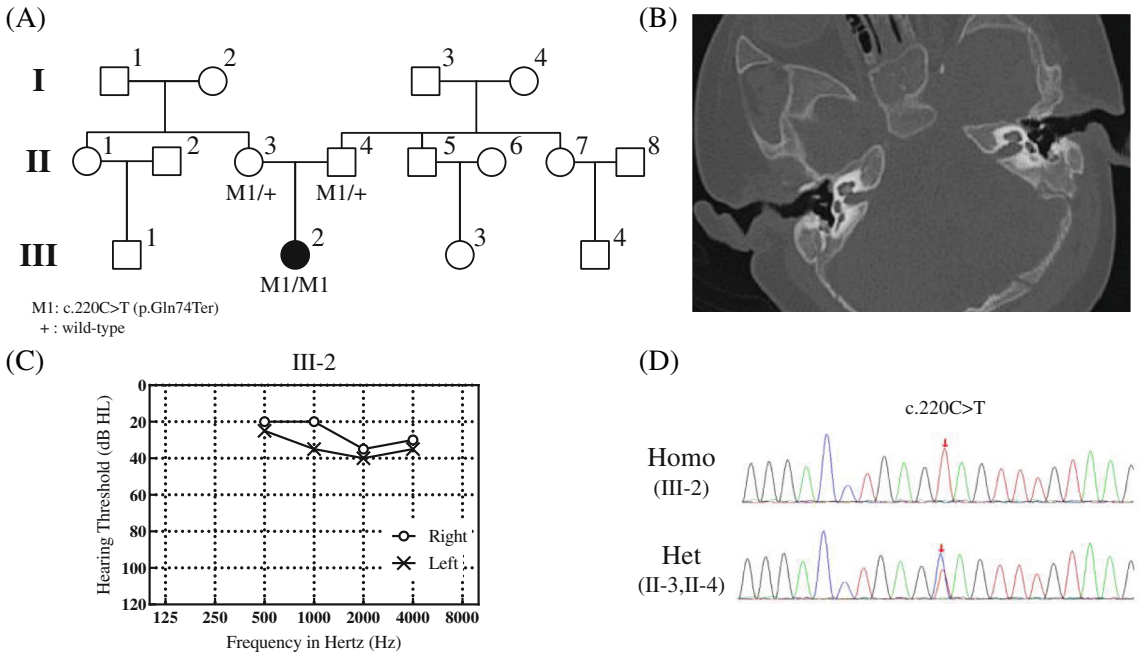

FIGURE 2 Clinical and genetic findings in Family 2. (A)The pedigree. (B) HRCT image from III-2. (C) Latest audiogram from III-2 tested by behavioral audiometry. (D) Sequence chromatogram

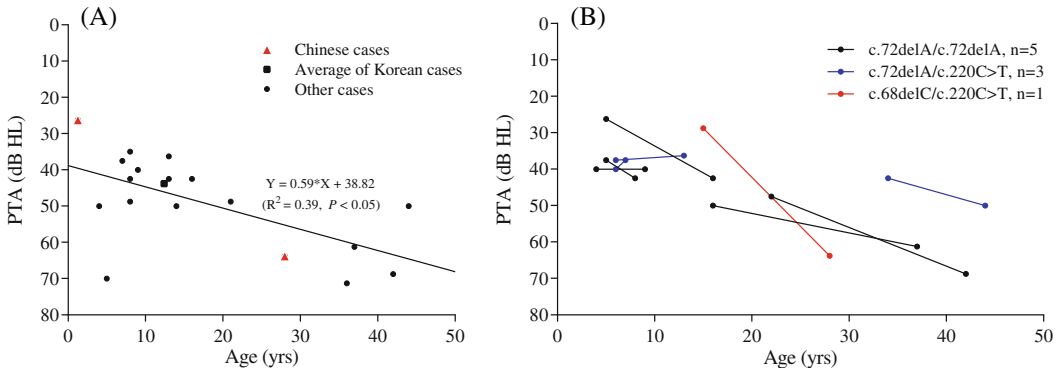

FIGURE 3 Hearing results for *MPZL2* cases in the literature. (A) PTAs of patients with *MPZL2* variants at different ages. (B) Hearing loss progression in patients with follow-up visits and having different *MPZL2* genotypes

pathogenicity. Besides, the proband's phenotype is also much milder than the *MYO15A*-associated, severe to profound hearing loss. Therefore, still the *MPZL2* gene variant was recognized as the pathogenic cause.

3.3 | Geno-phenotype of *MPZL2*-related hearing loss

In earlier studies, a total of 27 cases from 4 to 44 years of age with *MPZL2*-related hearing loss, have been reported. Their age, sex, genotype, and hearing results are summarized in Table 1. Consistently, the hearing results were based on pure tone audiometry, and PTAs were calculated by the average of air conduction hearing threshold at 0.5, 1, 2, and 4 kHz. Together with the two cases in our study, we analyzed PTAs of their better hearing ear by linear regression. Two Moroccan cases were not included, as their exact ages at the test were not reported; And PTAs of 9 Korean children were shown as a filled square, as only one average PTA (and age) were provided (Figure 3A). Of all these biallelic *MPZL2* individuals, the predicted PTA [dB HL] was $38.82 + 0.59 \times$ Age [years] ($R^2 = 0.383$, $P < 0.05$), indicating a rate of deterioration of hearing of 0.59 dB HL per year.

To improve our evaluation of hearing deterioration, we analyzed the PTAs of those patients reported in the literature and in this study who had had follow-up hearing tests. The nine patients identified were divided into three groups by their *MPZL2* genotypes: c.72delA/c.72delA, c.72delA/c.220C > T, and c.68delC/c.220C>T. The mean rates of deterioration of hearing for each genotype were 0.95, −0.64,

and 2.69 dB HL per year, respectively (Figure 3B). The patient with the novel c.68delC variant (marked in red) appears to have the most rapid rate of hearing loss among all of the patients. The abnormal negative (−0.64 dB HL per year) result may due to the low number of cases ($n = 3$) and the short follow-up period in the c.72delA/c.220C>T patient group.

4 | DISCUSSION

In this study, we identified two unrelated patients with *MPZL2*-related hearing loss in the Chinese population, and a novel variant c.68delC. One of the two patients was the youngest *MPZL2* patient reported in the literature. She was 15 months old and was diagnosed with mild hearing loss. The other patient with the novel variant c.68delC had rapid hearing loss between 15 and 28 years of age.

Progressive hearing loss has been observed in patients with *MPZL2* variants. On average, the hearing level was estimated to deteriorate by 0.59 dB HL per year. This is similar to another variant, c.109G>A (p.Val37Ile), in the most common deafness gene *GJB2*, which is also associated with progressive hearing loss.[14] According to a longitudinal study in children ranging from <1 year old to 6 years old with *GJB2* gene biallelic p.Val37Ile variants, the rate of deterioration of hearing was estimated to be 1.0 dB HL per year.[15] And in our study, a population-based large-scale investigation (N > 30,000), the average progression of hearing loss in 7–85 years old biallelic p.Val37Ile individuals was projected as 0.4 dB HL per year.[16] As for MPZL2-related hearing loss, the progression rate may also be influenced by ages or genotypes of variants, but the present data is not enough to draw further conclusion.

The variants associated with high allele frequency and steadily progressive hearing loss, such as the p.V37I variant of *GJB2*, probably merit widespread genetic screening. According to large-scale screening programs, in East Asians, the *GJB2* p.V37I variant had an extremely high allele frequency (up to 10%).[17,18] In contrast, the allele frequency (reported in gnomAD v2.1.1) of the *MPZL2* gene c.220C>T variant was 0.00515 in East Asians (0.01974 in Japanese and 0.009439 in Korean individuals),[10] and that of c.72delA was 0.00375 in Ashkenazi Jews. However, since there have been no large-scale screening programs for the *MPZL2* gene, its exact prevalence and penetrance in specific populations have yet to be clarified.

In addition, proband III-1 in Family 1 had a history of elevated blood uric acid levels, which required routine medication for over 10 years. Sensorineural deafness combined with hyperuricemia occur in a very rare X-linked disease called phosphoribosyl pyrophosphate synthetase (PRS) superactivity.[19] A mild phenotype of PRS superactivity is usually suspected in a juvenile or adult male with significant hyperuricemia[20] and a severe phenotype of PRS superactivity is usually suspected in a male infant or young child with additional clinical features including intellectual disability, sensorineural hearing impairment, hypotonia or ataxia.[19] Pathogenic variants of *PRPS1* gene would lead to this disease. However, NGS did not identify abnormalities of *PRPS1* in the proband. In addition, his late age at onset and relatively mild symptoms did not indicate PRS superactivity. Since none of the patients with *MPZL2* variants in earlier studies have been reported as having accompanying symptoms,[8,9] the occurrence of hyperuricemia might be an independent event.

The possibility that *MPZL2* variants lead to noise-induced hearing loss (NIHL) also needs to be discussed, since patient II-5 in Family 1 had moderate hearing loss with a history of exposure to occupational noise. Some indirect molecular evidence was provided in earlier studies: the cytoplasmic region of Mpzl2 was reported to have a consensus binding site for tumor necrosis factor receptor-associated factor 2 (Traf2),[21] a key regulator in the NF-kB signaling pathway,[22,23] which plays an important role in noise-induced cochlear inflammation.[24] Activation of this pathway could protect the primary auditory neurons from excitotoxic damage and age-related degeneration[25]; however, more evidence is required to confirm the association between *MPZL2* and NIHL.

In conclusion, our identification of the novel *MPZL2* variant c.68delC and *MPZL2*-related hearing loss in the Chinese population has expanded the mutation spectrum of progressive sensorineural hearing loss. We also analyzed hearing progression and genotype-phenotype correlations in all reported cases with *MPZL2* variants, and inferred a predicted rate of deterioration of hearing of 0.59 dB HL per year. More studies are required to further explore the prevalence, progression, and expression of *MPZL2*-related hearing loss.

AUTHOR CONTRIBUTIONS

Zhili Wang, acquisition, analysis and interpretation of data, drafting of the manuscript; Mengda Jiang, analysis and interpretation of data, technical and material support; Hao Wu, administration, technical and material support; Yun Li, administration, study concept and design; Ying Chen, study concept and design, analysis and interpretation of data, critical revision, and administration.

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CONFLICT OF INTEREST

The authors declared no conflicts of interest to this work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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