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CASE REPORT

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Delayed progressive sensorineural hearing loss due to a novel compound heterozygous PTPRQ mutation in a Chinese patient

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Abstract

Background: The *Protein tyrosine phosphatase receptor Q* (*PTPRQ*) gene encodes a member of the type III receptor-like protein tyrosine phosphatase family found in the stereocilium. Mutations in *PTPRQ* are mostly associated with deafness, autosomal recessive type 84 (DFNB 84), which usually results in progressive familial hearing loss.

Methods: A 25-year-old woman and her sister, both with postlingual-delayed progressive sensorineural hearing loss, were examined. They were from a nonconsanguineous marriage and had no family history of hearing loss. New compound heterozygous *PTPRQ* gene mutations, nonsense (c.90C>A, p.Y30X) and splice (c.5426+1G>A) mutations in two *PTPRQ* alleles, were identified in the two sisters and were presumably autosomal recessive. The c.90C>A (p.Y30X) mutation was mapped to exon 2 of *PTPRQ* (NM_001145026).

Results: The c.90C>A mutation leads to a premature stop codon and a truncated protein. The c.5426+1G>A mutation leads to a truncated protein lacking the extracellular domain. Hence, both mutations were predicted to be pathogenic, leading to a deficiency of the extracellular, transmembrane, and phosphatase domains because of nonsense-mediated mRNA degradation.

Conclusions: This study increases the spectrum of *PTPRQ* gene mutations that might be involved in delayed progressive autosomal recessive non-syndromic hearing loss.

KEYWORDS

compound heterozygous mutation, delayed progressive sensorineural hearing loss, hereditary disease, protein tyrosine phosphatase receptor Q

1 | INTRODUCTION

Sensory hearing loss is a major human disability. Nearly 328 million adults and 32 million children suffer from hearing loss around the globe.[1] Congenital sensorineural hearing loss (SNHL) is mainly caused by hereditary factors responsible for 60% of cases. About 80% of hereditary hearing loss cases are autosomal recessive non-syndromic hearing loss (ARNSHL).[2] Some genes related to ARNSHL have been identified, including *GJB2* and *SLC26A4*.[3,4] ARNSHL-related genes are rare, with only a few mutations reported in several families, including in *Protein tyrosine phosphatase receptor Q* (*PTPRQ*).[5–11]

The *PTPRQ* gene is located on chromosome 12q21.31 and comprises 58 exons.[6] *PTPRQ* plays a key role in hair cell functions as sound receptors in the acoustic system. *PTPRQ* encodes a stereocilium membrane protein.[10] *PTPRQ* mutation in mice is associated with deafness

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due to shaft connector and hair bundle malformation,[12] whereas the pathologic mechanism remains unclear in humans. Most ARNSHL cases are due to hair cell dysfunction.[6] Hair bundles at the top of the hair cell comprise about 100 static cilia filled with actin that help transmit sound from mechanical to electrical signals. The PTPRQ protein is widely believed to play a critical role in hair cell maturation, and its loss or dysfunction may result in shaft connector malformation of stereocilia in the inner ear.[12–15] *PTPRQ* was designated deafness autosomal recessive type 84 (DFNB84) by the HUGO Gene Nomenclature Committee.[6] *PTPRQ* mutations mostly involve DFNB84, which usually results in progressive moderate-profound familial hearing loss.[5,8] Sometimes autosomal-dominant deafness can also be caused by *PTPRQ* mutations, for example, DFNA73.[16]

Hereditary hearing loss attracts increasing attention. *PTPRQ* has been identified as underlying progressive deafness in several families, indicating that *PTPRQ* is not a common gene. Here, new compound heterozygous *PTPRQ* mutations were found in two Chinese sisters and were highly suspected of contributing to ARNSHL in that family. The two patients were described, and the literature was reviewed to provide more information about these mutations.

2 | CASE PRESENTATION

2.1 | Subjects

A 25-year-old woman and her sister, both with confirmed postlingual-delayed progressive SNHL and from a nonconsanguineous family without a history of hearing loss, were analyzed (pedigree in Figure 1A). The proband complained of hearing loss at 4 years old. A thorough family history was obtained, and audiological tests such as audiometry, tympanometry, acoustic stapedial reflex examination, speech recognition test, and physical examination were carried out in a soundproofed room. SNHL was diagnosed according to the existing clinical standards. Clinical exams revealed no signs of syndromic hearing loss. The proband started using hearing aids at 20 years old. Auditory and speech performances in these cases were assessed. This case report was approved by the Medical Ethics Committee of Peking University First Hospital. The patients provided signed informed consent.

2.2 | Sample collection

Blood sample collection from the proband and her family was carried out at the Department of Otolaryngology and Head and Neck Surgery, Peking University First Hospital. Genomic DNA extraction was performed using the Qiagen blood DNA extraction kit (Qiagen, Hilden, Germany).

2.3 | DNA analysis

Human exome capture was carried out based on the Illumina's TruSeq™ Exome Enrichment Guide (Illumina, San Diego, CA, USA). The Illumina's TruSeq 62 Mb Exome Enrichment kit provided exome enrichment probes, and 5 μg genomic DNA in 80 μL of Buffer EB (Qiagen) underwent fragmentation using a Biorupter UCD-200 (Diagenode, Belgium) to 100–500 bp fragments. DNA quantitation was done by OD_{260} reading and quantitative

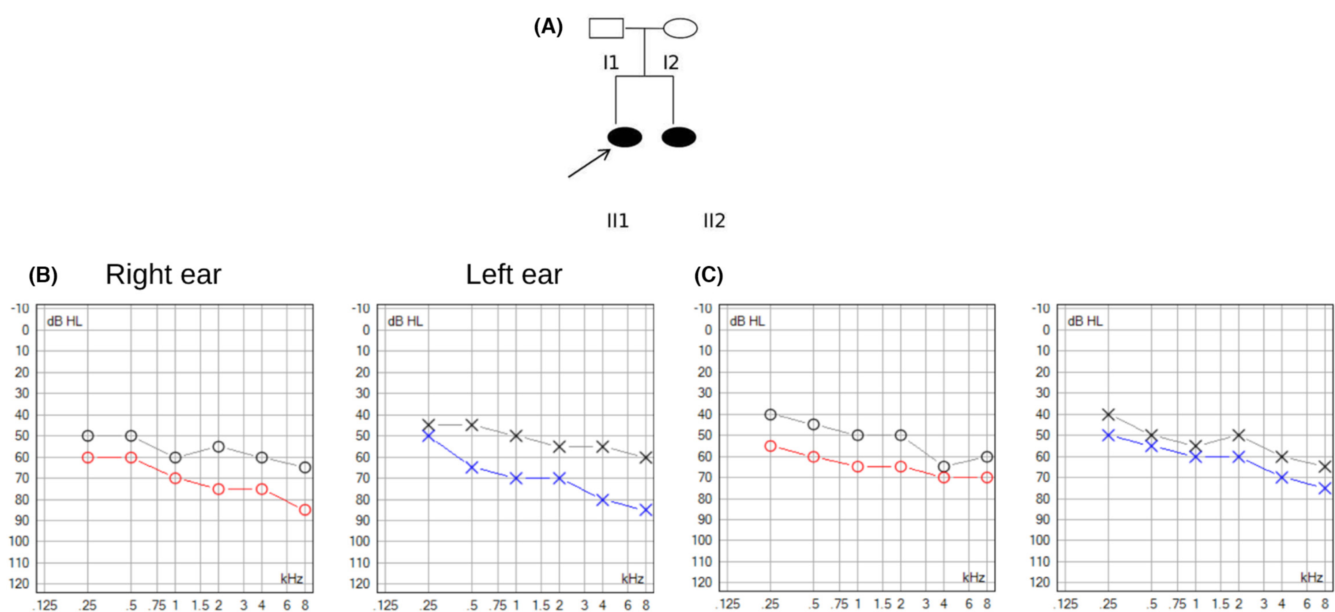

FIGURE 1 (A) The 25-year-old woman and her sister suffered from delayed progressive SNHL, whereas their parents had no history of hearing loss. (B) Audiograms of bilateral ears showing progressive hearing loss ranging from moderate to severe in subject II:1 (black: 20 y.o.; blue and red: 25 y.o.). (C) Audiograms of bilateral ears showing progressive hearing loss ranging from moderate to severe in subject II:2 (black: 18 y.o.; blue $ red: 23 y.o.).

real-time polymerase chain reaction (qPCR). Sequencing was performed on an Illumina HiSeq 2000, generating 200 (2 × 100) bp from the final library with the V2 reagent. Following whole-exon sequencing, raw data underwent conversion into FASTQ files. The bioinformatic evaluation was performed using Genome Analysis Toolkit (GATK) (https://gatk.broadinstitute.org/) for mutation calling, Burrows-Wheeler Aligner (BWA) (http://bio-bwa.sourceforge.net/) for genome alignment and mutation detection (hg19, NCBI Build 38), and Picard for duplicate read detection. Mutations were filtered based on homozygous missense, start codon change, splice site, nonsense, stop loss, and indel mutations with MAF <1% in multiple databases, including dbSNP version 147, 1000 genomes project phase 3 database (https://www.internationalgenome.org/), NHLBI GO exome sequencing project (ESP) (https://evs.gs.washington.edu/), and exome aggregation consortium (ExAC) (http://exac.broadinstitute.org).

Then, potential mutations underwent bidirectional Sanger sequencing for confirmation. PCR and sequencing used the following primers: exon 2 of *PTPRQ*, sense 5′-TAG CTT GCT TGC TTT CCA GA-3′ and antisense 5'-GCA GAA TGC AGG TTC TAA GCA-3′; exon 33 of *PTPRQ*, sense 5′-ATT TGC CAT GTT TGA GTC CA-3′ and antisense 5'-GCT TGG AGG TTT TTC CAA CA-3′. The reference sequence (NM_001145026) producing a 2299 amino acid protein (ENST00000644991.3) was used for chromatogram comparison using with SeqMan v5.00 (DNASTAR, Madison, WI, USA). The mutations were analyzed in the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/) and based on previous reports to determine their novelty or associations with hearing loss. The Human Genome Variation Society (HGVS) guidelines were used to identify the mutations.[17]

2.4 | Pathogenicity prediction for different mutations

The mutations were evaluated by silico software such as Mutation Taster (http://www.mutationtaster.org/), FSPLICE (http://www.softberry.com/), NetGene2 Server (www.cbs.dtu.dk/), PANTHER (http://www.pantherdb.org/), SIFT (https://sift.bii.a-star.edu.sg/), and CADD (https://cadd.gs.washington.edu/) for predicting their harmful effects on protein function. The mutations were also classified based on the American College of Medical Genetics and Genomics (ACMG) guidelines.[18]

3 | RESULTS

The proband, a 25-year-old woman, had bilateral postlingual-delayed progressive severe SNHL (Figure 1B). Syndromic hearing loss was excluded according to medical history and clinical assessment. The

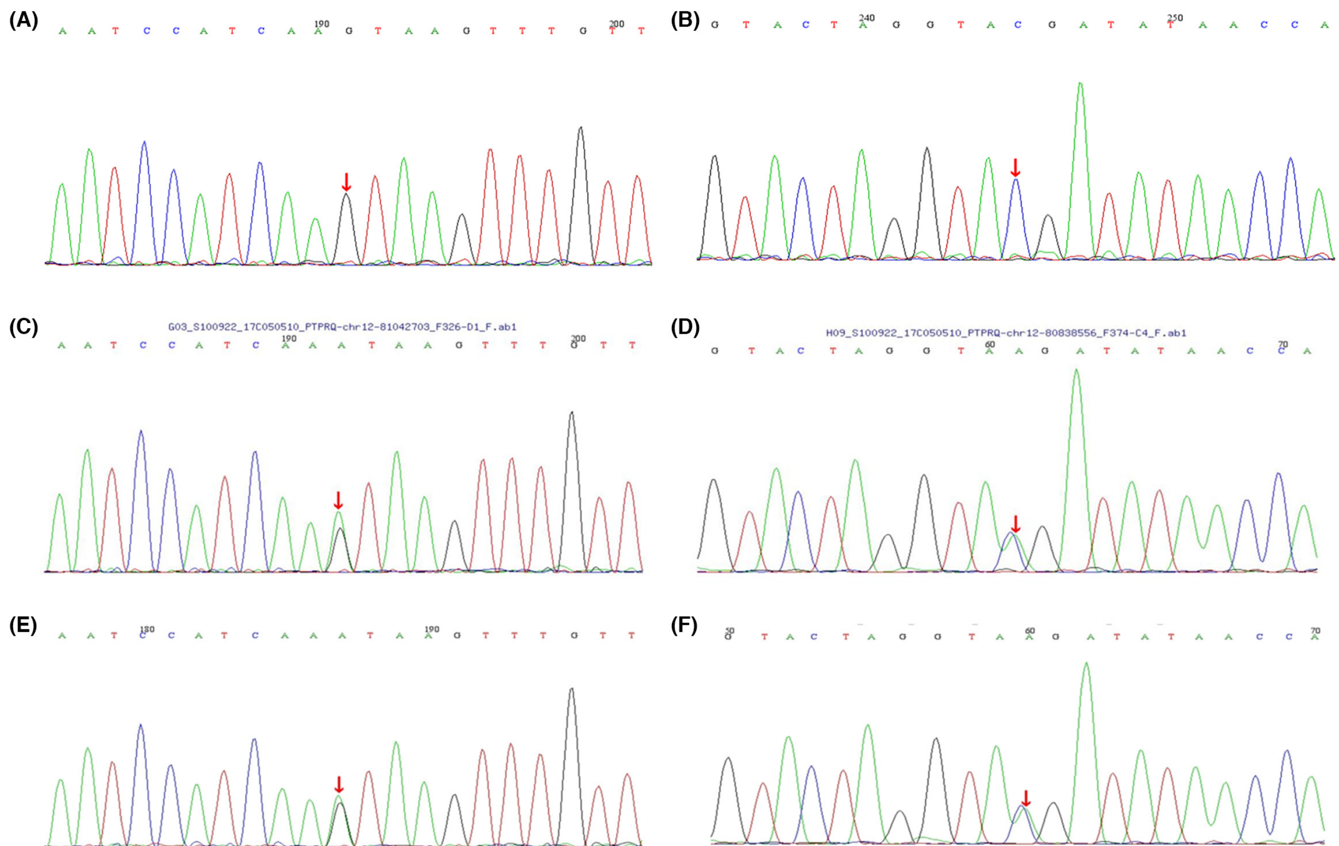

FIGURE 2 Splice mutation ([c.5426 + 1G > A]; A: control) and heterozygous nonsense mutation (c.90C > A [p.Y30X]; B: control) and in the *PTPRQ* gene of patient (C,D) and her proband's sister (E,F).

TABLE 1 Known *PTPRQ* gene mutations and associated phenotypes.

Variation	Amino acid alteration	Phenotype (non-syndromic HL)	Population (Hom or Het)	References
c.1285C>T	p.Q429X	Moderate–severe	Palestinian (Hom)	Shahin (2010)[5]
c.1491T>A	p.Y497X	Profound	Dutch (Hom)	Schraders (2010)[6]
c.1369A>G	p.R457G	Severe-profound	Moroccan (Hom)	Schraders (2010)[6]
c.1261C>T	p.R421X	Profound	Japanese (Hom)	Sakuma (2015)[7]
c.166C>G	p.P56A	Profound	Japanese (Com Het)	Sakuma (2015)[7]
c.4046T>C	p.M1349T	Profound	Japanese (Com Het)	Sakuma (2015)[7]
c.6453+3delA	p.M1349T	Profound	Japanese (Com Het)	Sakuma (2015)[7]
c.3125A>G	p.D1042G	Profound	Chinese (Com Het)	Gao (2015)[8]
c.5981A>G	p.E1994G	Profound	Chinese (Com Het)	Gao (2015)[8]
c.16_17insT	p.L8fsX18	Severe	Chinese (Com Het)	Sang (2015)[9]
c.2714delA	p.E909fsX922	Severe	Chinese (Com Het)	Sang (2015)[9]
c.5592dup	p.(Glu134Glyfs*6)	Profound	Algerine (Hom)	Ammar-Khodja (2015)[24]
c.6080dup	p.(Asn2027Lys*9)	Profound	Algerine (Hom)	Ammar-Khodja (2015)[24]
c.4472C>T	p.T1491M	Severe-profound	Chinese (Com het)	Wu (2018)[10]
c.1973T>C	p.V658A	Severe-profound	Chinese (Com het)	Wu (2018)[10]
c.2599T>C	p.S867P	Profound	Iranian (Hom)	Talebi (2018)[11]
c.6881G>A	p.W2294*	Mild-profound	Germany (Hom)	Eisenberger (2018)[16]
c.552delC	p.D184fs	Severe-profound	Chinese (Hom)	Sang (2019)[25]
c.5158_5159delAT c.6739–1G>A	p.(Ile1720Glnfs*7) splicing	Not mentioned Not mentioned	Pakistani (Hom) Pakistani (Hom)	Richard (2019)[26] Richard (2019)[26]
c.6881G>A	p.Trp2294*	Moderate–severe	German (Hom)	Oziębło (2019)[27]
c.1148G>A c.2521C>T	p.(Gly383Glu) p.(Arg841Trp)	Not mentioned Not mentioned	French (Hom) French (Hom)	Boucher (2020)[28] Boucher (2020)[28]
c.1057delC	p.L353SfsX8	Not mentioned	Chinese (Hom)	Yang (2021)[29]
c.55-2A>G	Splicing	Normal	Pakistani (Hom)	Mahmood (2021)[30]
c.4006C>T	p.(Gln1336Ter)	Not mentioned	India (Hom)	Vanniya (2021)[31]
c.997G>A c.6603-3T>G	Splicing Splicing	Severe Severe	Chinese (Com Het) Chinese (Com Het)	Jin (2021)[32] Jin (2021)[32]
c.6087-3T>G	Splicing	Not reported	Chinese (not reported)	Chen (2021)[33]
c.90C>A	p.Y30X	Moderate-profound	Chinese (Com Het)	This study study
c.5426+1G>A	Splicing	Moderate-profound	Chinese (Com Het)	This study

Note: Hom: homozygous, Het: heterozygous, and Com Het: compound heterozygous.

proband's parents were nonconsanguineous, and she was born by natural delivery at full-term. She had no developmental delay or regression. Similar SNHL was found in her sister (Figure 1C). No other genetic diseases were detected in the family tree.

Whole-exon sequencing detected a splice mutation ([c.5426+1G>A]; Figure 2A: control) and heterozygous nonsense mutation (c.90C>A [p.Y30X]; Figure 2B: control) and in the *PTPRQ* gene of patient (Figure 2C,D) and her proband's sister (Figure 2E,F). The c.5426+1G>A mutation was in the splice site of exon 33, eliminating part of the extracellular domain. This splice mutation was deleterious as determined by Mutation Taster, SIFT, PROVEAN, and PANTHER. The mutations were not found in the dbSNP version 147, 1000 genomes project phase 3, NHLBI GO ESP, ExAC, Iranome, HGMD, and Clinvar databases. The c.90C>A mutation leads to a premature stop codon, yielding a truncated protein that comprised only 30 residues (compared with 2299 amino acids in the full protein), with a small number of fibronectin type-III 1 (FNIII 1) domains.

The mutation co-segregated with the disorder in this family: it was heterozygous in the mother and the father but compound heterozygous in the proband and her sister, both biological children of the family (Figure 1A). Based on ACMG guidelines, these two mutations were categorized as pathogenic (one very strong, two moderate, and one supporting criteria):

– It is a nonsense mutation or a splice mutation (a null mutation) (PVS1).

– It is in a critical and well-established functional domain (PM1).

– This mutation is absent from controls (or at extremely low frequency if recessive) in the Exome Sequencing Project, 1000 Genomes Project, and Exome Aggregation Consortium (PM2).

– The mutation was co-isolated from the disease in the family (the mutation was found in multiple patients in the family) (PP1).

4 | DISCUSSION

In this study, new compound heterozygous *PTPRQ* mutations were identified in two sisters with postlingual severe hearing loss, which was considered ARNSHL and included a nonsense mutation (c.90C>A [p.Y30X]) and a splice mutation (c.5426+1G>A) in *PTPRQ*.

Hair bundles are composed of stereocilia, which have rows of rising heights and are intertwined via multiple links of different morphologies, translating sound from mechanical to electrical signals.[12] The *PTPRQ* protein in the inner ear is composed of three parts, including a long extracellular domain (composed of a varying number of FNIII domains), a short hydrophobic transmembrane domain, and an intracellular region with one phosphatase catalytic site.[19,20] It is critical for the normal maturation of cochlear hair bundles.

We used "*PTPRQ*" and "hearing loss" as keywords to search in PubMed, and 19 articles reporting on human patients were retrieved. Up to now, only a few families with hearing loss resulting from *PTPRQ* mutations have been reported (Table 1). Of all 29 cases associated with *PTPRQ* gene mutations, 11 were Chinese. Moreover, three compound heterozygous mutations were found in Chinese cases, while homozygous mutations resulting from consanguineous marriages were detected in other populations.

In this work, a compound heterozygous mutation was found in sisters born from nonconsanguineous parents. A nonsense mutation (c.90C>A [p.Y30X]) was mapped to exon 2 of *PTPRQ* (NM_001145026). The resulting premature stop codon was predicted to yield a truncated protein, leading to dysfunction or deficiency of the extracellular, transmembrane, and phosphatase domains because of nonsense-mediated mRNA decay. The second mutation was c.5426+1G>A, mapped to exon 33 and resulting in splice mutation in the extracellular domain. The extracellular domain helps bind ligands such as extracellular proteins, collagen, heparin, and cell surface ligands, and abnormalities of this domain might result in a dysfunction of hair cell stereocilia.[21–23] The mutations in the two alleles of *PTPRQ* were believed to be pathogenic because of their locations, and neither alteration was found in normal control individuals.

Overall, this study described two unique variations that include a nonsense mutation (c.90C>A [p.Y30X]) in one allele of *PTPRQ* and a splice mutation in the other allele. Such mutations eliminate *PTPRQ*'s extracellular domain, most likely inducing hearing loss. The *PTPRQ* gene should be examined in larger populations in Asia for a more comprehensive genotype–phenotype understanding of ARNSHL.

AUTHOR CONTRIBUTIONS

QY wrote the article. ZZG and ZZ helped with constructive discussions. LYH reviewed the article and is the corresponding author. QY and MYN contributed significantly to the analysis and article preparation. The author(s) read and approved the final article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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