Case Report

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Autosomal Recessive Non-Syndromic Hearing Loss: A Case Report with a Novel TRIOBP Gene Variant

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Citation Jangam Sh, Kurup M, Arora P, Jawale Sh, Duraphe P, Gupte S. Autosomal Recessive Non-Syndromic Hearing Loss: A Case Report with a Novel TRIOBP Gene Variant. Case Reports in Clinical Practice. 2024; 9(3): 108-113.

Running Title Novel TRIOBP Gene Variant for Non-Syndromic Hearing Loss

ABSTRACT

In the present case report, we have found a novel variant for TRIOBP in a patient with congenital hearing loss. The patient is an 8-year-old female with hearing loss, the first child of consanguineous parents. To identify the underlying genetic defect, whole genome sequencing was performed. Carrier screening of the parents was also conducted. The results showed a homozygous autosomal recessive missense c.5849C>T (p.Pro1950Leu) variant in exon 16 of the TRIOBP gene. To our knowledge, this variant has not been previously reported as either a pathogenic or a benign variant. The novel TRIOBP variant found in the present study broadens the range of TRIOBP mutations implicated in hearing loss. Accordingly, the results of this study may be important for genetic counseling.

Article info:
Received: April 29, 2024
Revised: May 25, 2024
Accepted: June 19, 2024

Keywords:
TRIOBP gene; Congenital hearing loss; Whole genome sequencing

Introduction

In India, the incidence of hearing loss has increased from 76.5 million in 2008 to 100 million in 2018. South Asian countries, including India, have contributed 28.2% to the global burden of hearing loss. In this region, 7.37% of the population, including 2.4% of all children, suffer from Disabling Hearing Loss (DHL) compared to 4.57% and 0.5%, respectively, in high-income countries [1]. The estimated prevalence of permanent bilateral hearing loss is 1.33 per 1,000 live births [2]. This rise over time likely reflects the gradual increase in people who have hearing loss due to progressive, acquired, or inherited causes. Because language abilities are still developing in babies and are not abnormal at that time, diagnostic findings for several types of hearing loss, such as Auditory Neuropathy Spectrum Disorder, are sometimes inconclusive; as a result, prevalence estimates for these conditions vary greatly [3].

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Congenital hearing loss is the impairment of the ear to convert vibratory mechanical energy into electrical energy of nerve impulses, present since the birth of the child. Based on the site of the lesion, it is divided into conductive hearing loss and sensorineural hearing loss (SNHL). The auditory nerve or central auditory pathway is affected by SNHL, whereas conductive hearing loss involves the outer or middle ear. In the absence of any other clinical symptoms, hereditary hearing impairment is indicated as "non-syndromic," which is a genetically heterogeneous disorder [4]. Early diagnosis, prediction, and prompt intervention are necessary to improve developmental outcomes in childhood.

Up to the present time, 123 HL genes implicated in non-syndromic hearing loss have been identified. However, pathogenic variants can be identified in only one-third of patients with SNHL [5], and in one-fourth of patients with cochlear implants, pathogenic mutations in common hearing loss genes can be identified [6-8]. Autosomal recessive hereditary hearing loss is an infrequent type of deafness associated with the TRIOBP gene. In 2006, Riazuddin et al. and Shahin et al. mapped DFNB28 to chromosome 22q13.1, showing significant deviations in the pathogenic mutations in TRIOBP [9,10]. Typically, pathogenic variants of TRIOBP lead to severe-to-profound prelingual hearing loss. The TRIOBP gene encodes TRIO- and filamentous-actin-binding proteins, which play a significant role in the durability and stiffness of hair cell stereocilia in the cochlea [11].

In the present case report, we have found a novel variant of TRIOBP in a patient with congenital hearing loss.

Case presentation

Here, we present an 8-year-old female patient with hearing loss, the first child of consanguineous parents. Her parents were clinically normal. No other abnormality has been observed in her clinical examination or past medical history. To identify the underlying genetic defect, genomic DNA was extracted from the blood samples of the patient after obtaining informed consent. The extracted DNA was subjected to whole genome sequencing to identify a genetic abnormality. The result showed a homozygous autosomal recessive missense c.5849C>T (p.Pro1950Leu) variant in exon 16 of the TRIOBP gene (Figure 1).

To our knowledge, this variant has not been previously reported as either a pathogenic or benign variant. The p.Pro1950Leu variant has been reported with an allele frequency of 0.02% in gnomAD Exomes. The amino acid change p.Pro1950Leu in TRIOBP is predicted as conserved by GERP++ and PhyloP across 100 vertebrates. The amino acid Pro at position 1950 is changed to Leu, altering the protein sequence and possibly its composition and physico-chemical properties. For these reasons, this variant has been classified as a Variant of Uncertain Significance (VUS). Variations in TRIOBP (TRIO and filamentous actin [F-actin] binding protein) are associated with autosomal recessive deafness-28 (DFNB28), characterized by severe to profound sensorineural hearing loss (Riazuddin S, et al., 2006). The above mutation was confirmed by Sanger sequencing in the patient. Carrier screening of her parents for the same variant was done. Bi-directional Sanger sequencing assay confirmed the presence of the heterozygous gene mutation in both parents of the patient (Table 1, Figures 2-4).

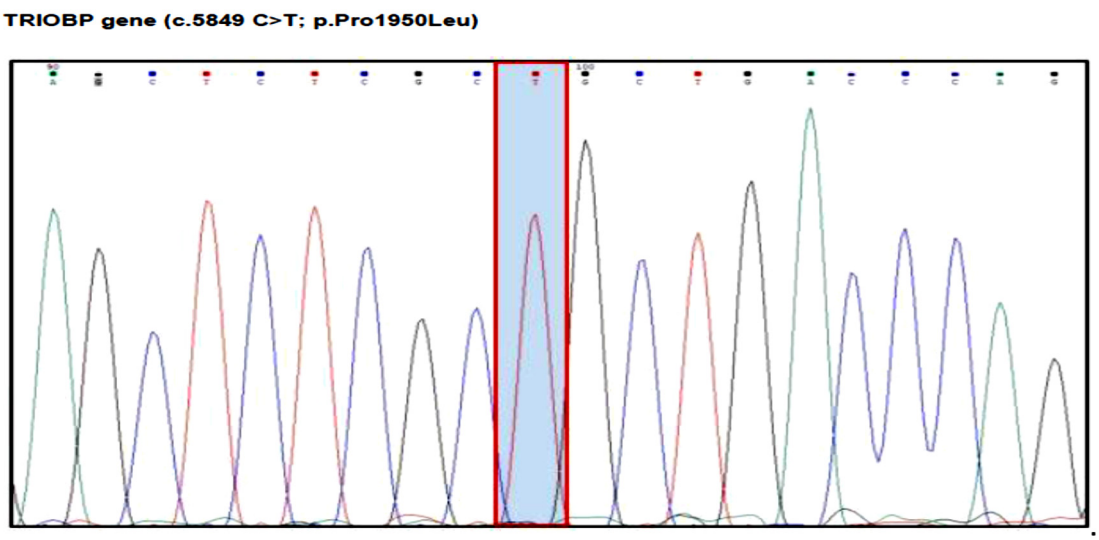

Fig. 1. Sanger sequencing confirmation of the variants in TRIOBP identified in the patient

Table 1. Results and interpretation of the data obtained after carrier screening of parents

Name	Gene	Chromosomal coordinates	Tested Variants	Comments	Interpretation
Patient	TRIOBP	Chr22: 37757774C>T	NM_001039141.3 c.5849 C>T; p.Pro1950Leu	Homozygous Variant Detected	Baby is affected by congenital hearing loss
Father&Mother	TRIOBP	Chr22: 37757774C>T	NM_001039141.3 c.5849 C>T; p.Pro1950Leu	Heterozygous Variant Detected	Carrier for congenital hearing loss

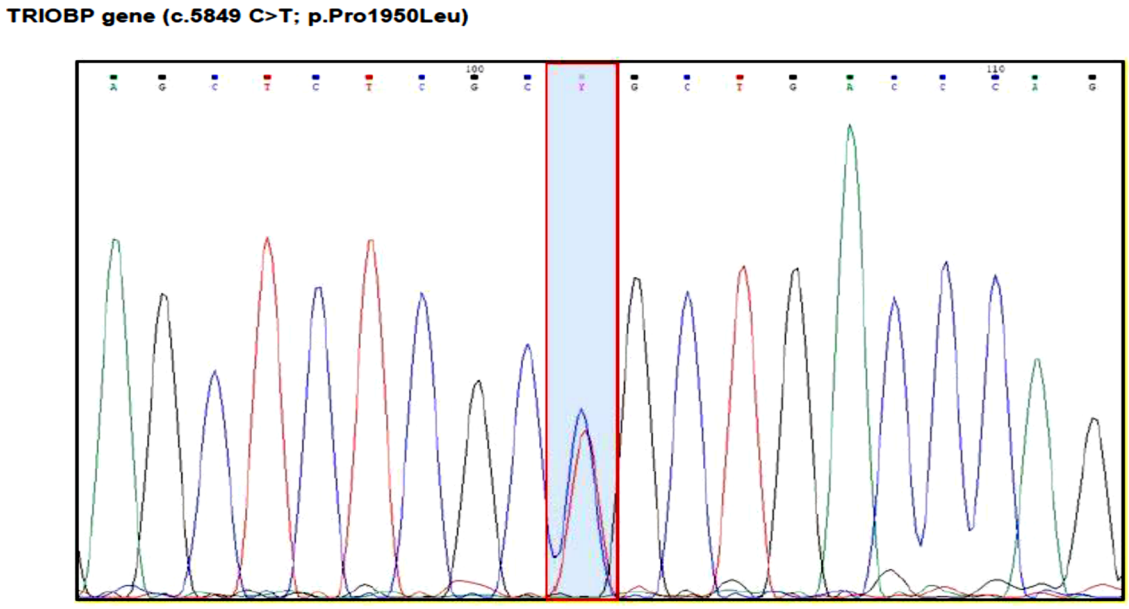

Fig. 2. Sanger sequencing confirmation of the variants in TRIOBP identified in the patient's father

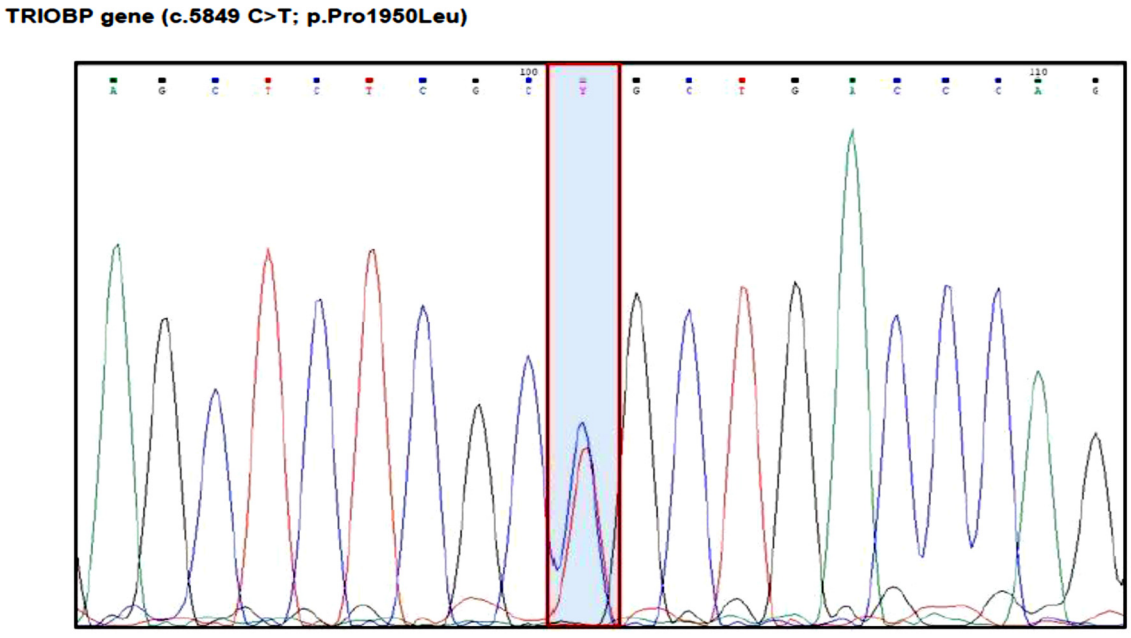

Fig. 3. Sanger sequencing confirmation of the variants in TRIOBP identified in the patient's mother

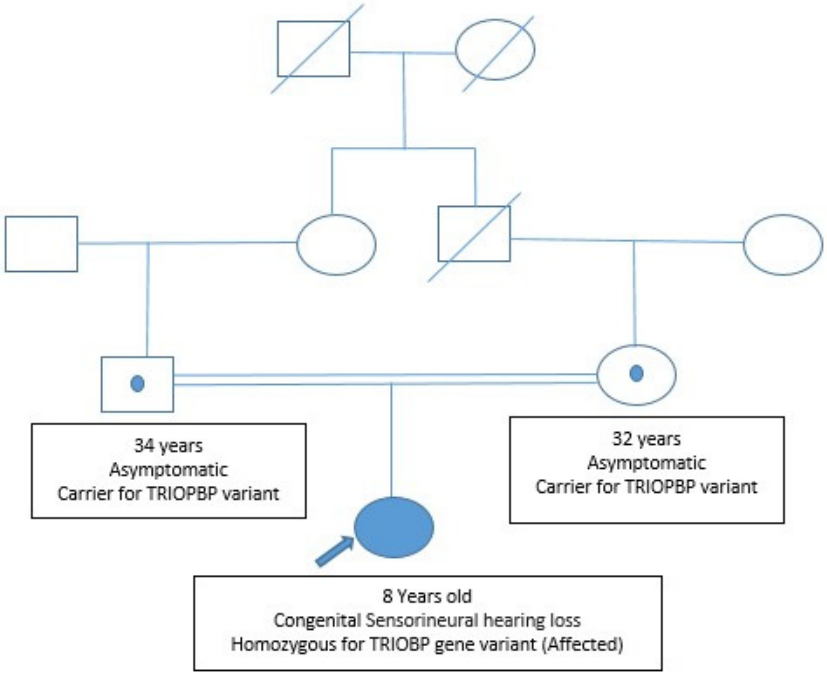

Fig. 4. Pedigree chart for the family

Discussion

Genetic variants in the TRIOBP gene result in DFNB28, characterized by sensorineural hearing loss. Modulation of cytoskeleton assembly is one of the major functions of the TRIOBP (TRIO and F-actin Binding Protein) gene, which encodes multiple proteins required in this process. The splicing of TRIOBP is a complex process. Out of the six known splice variants, three—TRIOBP-1, TRIOBP-4, and TRIOBP-5 transcripts—are the most studied. TRIOBP-4 and/or TRIOBP-5 are the major players in hearing loss [12-14].

A study in mice showed that stereocilia rootlets, which generally form in the first 16 days postnatal, were not formed in mice that could not produce either TRIOBP-4 or the longer isoforms. Although stereocilia do form, they are less rigid compared to the wild type and subsequently degenerate, resulting in profoundly deaf mice [11].

A wide range of pathogenic mutations in the TRIOBP gene in families or individuals with severe or profound prelingual hearing loss has been reported [14]. Consanguinity causes the majority of these pathogenic mutations in people with deafness to be homozygous. The bulk of TRIOBP-4 mutations found in patients to date are either nonsense or frameshift mutations that would cause the production of shortened TRIOBP-4 and longer splice variants like TRIOBP-5 and -6 but without a projected impact on TRIOBP-1. Although many of the mutations are found in the large exon 7, the placement of these mutations within the TRIOBP-4 protein differs significantly.

In the present case, the novel variant c.5849C>T (p.Pro1950Leu) detected is in exon 16. To the best of our knowledge, this variant has not been previously reported. As a result of consanguinity, where both parents were heterozygous for the same variant, the baby was born deaf, carrying the same homozygous trait. Neonatal hearing screening programs are available for this common problem in the majority of developed nations. Within a month after birth, all babies need to be screened as part of these programs. Early diagnosis, intervention, and therapy help children develop more successfully later in life [15]. Neonatal hearing screening programs may overlook children with progressive hearing loss since hearing loss can worsen over time. For newborns who are at risk, frequent screening at regular intervals is indicated.

Depending on the cause and kind of hearing loss, congenital hearing loss is treated medically and with supportive measures. Genetic factors, craniofacial abnormalities, and congenital infections are the most common causes of hearing loss, including non-syndromic types in which hearing loss is the sole clinical symptom, and syndromes including Usher, Jervell, and Lange-Nielsen syndromes. The new TRIOBP variant found in the present study broadens the range of TRIOBP mutations implicated in hearing

loss, which can be helpful in the detection of hearing loss.

The discovery of the novel TRIOBP variant, c.5849C>T (p.Pro1950Leu), in this case report provides critical insights into the genetic mechanisms underlying hereditary hearing loss. However, further research is necessary to fully understand the functional impact of this mutation and its broader role in auditory physiology. Future studies should focus on the functional characterization of the variant through in vitro and in vivo experiments. These studies would help assess the specific impact of the p.Pro1950Leu mutation on TRIOBP protein function, particularly its role in actin bundling and the formation of stereocilia in the inner ear. Investigating the structural changes caused by this mutation and its effects on protein stability and interactions within the cytoskeleton could provide deeper insights into its contribution to hearing loss.

Animal models, especially knock-in models like mice carrying the p.Pro1950Leu variant, would be invaluable in studying the phenotypic consequences and effects on auditory function. Such models could also pave the way for exploring therapeutic interventions that target TRIOBP-related hearing loss. Additionally, population screening, particularly in South Asia and other regions, is necessary to determine the prevalence of this variant and other TRIOBP mutations. A special focus on consanguineous populations could help identify more cases of this mutation, further establishing its potential role in autosomal recessive hereditary hearing loss.

Expanding the investigation to include other cases of TRIOBP mutations would also help clarify genotype-phenotype correlations, shedding light on the range of hearing loss severity and age of onset. Understanding how specific TRIOBP mutations influence the auditory phenotype would offer better clinical insights for diagnosis and management.

Conclusion

The identification of novel mutations like p.Pro1950Leu also opens the possibility of exploring gene therapy or targeted molecular therapies as potential treatment strategies. Future studies should investigate whether therapies aimed at restoring TRIOBP function or enhancing actin bundling within stereocilia could mitigate or reverse the effects of hearing loss. Furthermore, carrier screening becomes particularly important in populations where consanguineous marriages are common. Expanding databases of TRIOBP mutations will improve genetic counseling and help families with a history of hearing loss make more informed decisions.

In summary, these future research directions will not only broaden our understanding of TRIOBP mutations but also contribute significantly to developing targeted diagnostics and potential treatments for hereditary hearing loss.

Acknowledgment

Shweta and Ketaki have performed the experiments. Manju and Dr. Preeti were involved in data interpretation. Dr. Shruti has written and reviewed the original draft of the case report. Dr. Prashant, Dr. Sarjan, and Dr. Sanjay have reviewed the case report.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

Funding

No funding was received to assist with the preparation of this manuscript.

Conflict of Interests

The authors have no conflict of interest to declare.

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