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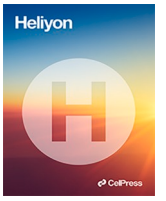

Case report

A sensorineural hearing loss harboring novel compound heterozygous variant in the *TRIOBP* gene: A case report

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ABSTRACT

Background: Autosomal recessive non-syndromic deafness-28 (DFNB28; OMIM #609823) specifically refers to prelingual sensorineural hearing loss (SNHL) resulting from homozygous or compound heterozygous mutations in the TRIO- and F-actin-binding protein, *TRIOBP* gene. In this report, we present a pediatric patient exhibiting novel compound heterozygous deleterious variants in the *TRIOBP* gene.

Methods: The auditory brainstem response result revealed both left- and right-sided deafness with a threshold of 20 dB normal hearing level in the proband. A comprehensive trio whole exome sequencing (WES) using the Celemics G-Mendeliome Whole Exome Sequencing Panel was employed.

Results: The WES analysis revealed compound heterozygous *TRIOBP* variants in the proband, namely c.1192_1195delCAACinsT/p.Gln398* classified as pathogenic and c.3661C > T/p.Arg1221Trp categorized as a variant of uncertain significance according to American College of Medical Genetics and Genomics guidelines. These variants are considered the most probable cause of the proband's SNHL.

Conclusion: TRIOBP isoforms are predominantly expressed in the inner ear, contributing to the formation of stereocilia rootlets. Further investigations are required to fully understand the phenotypic variability and establish the pathogenicity of the identified variant in relation to the *TRIOBP* gene and SNHL.

1. Introduction

Sensorineural hearing loss (SNHL) affects approximately 1 in 1000 newborns, with over half of these cases attributed to genetic factors [1]. Excluding pathogenic variants in GJB2 and GJB6, more than 90 genes may be involved in the pathogenesis of hearing impairment (http://hereditaryhearingloss.org). Clinically, about 30 % of SNHL cases present with syndromic features, while the

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remaining 70 % are non-syndromic. Currently, over 140 genes have been identified, and SNHL is documented in approximately 400 different syndromes [2–4]. Massively parallel sequencing enables comprehensive screening of all protein-coding sequences, allowing for a broad and unbiased search for pathogenic variants in many genetically heterogeneous diseases, including hearing impairment [3, 4]. Among them, autosomal recessive non-syndromic deafness-28 (DFNB28; OMIM #609823) specifically refers to prelingual SNHL resulting from homozygous or compound heterozygous mutations in the TRIO- and F-actin-binding protein, *TRIOBP* gene located on chromosome 22q13 [5]. TRIOBP produces proteins that interact with the triple functional domain (TRIO) and filamentous actin, playing a vital role in maintaining the durability and stiffness of hair cell stereocilia in the cochlea [5]. Stereocilia, which are found in the apical surface and roots of inner ear hair cells, along with the cuticular plate [6], serve as mechanosensory structures. The rigidity and flexibility of the stereocilia bundle are crucial for their proper function during stimuli. Rootlets, pliable structures anchoring the base of stereocilia to the cuticular plate, maintain the stiffness and durability of stereocilia. Their absence or dysfunction leads to hearing loss due to the degeneration of hair cells, which act as mechanical sensors. While the length of stereocilia varies in the cochlea, the dimensions of their rootlets remain consistent. Physical connections between the rootlets and the lateral wall, along with other cytoskeleton characteristics in the apex, contribute to somatic motility in the cochlear amplifier. These rootlets are composed of densely packed, tapered actin filaments. In 2006, Riazuddin et al. [7] and Shahin et al. [8] identified DFNB28 on chromosome 22q13.1, identifying pathogenic mutations in *TRIOBP* as the cause of hearing loss in 15 families. Multiple isoforms of the TRIOBP protein, varying in total length and expression pattern, have been discovered. This diversity in isoforms from a single gene may be attributed to the presence of six putative alternative promoters. Three TRIOBP isoforms have been identified: TRIOBP-1 (Transcript ID: ENST00000403663.6), TRIOBP-4 (Transcript ID: ENST00000492485.5), and TRIOBP-5 (Transcript ID: ENST00000344404.10). While TRIOBP-1 is broadly expressed across various tissues and plays a role in the regulation of adherens junctions and the reorganization of the actin cytoskeleton—particularly in stress fibers and cortical F-actin—TRIOBP-4 and TRIOBP-5 are exclusively found in the adult inner ear and retina of both humans and mice. In the inner ear, TRIOBP-4 and TRIOBP-5 are localized in the rootlets of stereocilia, with TRIOBP-4 also extending along the entire length of the stereocilia. The proper structure of these rootlets is crucial for the rigidity and stiffness of stereocilia, which is essential for effective sound transmission [5]. Conversely, *TRIOBP* is linked to modulation of the actin cytoskeleton and is implicated in malignancy, schizophrenia, and SNHL [9].

In this report, we present a family with isolated, perilingual to postlingual hearing loss exhibiting a recessive inheritance pattern. Trio whole exome sequencing (WES), followed by direct Sanger sequencing, enabled the identification of a novel compound heterozygous deleterious TRIOBP pathogenic variant, leading to the establishment of a molecular diagnosis. To our knowledge, this case represents the first documented instance of TRIOBP-related SNHL in Korea, featuring a unique combination of novel compound heterozygous variants in the TRIOBP gene.

2. Case presentation

A 4-year-old boy (II-2 in Fig. 1A) was referred to the Department of Pediatric Neurology, Daejeon St. Mary's Hospital (Daejeon,

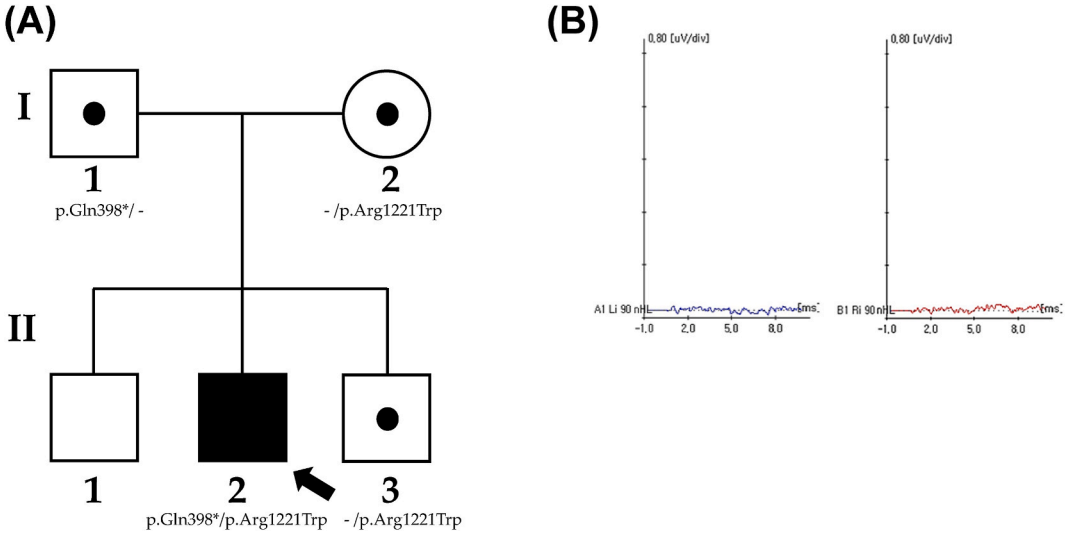

Fig. 1. Pedigree analysis and auditory brainstem response finding (A) Pedigree of the proband with bi-allelic TRIOBP variants in an autosomal recessive inheritance (arrow) and his family members. (B) Auditory brainstem response (ABR) utilizes click stimuli to elicit electrophysiological responses originating in the eighth cranial nerve and auditory brainstem. Surface electrodes capture these responses, establishing a "wave V detection threshold." This threshold, indicative of ABR detection, aligns most closely with hearing sensitivity in the 1500–4000 Hz range for neurologically normal individuals. In such cases, the average threshold for a normal hearing adult falls between 0 and 20 dB HL. As a result, the ABR result revealed both left- and right-sided deafness with a threshold of 20 dB normal hearing level. The x-axis presents: latencies (ms: millisecond); the y-axis presents: amplitude (mV: microvolt). Abbreviation: Li, left ear; Ri, right ear; nHL, normal hearing level.

Republic of Korea) due to the diagnosis of global developmental delay. Born via cesarean section at 37 weeks of gestational age, he was the second child of nonconsanguineous Korean parents, and the pregnancy had been uneventful. The child achieved head control at 3 months and began walking independently at 16 months. However, he did not utter a single word until the age of 5 years and exhibited poor responsiveness to his name. Limited gestures were observed, and he displayed a lack of shared interests with family or others. Assessment using the Bayley Scale of Infant and Toddler Development, Third Edition, at the age of 4 years revealed significant global developmental delay, and the language, cognitive, and motor ages were assessed at 6–9 months, 5–9 months, and 24–26 months, respectively. Brain magnetic resonance imaging showed normal structures and appropriate myelination. Auditory brainstem response (ABR) testing, using click stimuli, revealed profound hearing loss in the proband, with thresholds of ≥90 dB nHL or no ABR response at 90 dB nHL for both left and right ears. ABR thresholds below 20 dB nHL in diagnostic testing are considered indicative of normal hearing. This threshold closely corresponds to hearing sensitivity in the 1500–4000 Hz range for neurologically normal individuals (Fig. 1B). Visual evoked potential and ophthalmologic tests yielded normal results, and laboratory tests, including thyroid function and metabolic assessments, were within their normal range. The child's behavior progressively worsened, manifesting as aggression, tooth grinding, hand flapping, and hyperactivity. He frequently showed repetitive hand movements, such as clapping or jumping. He avoided eye contact with parents and caretakers and sometimes exhibited self-harming behaviors, including tapping his head. Social communication remained severely limited, requiring assistance with daily activities, such as feeding and dressing. Subsequently, he has been prescribed risperidone and methylphenidate.

3. Genetic analysis

To investigate the observed bilateral SNHL, we conducted sequential genetic testing for various SNHL disorders. Initial assessments, including conventional karyotyping and chromosomal microarray analysis, did not reveal any pathogenic structural and numerical chromosome changes or copy number variations. Subsequently, we employed a comprehensive trio WES using the Celemics G-Mendeliome Whole Exome Sequencing Panel, covering all exonic regions of major exome panels (37.1 Mb) with over 98 % coverage in the proband and his parents. This panel includes proprietary probes designed for flawless capture performance, even in challenging 'hard-to-capture' regions, such as GC-rich regions. Massive parallel sequencing was conducted using the DNBSEQ-G400RS High-throughput Sequencing Set and DNBSEQ-G400 sequencer (MGI Tech Co. Ltd., Shenzhen, China). Base calling, alignment, variant calling, annotation, and quality control reporting were conducted using the Genome Analysis Toolkit (GATK) best practice pipeline for

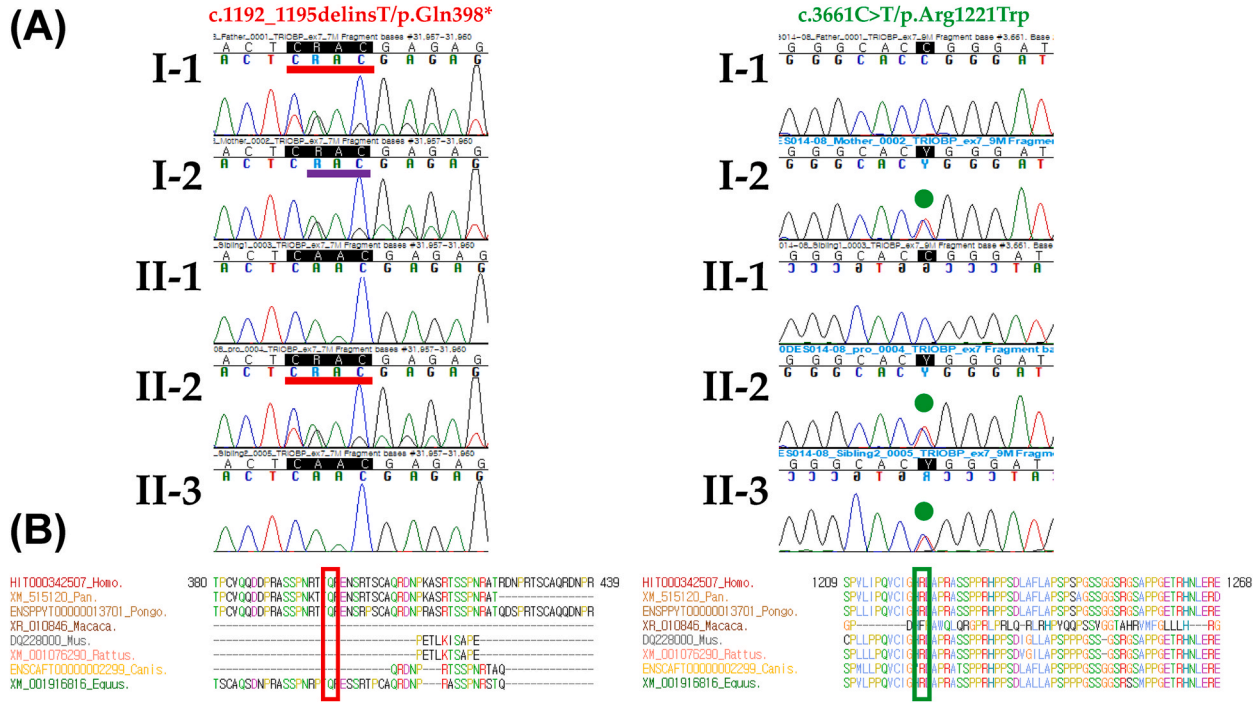

Fig. 2. Segregation analysis and conservation analysis (A) Sanger sequencing confirmed two bi-allelic TRIOBP variants, specifically compound heterozygous c.1192_1195delCAACinsT/p.Gln398* and c.3661C > T/p.Arg1221Trp, indicating an autosomal recessive origin in the proband (II-2) (Reference transcript ID: NM_001039141.3). The asymptomatic parents of the proband were identified as obligate heterozygotes, depicted by a red bar and green dot, respectively. A violet bar indicates a benign variant c.1193_1195del/p.Gln398del. (B) Sequence alignment of the conserved cytoplasmic domain of the TRIOBP protein across multiple vertebrate species shows that the protein sequence of TRIOBP p.Gln398 is highly conserved among Homo sapiens, Pan paniscus, Pongo pygmaeus, and Equus caballus, while the p.Arg1221 residue is conserved between Homo sapiens and Equus caballus except in Macaca mulatta. These conserved residues are highlighted in the empty red and green boxes, respectively.

germline short variant discovery (https://gatk.broadinstitute.org/hc/en-us). The interpretation of pathogenic variants followed the standards and guidelines established by the 2015 American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [10]. The filtering criteria applied to identify potential harmful variants are outlined as follows: (1) Variants located near or within the exons of protein-coding genes associated with Mendelian diseases. (2) Variants with allele frequencies less than 0.01. (3) Variants causing nonsynonymous or nonsense changes in codons within exons, altering highly conserved splice sites, or inducing frameshift mutations. (4) De novo variants, compound heterozygous, or homozygous variants of the same gene identified solely in the proband. (5) The specific deafness and/or autism, developmental delay, mental retardation are likely considered sporadic or inherited in an autosomal/X-linked recessive manner because the proband's parents and siblings were unaffected. Furthermore, the pathogenic effects of filtered variants were assessed using ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/, accessed on March 20, 2024). The allele frequencies of filtered variants were estimated in the general population using the Genome Aggregation Database (gnomAD v.2.1.1, https://gnomad.broadinstitute.org/, accessed on March 20, 2024).

WES generated a yield on target of 6,117,775,386, 6,566,495,910, and 4,417,509,378 reads from the proband, his father, and his mother by estimating sequence quality along all sequences. The mean read depth (x) was 76. Percentages of bases above read depth of 10x and 30x were 98.8 % and 93 %, 98.8 % and 93.8 %, and 97.8 % and 88.1 %, respectively. As a result, several variants were identified through WES in the proband with SNHL, as well as in his unaffected parents. Among these variants, compound heterozygous *TRIOBP* variants were identified, specifically c.1192_1195delCAACinsT/p.Gln398* and c.3661C > T/p.Arg1221Trp, as the most likely cause of SNHL in the proband (Reference transcript ID: NM_001039141.3). Sanger sequencing confirmed the presence of bi-allelic *TRIOBP* variants, compound heterozygous c.1192_1195delCAACinsT/p.Gln398* and c.3661C > T/p.Arg1221Trp, indicating an autosomal recessive origin in the proband (II-2). The asymptomatic parents of the proband were identified as obligate heterozygotes, depicted by a red bar and green dot, respectively (Fig. 2A). Two siblings, who were physically and neurologically normal children, did not carry bi-allelic *TRIOBP* variants. Notably, the c.1192_1195delCAACinsT/p.Gln398* variant was absent in the Genome Aggregation Database (https://gnomad.broadinstitute.org/; accessed on January 8, 2024), thus classified as a novel variant. In-silico analysis using VarSome (https://varsome.com/; accessed on March 20, 2024), a variant knowledge community, data aggregator, and variant data discovery tool, predicted the second *TRIOBP* c.3661C > T/p.Arg1221Trp variant as BP4 (multiple computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc)). Additionally, sequence alignment of the conserved cytoplasmic domain of the TRIOBP protein across multiple vertebrate species revealed high conservation of the protein sequence of the *TRIOBP* p.Gln398 between Homo sapiens, Pan paniscus, Pongo pygmaeus, and Equus caballus, whereas the p.Arg1221 residue is conserved between Homo sapiens and Equus caballus except Macaca mulatta, as highlighted in the empty red and green boxes, respectively (http://www.h-invitational.jp/evola_main/annotation.cgi?hit=HIT000342507; accessed on January 8, 2024) (Fig. 2B).

Even though the c.1193_1195del/p.Gln398del (dbSNP ID: rs55745992) is a known indel classified as benign (Clinvar accession: VCV000198447.15) [7,11,12] and the c.1195C > T/p.Arg399* (dbSNP ID: rs750078356) is a known nonsense variant classified as pathogenic (Clinvar accession: VCV000450619.4) [13], the c.1195C > T/p.Arg399* occurred alongside the c.1193_1195del located on the same allele in our proband, resulting in a novel *TRIOBP* variant, c.1192_1195delCAACinsT/p.Gln398*, following the HGVS Nomenclature definition. This variant is likely pathogenic based on the ACMG guidelines: PVS1 (null variants), PM2 (absence from controls), and PP3 (multiple lines of computational evidence). The second variant, c.3661C > T/p.Arg1221Trp (dbSNP ID: rs375575197), has a frequency of 0.0007723 in the East Asian population and 0.0001133 in the overall population. This missense variant is classified as PM2 (extremely low frequency if recessive), PM3 (found in trans with a pathogenic variant for recessive disorders), and BP1 (missense variant in a gene where primarily truncating variants are known to cause disease) according to ACMG guidelines. Although TRIOBP c.3661C > T/p.Arg1221Trp does not fully meet the criteria for pathogenicity under ACMG guidelines, a recent study employing a deep learning protein prediction algorithm associated this variant with hearing loss across a comprehensive deafness proteome (Table 1) [14]. Consequently, this missense variant has been classified as likely pathogenic and possibly responsible for non-syndromic hearing loss.

4. Discussion

The onset and severity of sensorineural hearing loss (SNHL) may vary, and this diversity could be associated with the specific loci of *TRIOBP* variants and their impact on different isoforms. Currently, 45 variants linked to SNHL have been documented in *TRIOBP* mutations [3,7,8,15–28]. Although these variants span from exon 4 to exon 23, notable hotspots for variations in *TRIOBP* are located in exon 7, which is known for its susceptibility to variations due to the accumulation of repeated sequences [19]. Truncated mutations within the R1 motifs of TRIOBP-4/-5 and the pleckstrin homology (PH) and coiled-coil (CC) domains of TRIOBP-5 are presumed to lack

Table 1
Solvent accessible surface areas, AlphaFold2 confidence scores [15], and DDGun free energy predictions for the *TRIOBP* c.3661C > T/p.Arg1221Trp variant in the Deafness Variation Database [16].

Impact	CADD Phred QS*	Interpro Domain	Max MAF (%)	Surface Area (SA)	Normalized SA	Confidence Score	ΔΔG_fold**
MODERATE	32	null	0.077232	246.3498	0.914352	31.4	0.1

CADD, combined annotation dependent depletion; Phred QS, Phred quality score; MAF, minor allele frequency in East Asian population.
*When filtered for CADD Phred score threshold of >25.7, variant of uncetain significane is determined as likely pathogenic at a probability of 99.0 %.
**Variants exhibiting a ΔΔGFold greater than 1.8 kcal/mol significantly disrupt the protein fold, often leading to loss of function or protein degradation. Setting the threshold at 1.8 kcal/mol yields a positive predictive value (PPV) of 97.1 % and a specificity of 98.2 %.

functionality, potentially reducing the actin binding activity of TRIOBP proteins. Advances in WES have enabled extensive screening of causative genes for SNHL [25]. *TRIOBP* encodes a protein with an N-terminal PH domain and a C-terminal CC region. This protein interacts with TRIO, a key player in neural tissue development, regulating actin cytoskeleton organization, cell growth, and migration [9,29,30]. Additionally, the protein is associated with F-actin, stabilizing its structures. TRIOBP also communicates with Trio, a protein derived from a group of Dbl-homology guanine nucleotide exchange factors (DH-GEFs) [31], which modulate actin cytoskeleton reorganization and cell adhesion, and function as transcription factors due to the activation of Rho GTPase [32]. Various alternatively spliced transcript variants encoding distinct isoforms have been identified for TRIOBP, although some transcripts may be affected by nonsense-mediated decay [31]. *TRIOBP* encodes three isoforms with variable sizes: TRIOBP-1 (593 amino acids, 73 kDa), TRIOBP-4 (1144 amino acids, 107 kDa), and TRIOBP-5 (2193 amino acids, 218 kDa). The variability in isoforms originating from a single gene may be explained by the presence of alternative promoters [33].

TRIOBP-1 acts as a regulator of adherens junctions and reorganization of the actin cytoskeleton, particularly in stress fibers and cortical F-actin [8]. The TRIOBP-1 protein consists of three folded domains: a PH domain near the N-terminus and two CC domains near the C-terminal half. The PH domain binds actin and stabilizes actin filaments, playing a critical role in cell viability. TRIOBP-1 is expressed ubiquitously, with notable expression in the brain, where it acts as a key regulator of actin in neurites [31,34–36]. Notably, TRIOBP-1 has been identified in the brains of patients with psychiatric disorders, revealing its involvement in aspects of schizophrenia related to protein degradation interruption [35,37,38]. Although TRIOBP-1 is present in the inner ear and stereocilia, it may not be involved in the formation of stereocilia or may not contribute to SNHL [6].

On the contrary, TRIOBP-4 interacts with F-actin via its R1-repeat motifs and does not share any amino acid sequence with TRIOBP-1. TRIOBP-5 encompasses the complete amino acid sequence of TRIOBP-4, most of the sequence of TRIOBP-1, and additional elements. The amino acid sequences of TRIOBP-4/-5 include two repeat motifs, namely the R1 repeat domain (amino acid residues 357–500) and the R2 repeat domain (amino acid residues 684–896). The R1 motif primarily serves as the primary actin-binding region of TRIOBP-4/-5, while the R2 motif plays a secondary role [39,40]. TRIOBP-4 functions as an actin-bundling protein, covering actin fibers in stereocilia with bundle flexibility. This binding occurs through the R1 repeat motif, bundling them together during rootlet formation and early stereocilia growth [5,40]. Meanwhile, TRIOBP-5 has a similar but distinct role, retaining the actin core of stereocilia in the inner ear enabling hearing, whereas TRIOBP-4 is expressed throughout the rootlets and the entire length of the stereocilia [5,7,8,41]. Both TRIOBP-4 and TRIOBP-5 are present in human and mouse retina, brain, and inner ear [19,29,30]. Transcripts encoding long variants, such as TRIOBP-5, have been expressed in mouse brain cDNA, suggesting a potential function in human brain development, including the sequence of TRIOBP-4 [7]. The identified novel pathogenic variant, c.1192_1195delCAACinsT/p.Gln398*, has the potential to disrupt the TRIOBP-4 and TRIOBP-5 isoforms, while the c.3661C > T/p.Arg1221Trp classified as likely pathogenic specifically may affect TRIOBP-5. These isoforms are predominantly expressed in the inner ear, and they contribute to the formation of stereocilia rootlets. Importantly, both variants do not impair TRIOBP-1. However, a few animal model studies have suggested that TRIOBP-5 mutations in a shorter isoform that expressed in the brain, can be related to mental illness. Historically recognized as a cause of nonsyndromic SNHL such as DFNB28, TRIOBP has now been implicated in neurodevelopmental disorders [42,43]. However, further investigations are required to fully understand the phenotypic variability and establish the pathogenicity of the identified variants in

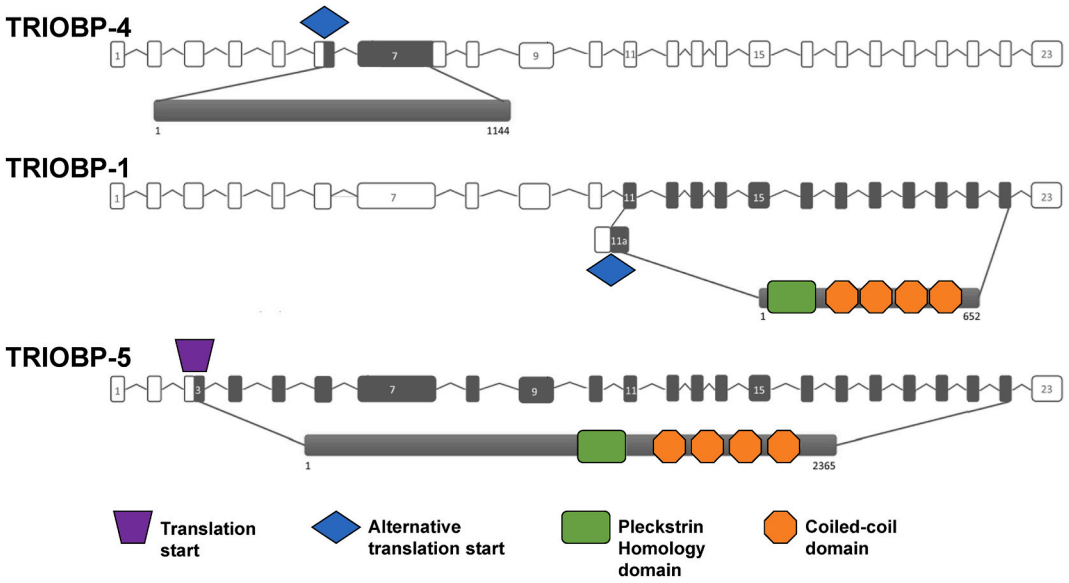

Fig. 3. The structure of TRIOBP isoforms 1, 4, and 5. The structure of TRIOBP isoforms is depicted in the upper panels, illustrating the gene structure of TRIOBP. The lower panels display three isoforms: TRIOBP-4, TRIOBP-1, and TRIOBP-5, respectively. All isoforms are in the same reading frame. Translation of TRIOBP-4 begins from an alternative start site in exon 6, while translation of TRIOBP-1 starts within an alternative exon 11a. The numbers provided below each specific isoform indicate the first and last amino acid positions.

relation to the *TRIOBP* gene and SNHL, as well as neuropsychiatric disorders, cancer. Structure of TRIOBP isoforms 1, 4, and 5 is illustrated in Fig. 3.

Interestingly, mutations in *TRIOBP* have been associated with bilateral SNHL, suggesting a potential comorbidity between SNHL and neuropsychiatric problems according to several reports [8,44,45]. In a study of over 50,000 individuals in the Swedish population, an increase in severe SNHL was found in the schizophrenia group. Similarly, a World Health Organization (WHO) study of over 220, 000 individuals from various ethnicities identified hearing impairments as a common comorbidity in individuals with psychotic problems [46,47]. A study in Sweden found that hearing impairment and speech impairment at the age of 4 years were linked to an increased risk of non-affective psychotic illness [48]. Deficiencies in gene expression or coinheritance combinations of polymorphisms within the *TRIOBP* gene may contribute to these comorbidities in some patients. In a Pakistani family study, three siblings with schizophrenia and hearing impairment, with or without epilepsy, showed causative mutations in two chromosomal regions, one of which contained the *TRIOBP* locus through homozygosity mapping [49]. Even though in-silico analysis predicted our indel to have a harmful effect, additional functional studies are needed to demonstrate the functional impairment caused by the frameshift that leads to a premature stop codon at position 398 of the protein coding sequence. Understanding the functional consequences of distinct TRIOBP gene variants is essential for developing targeted therapies. Functional studies can elucidate how these mutations impair hearing, enabling the development of specific interventions to counteract these effects. For instance, if a particular variant is found to disrupt protein function in a specific manner, therapies could be designed to compensate for or correct this dysfunction.

Personalized medicine and genetic counseling play a crucial role in managing suspected congenital SNHL, especially when there is a strong family history of hearing impairment. These approaches are also essential for all infants who do not pass the newborn hearing screening. Personalized medicine allows for tailored treatment and management strategies based on an individual's unique genetic profile, while genetic counseling provides families with information about the genetic basis of the condition, inheritance patterns, and potential outcomes. This integrated approach helps in accurate diagnosis, informed decision-making, and targeted interventions, ultimately improving patient outcomes and family support [50]. Additionally, personalized medicine can incorporate environmental and lifestyle factors, providing a comprehensive approach to managing SNHL. This can include strategies to mitigate environmental influences that may exacerbate the condition or personalized hearing aid solutions that cater to the specific hearing profile caused by the *TRIOBP* mutation. Genetic counseling is essential for managing patients with hereditary SNHL. It offers patients and their families detailed information about the genetic underpinnings of SNHL, the implications of genetic testing, and the risks associated with inheritance. Counselors assist in interpreting genetic test results, discussing potential outcomes, and guiding families through subsequent steps, which may involve additional testing, monitoring, and treatment options. They facilitate personalized treatment plans, offer critical support and information to affected families, and enhance understanding of the genetic and environmental factors impacting the condition.

In conclusion, this report presents the first case of *TRIOBP*-related prelingual bilateral SNHL caused by compound heterozygous *TRIOBP* variants in the proband, c.1192_1195delCAACinsT/p.Gln398* classified as pathogenic and c.3661C > T/p.Arg1221Trp categorized as a likely pathogenic according to ACMG guidelines. Further investigation is necessary to determine the pathogenicity of the identified variant and any related genes. Additionally, additional studies are needed to elucidate the specific functions of TRIOBP across its isoforms. Conducting functional studies will provide a more comprehensive understanding of the diverse roles of the *TRIOBP* gene in both auditory function and neurodevelopment.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of the Catholic University of Korea (Approval number: DC23ZASI0004; Date of approval: January 17, 2023).

Consent for publication

Written informed consent was obtained from the parents on behalf of their children for the clinical and molecular analyses and for the publication of any potentially identifiable images or data included in this study.

Data availability statement

Data are contained within the article.

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CRediT authorship contribution statement

Jung Woo Rhim: Writing – original draft, Formal analysis, Data curation. **Dong-Kee Kim:** Formal analysis, Data curation. **Ji Yoon Han:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Joonhong Park:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

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