Research Article

Autosomal Recessive Congenital Sensorineural Hearing Loss due to a Novel Compound Heterozygous PTPRQ Mutation in a Chinese Family

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PTPRQ gene, encoding protein tyrosine phosphatase receptor Q, is essential for the normal maturation and function of hair bundle in the cochlea. Its mutations can cause the defects of stereocilia in hair cell, which lead to nonsyndromic sensorineural hearing loss. Using next-generation sequencing and Sanger sequencing method, we identified a novel compound heterozygous missense mutation, c.4472C>T p.T1491M (maternal allele) and c.1973T>C p.V658A (paternal allele), in PTPRQ gene. The two mutations are the first reported to be the cause of recessively inherited sensorineural hearing loss. Hearing loss levels and progression involved by PTPRQ mutations among the existing cases seem to be varied, and the relationship between genotypes and phenotypes is unclear. Our data here further prove the important role of PTPRQ in auditory function and provide more information for the further mechanism research of PTPRQ-related hearing loss.

1. Introduction

Hearing loss is one of the most common sensory disabilities in humans. According to the latest data of WHO, there are 360 million people—over 5% of the world’s population—suffering from hearing loss, with 32 million are children (http://www.who.int/mediacentre/factsheets/fs300/en/). Genetic factors are the major cause of congenital sensorineural hearing loss (SNHL). Approximately 80% of nonsyndromic genetic hearing loss is autosomal recessive inheritance [1]. Currently, 64 genes for autosomal recessive nonsyndromic SNHL have been mapped (http://hereditaryhearingloss.org).

PTPRQ gene, encoding protein tyrosine phosphatase receptor Q, is one of the latest identified causes accounting for nonsyndromic SNHL. It is assigned DFNB84 locus on chromosome 12q21.31 and comprised of 58 exons [2]. The PTPRQ protein, localized in the basal region of the stereocilia membrane, is one of the membrane proteins which composed of 2299 amino acids. It has been reported that PTPRQ may have key roles in hair cells: establishing the membrane at the base of the stereocilia, regulating actin dynamics, and tethering the stereocilia membrane to the cytoskeleton with Myosin VI [3–5]. It is known to be required for the development of hair bundles, regulation of normal maturations, and formation of shaft connectors [6].
To date, there are eight families with inherited recessive mutations of PTPRQ which have been published [2, 7–10]. Identifications of PTPRQ mutations could be helpful to establish a better understanding of the relationship between PTPRQ and SNHL. Here, we present a Chinese family with congenital SNHL caused by a novel compound heterozygous PTPRQ mutation.

2. Materials and Methods

2.1. Family Description. This Chinese family, named Family 1, is a two-generation family associated with autosomal recessive nonsyndromic SNHL (Figure 1). The affected member III1, a 4-year and 2-month-old child, was diagnosed with congenital SNHL. The other individuals (I1, I2, and II2) had no history of hearing impairment. The child who was born in Hubei Province failed the newborn hearing screening and was diagnosed as congenital sensorineural hearing loss.

2.2. Audiological Examination. Visual reinforcement audiometry (VRA) was performed after the patient underwent otoscopic examination in our department. Degree of hearing loss was assessed by using pure tones. The stimuli were produced in the frequencies of 0.25, 0.5, 1, 2, 4, and 6 kHz. By using the stimulus-reply-visual reinforcement conditioning, the minimum response level was obtained in the lowest intensity which the child responded.

2.3. DNA Preparation. Peripheral venous blood samples from all the family members were obtained for genetic analysis. Genomic DNA was extracted from the blood samples using QIAamp DSP DNA Blood Mini Kit (61104, Qiagen Inc., Germany) according to kit’s protocol.

2.4. Next-Generation Sequencing + Sanger Sequencing. The target deafness-related gene capture and Next-generation sequencing + Sanger sequencing were performed by MyGenostics Inc. (Beijing, China). First, the genomic DNA was fragmented to special size about 350–400 base pair for library construction. End-repair and Illumina adapter ligation were taken according to the Illumina protocols. After PCR amplification, target DNA fragments were captured with biotinylated single-strand DNA capture probe (MyGenostics, MD, USA) by hybridization. The target gene fragments were enriched, and then high-throughput sequencing was performed using Illumina HiSeq2000 Analyzer for automated cycles per read. Primary data were generated using TrimGalore software (version 0.4.3). Reads were matched to NCBI37/hg19 using BWA program. Previously identified SNPs were annotated using CCDS, human genome database (HG19), and dbSNP (v138). SIFT and POLYPHEN2 were utilized to predict the function of SNP-affected protein.

2.5. Structural-Based Model Building and Analysis. The molecular homology modeling of the human wild type and mutations was built by SWISS-MODEL (http://www.swissmodel.expasy.org/). The complete protein sequence of human PTPRQ is available in the NCBI GenBank (NP_001138498.1). Data were showed by JavaScript Protein Viewer.

3. Results

3.1. Mutation Detection and Analysis. Mutations in mitochondrial and miRNA regions were excluded. After aligning to the human reference genome (GRCh37/hg19), these mutations corresponded to c.4472C>T and c.1973T>C, occurring in exon26 and exon13 of PTPRQ. The c.4472C>T leads to a single substitution within the fibronectin type III (FNIII) domain, from threonine to methionine (p.T1491M), and the other, c.1973T>C, leads to a single substitution (valine to alanine; p.V658A) within the FNIII domain. SIFT (http://sift.jcvi.org/) and POLYPHEN2 (http://genetics.bwh.harvard.edu/pph2/) were used to analyze the amino acid substitutions of p.T1491M and p.V658A. Both programs predicted these two mutations to be deleterious, which means they probably damage and affect protein functions. The sequencing results showed that the two parents were heterozygous carriers of c.4472C>T (maternal allele) and c.1973T>C (paternal allele), which demonstrated the compound heterozygous cosegregating mutation with the phenotype in III1 (Figure 2). The frequency of c.4472C>T mutation is 0.0016 in the East Asian population of EXAC database as well as 0.0002 in 1000 Genome Project. The c.1973T>C mutation rate accounts for 0.0222 in 1000 Genome Project. The frequency of c.1973T>C mutation was not found in the East Asian population of EXAC database.

3.2. Structure Modeling. Protein tertiary structures were modelling with SWISS-MODEL (http://www.swissmodel.expasy.or-g/), which predict the sequence homology. The p.T1491M protein model, covering the target sequence (residues 1163–1564), was constructed based on the receptor-type protein tyrosine phosphatase S (PDB ID: 4pbx.1.A).
Sequence identity between the target and template was 25.78%. As shown in Figure 3(a), the mutation probably affected the amino acid side chain through the substitution of threonine acid to methionine. The p.V658A protein model, covering the target sequence (residues 618–880), was constructed based on the receptor-type protein tyrosine phosphatase delta (PDB ID: 4yh7.1.A). Sequence identity between the target and template was 28.69%. As shown in Figure 3(b), it predicted that the mutation affected the amino acid side chain by the substitution of valine acid to alanine.

3.3. Clinical Data. Patient II1 is a 4-year and 2-month-old girl. Newborn hearing screening was failed at the age of 42 days. She had been referred to the Department of Otorhinolaryngology, Wuhan Union Hospital, for hearing...
Figure 4: Pure tone audiometry. Visual reinforcement audiometry showed severe-profound SNHL at month 7. After hearing aids (HAs), sound field threshold test showed improvement of hearing levels.
maldevelopment, while there was no abnormality of the auditory canal and middle ear. The CT showed narrow of both internal auditory canals without any malformation of middle ear and ossicular chain. The MR showed bilateral cochlear nerves abnormality and hearing loss is still needed for a better understanding of the gene. These two mutations have been predicted in previous studies [10]. Here, novel compound heterozygous mutations in the c.1491T>G and c.5981A>G in Chinese [8]; c.16_17insT and c.2714delA in a Kazakh family of China [9]; p.V658A (paternal allele), as a probable cause of autosomal recessive congenital SNHL in this family. The identification of additional hearing genes may improve the understanding of hearing function and hearing loss. More precise mechanism remains to be studied.

PTPRQ gene mutations were identified in different ethnic groups and countries, including c.1285C>T in Moroccan [2]; c3125A>G in Chinese [8]; c.1369A>G in Japanese [9]; and c.1491T>G and c.5981A>G in Chinese [8]. These mutations have been reported until now. The mutations were identified in different patients with SNHL. The mutations were also predicted by using next-generation sequencing + Sanger sequencing method in this study. The mutations were identified in four patients with SNHL. The mutations were also predicted by using next-generation sequencing + Sanger sequencing method in this study. The mutations were identified in four patients with SNHL. The mutations were also predicted by using next-generation sequencing + Sanger sequencing method in this study. The mutations were identified in four patients with SNHL. The mutations were also predicted by using next-generation sequencing + Sanger sequencing method in this study. 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of Science and Technology) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Consent

Informed consent was obtained from all patients for being included in the study.

Conflicts of Interest

Xia Wu, Shan Wang, Sen Chen, Ying-ying Wen, Bo Liu, Wen Xie, Dan Li, Lin Liu, Xiang Huang, Yu Sun, and Wei-jia Kong declare that they have no conflict of interest.

Authors’ Contributions

Xia Wu and Shan Wang contributed equally to this work.

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