

Original Research

Novel *SLITRK6* Nonsense Mutation in an Iranian Family with Autosomal Recessive Syndromic Hearing Loss

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Abstract

SLITRK6 is essential for inner-ear neuronal survival and retinal development, and pathogenic variants in this gene cause syndromic sensorineural hearing loss (HL) with high myopia. This study aimed to identify the genetic basis of HL and myopia in a consanguineous Iranian family with two affected children and to characterize the molecular consequences of the detected



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variant. One sibling with bilateral congenital HL and myopia was evaluated using whole-exome sequencing (WES). Common variants (MAF >1%) were excluded, and rare exonic changes were prioritized. Variant pathogenicity was assessed according to ACMG guidelines, and segregation was confirmed by Sanger sequencing in two affected children and their parents. ProtParam was used to compare physicochemical properties of wild-type and truncated proteins, and STRING was applied to assess predicted protein-protein interactions. WES identified a novel homozygous nonsense variant in *SLITRK6*, NM_032229.3:c.1795C>T (p.Arg599Ter), located in exon 2. The parents were heterozygous carriers, and the variant was ultra-rare in public databases. In silico analyses predicted that the premature termination codon produces a truncated protein with loss-of-function effects. These findings are consistent with previously described *SLITRK6*-associated HL with myopia. We report a novel likely pathogenic *SLITRK6* variant associated with congenital HL and myopia in an Iranian family. The predicted loss-of-function supports an important role for *SLITRK6* in auditory and visual system development. Further studies are needed to elucidate the molecular mechanisms underlying *SLITRK6*-related disorders.

Keywords

SLITRK6; whole exome sequencing; loss of function mutation; stop mutation; truncated protein; auditory impairment

1. Introduction

Hearing loss (HL) is one of the most common neurosensory disorders, affecting 1 to 2 out of every 1,000 neonates and approximately 1 out of every 1,000 adolescents [1, 2]. This condition is projected to increase with global population growth and poses substantial challenges to language, cognitive, and social development [3-5].

In Iran, the prevalence of hereditary HL is notably high, with genetic factors accounting for 50% of cases. Previous studies have highlighted the prominent roles of mutations in genes such as *GJB2*, *SLC26*, *TECTA* and *PJVK* genes in Iranian patients. Despite significant research efforts over recent decades, the full extent of phenotypic and genetic heterogeneity of HL in the Iranian population remains incompletely understood [6, 7].

HL can be classified as syndromic or non-syndromic (NSHL). NSHL accounts for 70-80% of genetic deafness cases [8] and exhibits extensive heterogeneity, with over 150 loci and more than 40 causative genes identified to date [3-5, 9]. Inheritance patterns are predominantly autosomal recessive (75-85%), followed by autosomal dominant (15-25%), X-linked (1-2%), and mitochondrial (~1%) [4, 10]. Syndromic HL, characterized by additional systemic features, accounts for 20-30% of genetic cases and has been reported to comprise approximately 400 distinct forms [3-5, 9].

The advent of next-generation sequencing (NGS), particularly whole-exome sequencing (WES), has revolutionized the identification of rare and novel variants underlying inherited HL. WES targets protein-coding regions, where the majority of pathogenic variants reside, offering a practical and cost-effective diagnostic approach [4, 11, 12].

SLITRK6 (located at 13q31) encodes a transmembrane protein belonging to the *SLITRK* family, characterized by leucine-rich repeats involved in neuronal development. This protein is expressed primarily in the inner ear and retina, where it supports the growth of auditory nerve fiber and regulates postnatal eye development, including axial length. Pathogenic variants in *SLITRK6*, typically truncating, cause autosomal recessive syndromic HL with high myopia [13-15].

While several *SLITRK6* mutations have been reported in different populations, including Turkish, Moroccan, Amish, and South Asian/Indian ancestries [13, 15-17], evidence from Middle Eastern and specifically Iranian cohorts remains limited. In the present study, we identified a novel homozygous nonsense variant in *SLITRK6* (NM_032229.3:c.1795C>T; p.Arg599Ter) in an Iranian consanguineous family with autosomal recessive syndromic HL and myopia. In silico analyses were performed to explore the potential functional consequences of the variant and its possible impact on *SLITRK6*-related pathways. This work expands the mutational spectrum of *SLITRK6* and underscores the value of population-specific genetic studies for improving the diagnosis and management of hereditary HL.

2. Materials and Methods

2.1 Ethics Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. It was approved by the Research Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (Ethics Code: IR.KUMS.MED.REC.1403.319). Written informed consent was obtained from all participants or their legal guardians.

2.2 Subjects and Clinical Evaluation

The family was recruited through the clinical genetics and otolaryngology outpatient clinics at Kermanshah University of Medical Sciences. A consanguineous Iranian family from Kermanshah province, consisting of two affected siblings (a 22-year-old male proband and his 16-year-old sister) presenting with syndromic congenital sensorineural HL accompanied by myopia, was enrolled. Their parents (III.5 and IV.1) were unaffected. A comprehensive family history was obtained through genetic counseling, and a pedigree was constructed (Figure 1).

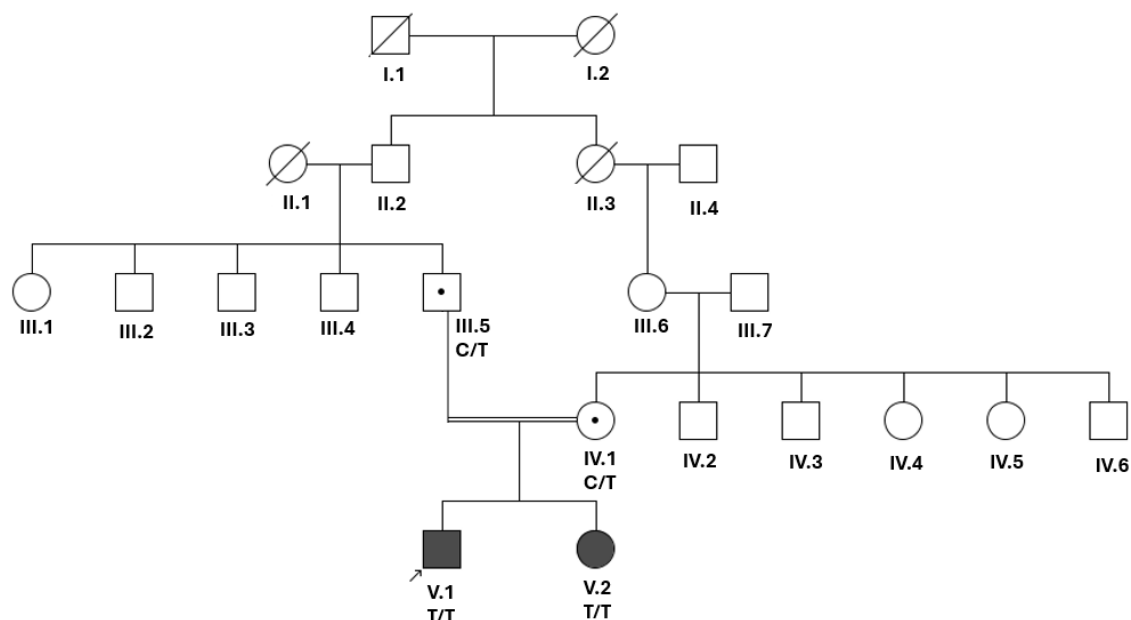


Figure 1 Pedigree of the Iranian family with autosomal recessive syndromic hearing loss. Genotypes for the *SLITRK6* c.1795C>T variant are provided below for the relevant individuals: C/T for heterozygotes and T/T for homozygotes.

HL was diagnosed through detailed audiological evaluation, including pure-tone audiometry, speech audiometry, tympanometry, and auditory brainstem response (ABR) testing, confirming bilateral congenital severe-to-profound sensorineural HL. Ophthalmologic assessment, including visual acuity testing, refraction, slit-lamp examination, and fundoscopy, confirmed the diagnosis of myopia in both affected individuals. No additional neurological, vestibular, or developmental abnormalities were observed.

Comprehensive neurological examination and developmental assessment revealed normal motor and cognitive development. No vestibular symptoms, additional neurological abnormalities, or other systemic features were observed.

2.3 Exome Sequencing, Variant Calling, and Filtering Criteria

After obtaining ethics approval and informed consent, 5-mL of peripheral blood samples were collected from the two affected siblings and their parents in EDTA-containing tubes, and genomic DNA was isolated using a conventional salting-out procedure [18]. DNA concentration and purity were quantified using a Thermo Scientific™ NanoDrop™ One UV-Vis spectrophotometer and further verified by 2% agarose gel electrophoresis.

Genomic DNA libraries were prepared following standard protocols. Briefly, DNA was fragmented to 150-300 bp. Exonic regions were captured using the Agilent V.6 kit (Agilent, USA). Captured libraries were sequenced on an Illumina NextSeq500 instrument, achieving an average sequencing depth of the target regions (including all exons and several other critical genomic regions such as splicing sites of protein-coding genes) of 100× for 150 bp paired-end reads.

The generated data were analyzed using a multi-step bioinformatics pipeline. Raw sequencing reads were quality-controlled using FastQC and IlluQC. Reads were aligned to the human reference genome (GRCh38) using the Burrows-Wheeler Aligner (BWA-mem algorithm). Duplicate reads were

marked and removed using Picard Tools, followed by sorting and base quality score recalibration (BQSR) with Samtools and GATK4. Variant calling was performed using the Genome Analysis Toolkit (GATK) [19].

Variants were annotated using ANNOVAR [20] with data from multiple databases, including the 1000 Genomes Project, ExAC, gnomAD, dbSNP, and the in-house Iranome database. A virtual hearing loss gene panel (Supplementary Materials) was later used to prioritize the variants relevant to the proband's phenotype. However, all variants, including those outside this panel, were comprehensively analyzed. Detailed variant filtering criteria were applied as follows: variants with a minor allele frequency (MAF) greater than 1% in any population database were first excluded. Benign, intronic, and intergenic variants were removed. Prioritization was given to exonic and splicing variants (± 10 bp of exon-intron boundaries) as well as nonsynonymous changes. Given the consanguineous pedigree, homozygous variants consistent with autosomal recessive inheritance were particularly prioritized. Common benign variants were additionally excluded based on in-house controls. Finally, only variants consistent with the clinical phenotype of syndromic hearing loss with high myopia were retained for manual review. After automated filtering with ANNOVAR, the remaining candidate variants were manually prioritized and reviewed using the VarSome and Franklin platforms, considering variant rarity, predicted functional impact, inheritance pattern, and phenotypic concordance with known disease-associated genes. Pathogenicity was assessed according to ACMG guidelines [21] using in silico tools including ClinVar, VarSome, PolyPhen-2, Franklin, Ensembl VEP, PROVEAN, I-Mutant2.0, MUpro, and HOPE.

The impact of the candidate variant on protein physicochemical properties was evaluated using the ProtParam tool [22] available on the ExPASy server [23]. Full amino acid sequences of wild-type and mutant *SLITRK6* proteins (in FASTA format) were analyzed for parameters including molecular weight, theoretical isoelectric point (pI), instability index, aliphatic index, and grand average of hydropathicity (GRAVY). Protein-protein interaction (PPI) networks were analyzed using the STRING database (v12.0) [24].

2.4 Variant Confirmation and Segregation Analysis

The identified *SLITRK6* variant was confirmed, and its segregation in the family was validated by Sanger sequencing. Primers were designed using Primer3 and specificity checked with NCBI Primer-BLAST. The primer sequences were: forward 5'-CTGCAGCAATGGATACAA-3' and reverse 5'-CAATAGTGATGAACATAATCAGA-3'. PCR products were sequenced on an ABI 3700 sequencer (Kawsar Company, Tehran, Iran). Sequence data were analyzed using SnapGene® 5.3.1 software.

3. Results

3.1 Clinical Findings

We describe a consanguineous Iranian family from Kermanshah province with two affected siblings exhibiting autosomal recessive syndromic HL accompanied by myopia. The affected individuals were a 22-year-old male (proband, V.1) and his 16-year-old sister (V.2), born to unaffected parents (III.5 and IV.1) (Figure 1).

Detailed clinical evaluation revealed bilateral congenital severe-to-profound sensorineural hearing loss (SNHL) in both siblings. Pure-tone audiometry showed average thresholds of 85-110 dB

HL across 500-4000 Hz, consistent with severe-to-profound hearing impairment. Speech discrimination scores were <20%, and auditory brainstem response (ABR) testing confirmed the absence of identifiable waveforms at maximum stimulus levels. Tympanometry indicated normal middle ear function (Type A). No vestibular symptoms (e.g., vertigo or balance issues) were reported.

Ophthalmologic assessment, including visual acuity testing, refraction, slit-lamp examination, and fundoscopy, confirmed high myopia in both patients. No retinal detachment or other major ocular complications were noted.

Comprehensive neurological examination and developmental assessment demonstrated normal motor and cognitive development with no additional syndromic features or systemic involvement. These clinical findings establish the syndromic nature of the condition, characterized by congenital severe-to-profound sensorineural HL and high myopia.

3.2 Identification of a Novel *SLITRK6* Nonsense Variant

Following clinical diagnosis of autosomal recessive syndromic HL and exclusion of common causes (e.g., *GJB2* mutations), WES was performed on the two affected siblings (V.1 and V.2). After applying stringent filtering criteria (MAF <1%, focus on homozygous/compound heterozygous exonic and splice-site variants consistent with recessive inheritance), a novel homozygous nonsense variant, NM_032229.3:c.1795C>T; p.(Arg599Ter), located in exon 2 of the *SLITRK6* gene, was identified as the top candidate. The variant is ultra-rare in gnomAD v4.1 (observed in 4 heterozygous alleles out of 1,613,184 total alleles; AF = 2.48×10^{-6}) and absent in the homozygous state. It is also absent from the in-house Iranome database and other major population databases such as ExAC and the 1000 Genomes Project. Sanger sequencing confirmed that both unaffected parents were heterozygous carriers (C/T), consistent with autosomal recessive inheritance.

3.3 Sanger Sequencing Confirmation and Segregation Analysis

Sanger sequencing validated the WES findings and confirmed segregation of the variant within the family (Figure 2). Both affected siblings (V.1 and V.2) were homozygous for the c.1795C>T (T/T) allele, while their parents (III.5 and IV.1) were heterozygous carriers (C/T). Only the two affected individuals and their parents were available for genetic testing; no additional family members could be tested. This limited segregation analysis is acknowledged as a limitation of the study. The clear heterozygous double peaks in both parental chromatograms support carrier status.

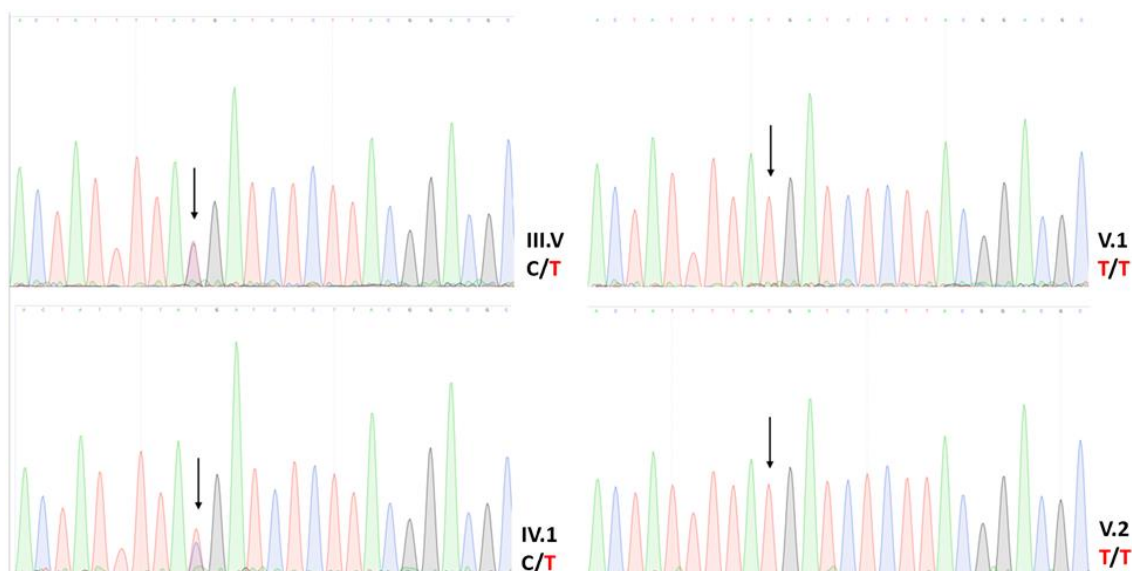


Figure 2 Representative Sanger sequencing chromatograms showing the *SLITRK6* c.1795C>T variant. Homozygous T/T in affected siblings (V.1, V.2) and heterozygous C/T double peaks in both parents (III.5, IV.1).

3.4 Pathogenicity Assessment of the *SLITRK6* Variant

According to the American College of Medical Genetics and Genomics (ACMG) guidelines [21], the homozygous nonsense variant *SLITRK6* NM_032229.3:c.1795C>T; p.(Arg599Ter) was classified as likely pathogenic. This classification is supported by: (1) PVS1 (null variant predicted to cause loss-of-function via nonsense-mediated mRNA decay); (2) PM2 (ultra-rare in population databases); and (3) PP1 (co-segregation with the disease phenotype in the family). These criteria strongly support the variant as the likely causative mutation for the observed syndromic HL in this family.

3.5 *In silico* Analyses of the *SLITRK6* Variant

To assess conservation of arginine at position 599, multiple sequence alignments across various species were performed (Figure 3). This residue is highly conserved among mammals and vertebrates. Its substitution with a stop codon represents a non-conservative change, predicted to disrupt local electrostatic interactions and compromise structural stability, thereby supporting the potential pathogenicity of the variant.

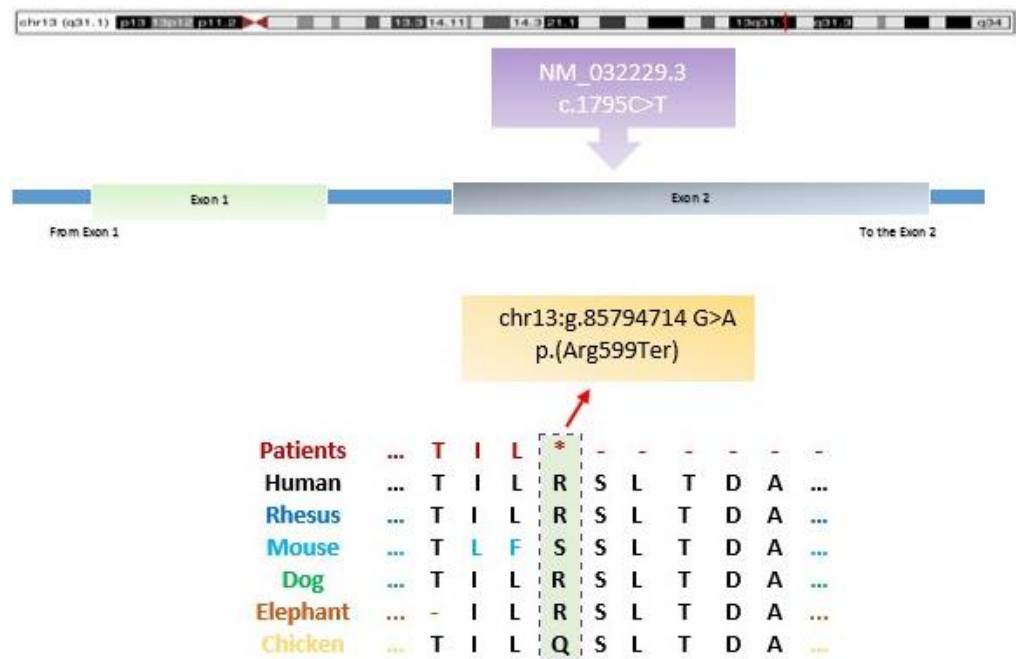


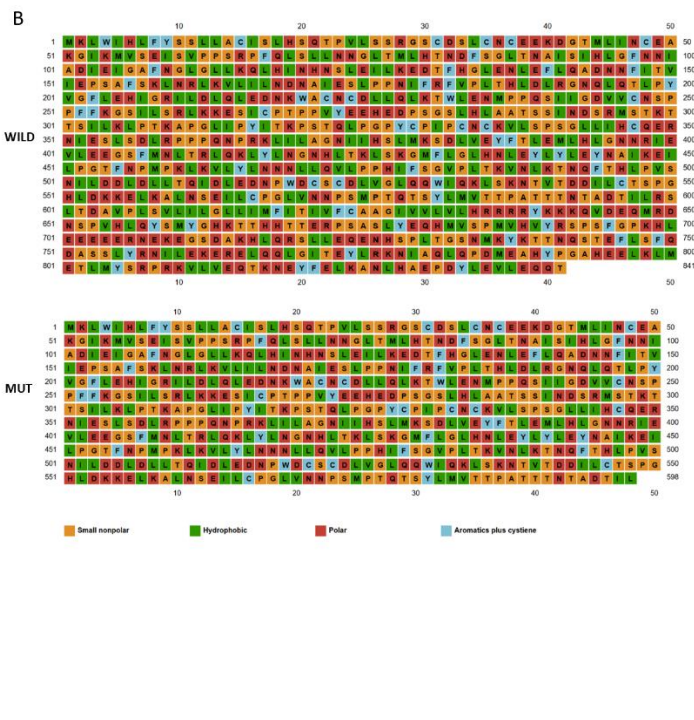
Figure 3 A schematic diagram of the *SLITRK6* gene is provided, highlighting the location of the identified pathogenic variant (c.1795C>T) in the human genome (GRCh38 assembly). The conservation of the mutation-containing region across different species is also illustrated.

The effects of the p.Arg599Ter variant on the properties of the *SLITRK6* protein were evaluated using the ProtParam tool [22]. As expected for a truncating mutation, the mutant protein was substantially shorter (598 amino acids, 66,718.32 Da) compared to the wild-type protein (841 amino acids, 95,109.61 Da). Minor differences were observed in other physicochemical parameters (Table 1), including a slight decrease in theoretical pI (5.88 vs. 6.07), reduced instability index (52.01 vs. 55.52), increased aliphatic index (106.77 vs. 99.68), and a less negative grand average of hydropathicity (GRAVY -0.058 vs. -0.239). These in silico predictions provide supportive computational evidence of structural alteration due to C-terminal truncation but do not constitute direct functional validation.

Table 1 Comparison of physicochemical properties of wild-type and mutant *SLITRK6* proteins (ProtParam analysis).

Protein variant	Theoretical isoelectric point	Instability index	Aliphatic index	Grand average of hydropathicity	Molecular weight	Number of amino acids
Mut	5.88	52.01	106.77	-0.058	66718.32	598
Wild	6.07	55.52	99.68	-0.239	95109.61	841

In parallel, Clustal Omega sequence alignment confirmed that the variant introduces a premature termination codon (PTC) at position 599. Secondary structure prediction using PSIPRED revealed a substantial reduction in structural elements in the truncated protein compared with the wild-type, with the number of residues involved in α -helices, β -sheets, and coils decreasing from 191, 46, and 604 to 103, 36, and 459, respectively (Figure 4).



PPI networks for *SLITRK6* were analyzed using the STRING database (v12.0) [24]. The wild-type *SLITRK6* is predicted to interact with several key partners involved in neurotrophin signaling and neuronal development, including NTRK1, NTRK2, BDNF, NGF, NTF3, SHC1, SHC2, SHC3, and GRB2 (Figure 5). Due to the C-terminal truncation in the p.Arg599Ter mutant, the protein is predicted to lack critical intracellular domains, potentially leading to reduced or abolished interactions with several of these important partners, particularly the NTRK receptors and SHC adaptor proteins.

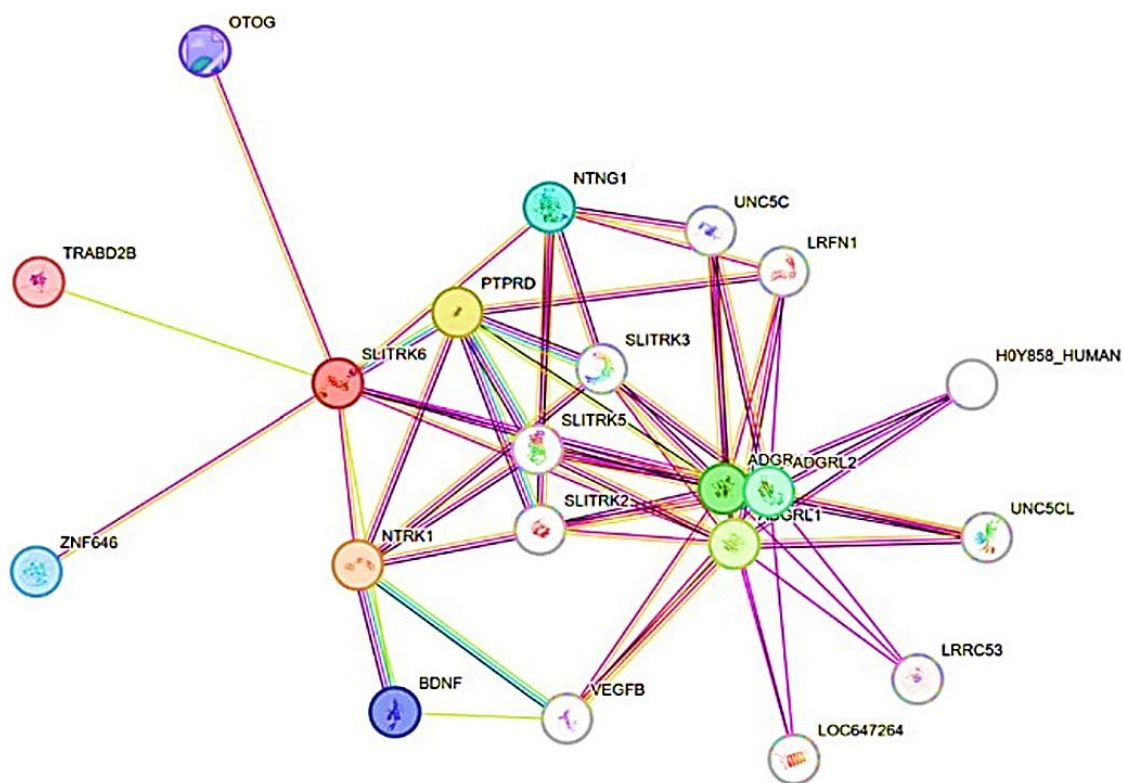


Figure 5 The in-silico prediction of the functional protein-protein interaction (PPI) network using online STRING server for *SLITRK6* interaction.

Although advanced three-dimensional (3D) protein modeling was not performed in this study, the major C-terminal truncation caused by the p.Arg599Ter variant is predicted to result in significant structural deformities, including loss of the transmembrane and intracellular domains essential for *SLITRK6* function. Future studies using tools such as AlphaFold or molecular dynamics simulations could further characterize these structural alterations.

4. Discussion

In the present study, we identified a novel homozygous nonsense variant in *SLITRK6* (NM_032229.3:c.1795C>T; p.Arg599Ter) in a consanguineous Iranian family presenting with autosomal recessive syndromic HL and high myopia. This variant is ultra-rare in public databases, with only 4 heterozygous alleles observed in gnomAD v4.1 (allele frequency = 2.48×10^{-6}) and no homozygotes reported. It is absent from ExAC, the 1000 Genomes Project, and our in-house Iranome database. The variant showed perfect co-segregation with the syndromic HL and high myopia phenotype in the family and met key ACMG criteria for likely pathogenicity (PVS1 for a null variant, PM2 for extreme rarity, and PP1 for co-segregation). To our knowledge, this is the first reported *SLITRK6* pathogenic variant in the Iranian population, thereby expanding the known mutational spectrum and ethnic diversity of *SLITRK6*-related disorders.

Previous studies have consistently linked biallelic truncating variants in *SLITRK6* to an autosomal recessive syndrome characterized by congenital or early-onset severe-to-profound sensorineural HL and high myopia. In the seminal report by Tekin et al. [13], homozygous nonsense mutations (e.g., p.Arg181Ter and others) were identified in consanguineous families of various ancestries, resulting

in truncated proteins that fail to localize properly to the cell membrane [13]. Subsequent reports, including a Moroccan family with a frameshift mutation (p.Trp232Cysfs*10) [16] and an Amish family with the p.Gln414Ter variant, described highly similar phenotypes with congenital severe SNHL and progressive high myopia (typically -6 to -15 diopters) [13, 15]. The p.Arg599Ter variant identified here introduces a premature termination codon in exon 2, leading to loss of the C-terminal transmembrane and intracellular domains, consistent with the recurrent loss-of-function mechanism observed in prior truncating and frameshift mutations. The clinical severity in our patients (congenital severe-to-profound SNHL and high myopia, with onset in early childhood) aligns closely with previously reported cases [13, 15], supporting strong genotype–phenotype consistency for *SLITRK6*-related DFNMYP syndrome.

Computational analyses provided evidence of the variant’s deleterious impact. Comparison of wild-type and mutant *SLITRK6* proteins using ProtParam revealed a substantial reduction in protein length (from 841 to 598 amino acids) and alterations in several physicochemical parameters. While these changes are consistent with potential structural instability due to C-terminal truncation, such in silico predictions should be interpreted as supportive computational evidence rather than definitive proof of in vivo dysfunction [21].

Similarly, STRING-based PPI analysis indicated that wild-type *SLITRK6* interacts with key components of the neurotrophin pathway (e.g., NTRK1, NTRK2, BDNF, NGF), which are critical for neuronal survival and synaptogenesis in the inner ear and retina [25, 26]. The truncated p.Arg599Ter protein is predicted to exhibit reduced interactions with several of these partners. However, our in-silico analyses (ProtParam, PSIPRED, and STRING) remain computational predictions and do not constitute direct functional validation. Advanced experimental studies, including protein expression, subcellular localization, 3D structural modeling (e.g., AlphaFold), and functional assays, are required to confirm the predicted structural deformities and disruption of protein interactions.

Although our findings support *SLITRK6* loss-of-function as the likely cause of the observed auditory and ocular phenotypes, we acknowledge important limitations. No functional studies (e.g., protein expression, membrane localization, or neuronal signaling assays) were performed in this study. Therefore, mechanistic conclusions regarding the disruption of neurotrophin signaling and retinal development remain partly speculative and should be confirmed in future cellular or animal models. Nevertheless, the identification of this variant supports an important role for *SLITRK6* in auditory nerve development and ocular axial length regulation.

Clinically, this report has several implications. In patients presenting with congenital sensorineural HL and high myopia, particularly in consanguineous populations, *SLITRK6* should be considered for targeted gene panels or WES. Given the autosomal recessive inheritance pattern, genetic counseling is essential for accurate risk assessment of recurrence, carrier screening, and reproductive planning. Early interventions such as hearing aids or cochlear implantation can significantly improve outcomes.

Overall, this study expands the genetic landscape of *SLITRK6*-related disorders in the Middle East and highlights the power of WES in resolving rare syndromic forms of hereditary HL.

5. Conclusions

Our findings, integrating WES, segregation analysis, and in silico protein analysis, support the likely pathogenic role of the *SLITRK6* p.Arg599Ter variant in this family with syndromic HL and

myopia. They also reinforce the importance of *SLITRK6* in sensory system development and highlight the value of current genetic diagnostics in resolving inherited disorders. Further research using appropriate model systems will be necessary to clarify the molecular consequences of *SLITRK6* truncating mutations.

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Author Contributions

EA and RA conceived the study. EE and EA prepared the manuscript. EE, PN, FM, and MJA collected the clinical information of patients. EA, PN, FM, MJA and RA analyzed the data. All authors contributed to this study, read, and approved the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to ethical and privacy considerations involving human participants. Reasonable requests for access to anonymized data may be directed to the corresponding author.

AI-Assisted Technologies Statement

The authors used AAI Technologies to assist with language editing, including grammar correction and improvement of clarity and readability of the manuscript. No AI tools were used for data analysis, interpretation of results, or generation of scientific content. All content was reviewed and validated by the authors, who take full responsibility for the integrity and accuracy of the paper.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Supplementary Materials.

References

1. Lieu JE, Kenna M, Anne S, Davidson L. Hearing loss in children: A review. *JAMA*. 2020; 324: 2195-2205.

2. Wrobel C, Zafeiriou MP, Moser T. Understanding and treating paediatric hearing impairment. *EBioMedicine*. 2021; 63: 103171.
3. Bengl D, Koparir A, Prastyo WE, Remmele C, Dittrich M, Flandin S, et al. Whole-genome sequencing, as a powerful diagnostic tool in hearing loss, reveals novel variants in *PTPRQ* missed by whole-exome sequencing. *BMC Med Genomics*. 2025; 18: 59.
4. Rezaie N, Mansour Samaei N, Oladnabi M. Identification of novel and known genetic variants associated with hereditary hearing loss in Iranian families using whole exome sequencing. *Mol Biol Rep*. 2024; 51: 662.
5. Akansha A, Agarwal AC. Genetic foundations of hearing loss: A comprehensive review. *Indian J Otolaryngol Head Neck Surg*. 2025; 77: 3866-3875.
6. Mahdih N, Rabbani B, Wiley S, Akbari MT, Zeinali S. Genetic causes of nonsyndromic hearing loss in Iran in comparison with other populations. *J Hum Genet*. 2010; 55: 639-648.
7. Beheshtian M, Babanejad M, Azaiez H, Bazazzadegan N, Kolbe D, Sloan-Heggen C, et al. Heterogeneity of hereditary hearing loss in Iran: A comprehensive review. *Arch Iran Med*. 2016; 19: 720-728.
8. Mohammadi A, Hoseinzadeh M, Narrei S, Pourreza MR, Mohammadi Y, Norouzi M, et al. Identification of novel likely pathogenic variant in *CDH23* causing non-syndromic hearing loss, and a novel variant in *OTOGL* in an extended Iranian family. *Egypt J Med Hum Genet*. 2024; 25: 102.
9. Quaio CR, Battelino S. Genetics of non-syndromic hearing loss. *Front Genet*. 2025; 16: 1665942.
10. Vallian Broojeni J, Kazemi A, Rezaei H, Vallian S. Exome sequencing identifies novel variants associated with non-syndromic hearing loss in the Iranian population. *PLoS One*. 2023; 18: e0289247.
11. Imizcoz T, Prieto-Matos C, Manrique-Huarte R, Calavia D, Huarte A, Pruneda PC, et al. Next-generation sequencing improves precision medicine in hearing loss. *Front Genet*. 2023; 14: 1264899.
12. Nurchis MC, Radio FC, Salmasi L, Heidar Alizadeh A, Raspolini GM, Altamura G, et al. Cost-effectiveness of whole-genome vs whole-exome sequencing among children with suspected genetic disorders. *JAMA Netw Open*. 2024; 7: e2353514.
13. Tekin M, Chioza BA, Matsumoto Y, Diaz-Horta O, Cross HE, Duman D, et al. *SLITRK6* mutations cause myopia and deafness in humans and mice. *J Clin Invest*. 2013; 123: 2094-2102.
14. Aruga J, Yokota N, Mikoshiba K. Human *SLITRK* family genes: Genomic organization and expression profiling in normal brain and brain tumor tissue. *Gene*. 2003; 315: 87-94.
15. Morlet T, Rabinowitz MR, Looney LR, Riegner T, Greenwood LA, Sherman EA, et al. A homozygous *SLITRK6* nonsense mutation is associated with progressive auditory neuropathy in humans. *Laryngoscope*. 2014; 124: E95-E103.
16. Salime S, Riahi Z, Elrharchi S, Elkhatabi L, Charoute H, Nahili H, et al. A novel mutation in *SLITRK6* causes deafness and myopia in a Moroccan family. *Gene*. 2018; 659: 89-92.
17. Sebastian S, Jasper P, Mammen MD, Augustine AM. Audiological phenotype of siblings with dual sensory impairment caused by *SLITRK6* mutation-case report. *Egypt J Otolaryngol*. 2026; 42: 41.
18. Miller SA, Dykes DD, Polesky H. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res*. 1988; 16: 1215.

19. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, et al. The genome analysis toolkit: A Mapreduce framework for analyzing next-generation DNA sequencing data. *Genome Res.* 2010; 20: 1297-1303.
20. Wang K, Li M, Hakonarson H. ANNOVAR: Functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res.* 2010; 38: e164.
21. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet Med.* 2015; 17: 405-423.
22. Gasteiger E, Hoogland C, Gattiker A, Duvaud SE, Wilkins MR, Appel RD, et al. Protein identification and analysis tools on the ExPASy server. In: *The proteomics protocols handbook*. Totowa, NJ: Humana Press; 2005. pp. 571-607.
23. Artimo P, Jonnalagedda M, Arnold K, Baratin D, Csardi G, De Castro E, et al. ExPASy: SIB bioinformatics resource portal. *Nucleic Acids Res.* 2012; 40: W597-W603.
24. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: Protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res.* 2023; 51: D638-D646.
25. Aruga J, Mikoshiba K. Identification and characterization of Slitrk, a novel neuronal transmembrane protein family controlling neurite outgrowth. *Mol Cell Neurosci.* 2003; 24: 117-129.
26. Puranik N, Song M. Insight into the association between Slitrk protein and neurodevelopmental and neuropsychiatric conditions. *Biomolecules.* 2024; 14: 1060.