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ORIGINAL ARTICLE

A novel biallelic frameshift variant in *MYO15A* causing nonsyndromic hearing loss in Saudi family

Faisal Almalki[1]*, Hamzah Wali[2], Reham M. Balahmar[3], Abdularaheem Alshareef[1], Mansour Rabeh Alshamani[2], Roa Talal Halawani[2]

ABSTRACT

Background: Sensorineural hearing loss is among the most common sensory defects worldwide. Nonsyndromic hearing loss (NSHL) accounts for 70% of inherited hearing loss. The genetic causes of NSHL are considered heterogeneous. The high rate of consanguineous marriages in Saudi Arabia increases the population's prevalence of autosomal recessive inheritance patterns.

Objective: To discover a novel variant for NSHL patients.

Methods: A family with two hearing-impaired children was recruited. Targeted exome sequencing, the Twist Exome 2.0 kit (Twist Bioscience) using the Novaseq X plus platform, was used to identify the variant. Sanger sequencing was carried out to confirm the finding and perform segregation analysis. MutationTaster tool was used to determine the pathogenicity effect on the protein structure.

Results: A homozygous two-bp duplication variant on the (c.8813_8814dup) *MYO15A* gene was identified in a Saudi family of two hearing-impaired children. Sanger sequencing confirmed the variant in the affected children and their parents. The prediction tool indicated the frameshift effect on the protein level, which leads to protein function disruption. Based on the American College of Medical Genetics and Genomics guidelines, it is classified as a pathogenic variant.

Conclusion: A novel biallelic frameshift variant in *MYO15A* causes NSHL in a Saudi family. This variant is considered rare and isolated to the Saudi population. Expanded genotype-phenotype correlations for hearing loss patients are likely to confirm the findings and reveal novel variants.

Keywords: Nonsyndromic hearing loss, *MYO15A*, novel, frameshift, Saudi.

Introduction

Sensorineural hearing loss (SNHL) is among the most common sensory defects worldwide, with a prevalence ranging from 0.2% to 1% (1). Nonsyndromic hearing loss (NSHL) accounts for 70% of inherited hearing loss, while autosomal recessive NSHL represents 80% of NSHL cases (2,3). To date, more than 120 genes have been identified as causing NSHL (3–5). Early detection of SNHL would help patients proceed to hearing aids, or/and cochlear implantation. Therefore, it would accelerate the process of language acquisition and learning ability. Affordability and accessible genetic testing can facilitate a more convenient diagnosis of NSHL.

The myosin XVA (*MYO15A*) gene (OMIM 602666) is among the main genes causing NSHL (6–8). It was first identified in a small village in Bengal, Bail, and it was classified as deafness, autosomal recessive 3 (DFNB3; OMIM #600316) (8). *MYO15A* is located on the short arm of chromosome 17 at position 11.2 (8). The *MYO15A* gene comprises 66 to 67 exons, spanning approximately 71 kb in the genomic sequences (6). Around 200 variants have been identified as causing NSHL in different populations (6). However, considering the heterogeneity of NSHL and the complexity of the *MYO15A* gene,

Correspondence to: Faisal Almalki
*Clinical Laboratory Sciences Applied Medical Science, Taibah University
Email: fmalki@taibahu.edu.sa
Full list of author information is available at the end of the article.
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novel variants might be identified with additional studies focusing on genotype-phenotype in NSHL may reveal novel variants (6).

The MYO15A protein shows different isoforms with distinct functions in developing and maintaining the sensory hair cell stereocilia (6,9). The first isoform has 3,530 residues and encodes 395 kDa (9). It is responsible for the initial development of stereocilia, stabilizing the actin cytoskeleton and ensuring the formation of mature mechanotransducing stereocilia (6,9). The second isoform has 2,327 amino acid residues and encodes 262 kDa, but lacks exon 2, which contains 1,203 amino acid residues (9). It has a role in forming hair cell stereocilia by controlling the differentiation and driving the core actin cytoskeleton elongation (6,9).

In Saudi Arabia, the consanguinity rate reaches up to 65% of marriages (10,11). In small specific cohorts related to genetic causes of NSHL, consanguinity reaches 85% of the cohort (28 families out of 33) (12). The high prevalence of consanguineous marriages contributes to the increased autosomal recessive inheritance patterns in the population. Recessive alleles are more likely to be reintroduced because of less efficient selection for a deleterious allele. Therefore, private and extremely rare variants are more likely to be discovered (13,14).

The current study recruited a family with two hearing-impaired children. Targeted exome sequencing was applied on the index child and revealed a novel frameshift variant at the *MYO15A* gene.

Material and Methods

Family recruitment and ethical approval

The research study was approved by the Institutional Review Board of Taibah University (2023/146/103 MLT). The research took place between January 2023 and October 2024. Written informed consent was obtained from the family members after explaining the study's aims to them in Arabic. All the experiments conducted in this research were in accordance with the guidelines of the ethical committee. A family with two children who have impaired hearing only and do not have other phenotypes was recruited. The family history was taken from the parents, and the family pedigree was drawn (Figure 1). The clinical examinations, including hearing assessments, were conducted at Ohud Hospital, Medina. Patients were examined for electrocardiogram abnormalities. CT and MRI scans were also conducted to assess the anatomical structure of the inner ear.

DNA extraction and quantifications

Three milliliters of blood were collected in Ethylenediaminetetraacetic acid tubes for the affected children and their parents. The DNA was extracted using a QIAmp DNA mini kit (Qiagen cat no.51306) based on the manufacturer's protocol. The integrity and purity of the DNA were carried out using a Qubit fluorometer and NanoDrop-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

Targeted exome sequencing

Targeted exome sequencing data were carried out for a single affected child in the family (Figure 1-affected child II-1). The sequencing library was prepared using a Twist Exome 2.0 kit (Twist Bioscience). Sequence reads were generated using the NovaSeq X plus platform on an average depth of 100x. Adapters were trimmed from fastq sequence using automatic trimming. The bioinformatics pipeline, including the mapping process, quality filtering and variant calling, was carried out using commercially available algorithms. The sequence reads were mapped to the reference human genome assembly GRCh38.

Variant filtration and annotation of the VCF files were carried out using commercial software: QIAGEN Clinical Insight (QCI). It was based on several databases, data reference sets, and tools. This is included QCI-Interpret (6.0.20200609), Ingenuity Knowledge Base (X-release), CADD (v1.4), gnomAD (2.1.1), Allele Frequency Community (2019-09-25), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), dbSNP (151), JASPAR (2013-11), COSMIC (v89), ClinVar (2019-11-06), TargetScan (7.2), Clinical Trials (X-release), HGMD (2020.2), OMIM (May 26, 2017), GENCODE (Release 31), Ingenuity Knowledge Base Snapshot Timestamp (2020-08-19 13:28:30.0), RefSeq Gene Model (2019-10-01), EVS (ESP6500SI-V2), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), CentoMD (5.3), iva (May 11 16:21 iva-1.0.1458.jar), PolyPhen-2 (v2.2.2), PhyloP hg18 (2009-11), PhyloP hg19 (2009-11), BSIFT (2016-02-23), OncoTree (oncotree_2019_03_01), and SIFT4G (2016-02-23).

Based on the family pedigrees (Figure 1), the variant was predicted to be inherited on an autosomal recessive basis. Therefore, variants were prioritized for homozygous and compound heterozygous variants. The variant was reported based on the GHVS nomenclature, and the classification of the variant was based on the American College of Medical Genetics and Genomics (ACMG) guidelines (15).

Sanger sequencing

The identified variants were sequenced using the Sanger sequence following general protocol. A primer pair for the specified variant was carried out to confirm the variant in the index and validate the variant in the family members. It was designed using the Primer 3 tool (http://primer3.ut.ee/ accessed on 10 June 2024). The forward (5'-ACTTCCCCTTTATGGTCCTG-3') and reverse (5'-ACACTGGTCTCACCTCTCTCC-3') primers were used for the Sanger sequence. The reference sequence for the gene of interest (*MYO15A*) was downloaded from the Ensembl genome browser (https://m.ensembl.org/ accessed on 30 June 2024). The Sanger sequence reads were mapped to the reference sequence using Clustal Omega (16).

In silico analysis: prediction tool and evolutionary analysis

The identified variant was additionally predicted by a MutationTaster tool to determine the pathogenicity effect

of the protein structure (17). The conservative status among different orthologs for the identified variant was carried out using NCBI HomoloGene (https://www.ncbi.nlm.nih.gov/search/ accessed on 30 June 2024).

Results

Clinical findings

A consanguineous Saudi family with two affected members born with profound hearing loss was recruited for genetic analysis. The index older patient, Patient II-1, failed neonatal hearing screening (NHS) performed after birth using automated auditory brainstem response. However, parents did not follow up until they noticed a lack of response to sounds at the age of 14 months. The child visited the audiology clinic at the age of 1 year and 5 months. Diagnostic hearing assessment was carried out using tympanometry, auditory brainstem response, and distortion product otoacoustic emission (DPOAE). The hearing assessment revealed a normal bilateral tympanogram with no detected ABR responses at 85–90 dBnHL in response to CE-Chirp level specific (LS) stimuli, and 0.5k, 1k, 2k, and 4k narrowband (NB) CE-Chirp LS stimuli. Cochlear microphonic and DPOAE were also absent bilaterally, indicating bilateral profound SNHL. The audiogram was plotted based on ABR findings (Figure 1). The patient was fitted with powerful bilateral hearing aids; however, no benefit was noticed. The patient then underwent bilateral cochlear implantation aged 1 year and 8 months. The child now hears adequately and communicates verbally.

The younger child also failed NHS and was referred for diagnostic hearing assessment. The assessment was carried out when he was 5 months old and showed a normal bilateral tympanogram using a 1 kHz probe tone. Moreover, ABR showed no recordable responses at 90 dBnHL in response to CE-Chirp LS stimuli and 0.5k, 1k, 2k, and 4k NB CE-Chirp LS stimuli (supplemental material). Additionally, cochlear microphonic and DPOAE were absent bilaterally, indicating bilateral profound SNHL. Figure 1 shows the audiogram that was plotted based on the ABR results. The child was fitted with powerful hearing aids bilaterally but showed no benefit; therefore, he underwent bilateral cochlear implantation aged 1 year. Currently, he has adequate hearing and age-appropriate speech and language skills. The CT and MRI for both children show normal middle and inner ear structures with preserved vestibulocochlear nerves.

Genetic testing

The sequencing result for the index child reveals a novel homozygous two-bp duplication at position c.8813_8814 of the *MYO15A* gene (NM_016239.4:c.8813_8814dup(p.Arg2939Glyfs*96)). This duplication causes a shift in the reading frame starting at amino acid position 2939 (arginine), which leads to a premature stop codon 96 positions later at another arginine (amino acid 3031, Figure 2). The MutationTaster tool predicts this variant as deleterious. This variant is located at exon 51, which is part of the Src homology 3 (SH3) domain (Figure 2). The variant is highly conservative among other species (Figure 1). The variant was confirmed using Sanger sequencing for the index child (Figure 1: II.1), and his younger affected sibling (Figure 1: II.2). A linkage analysis showed that the variant was segregated from both heterozygous parents for the variant. The variant was not found in the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar accessed on 5 Feb 2025), HGMD, and Hereditary Hearing Loss Homepage (4,18). The variant was not identified on the local database of 200 exome data, and it was never reported in gnomAD, ESP, and the 1000 Genomes Project (19–21). According to ACMG guidelines, this variant would be classified as pathogenic since a novel frameshift variant identified in a known gene-causing disease and segregated in the family is classified as pathogenic (15).

Discussion

The SNHL is among the most common sensory disabilities worldwide. Early detection of SNHL facilitates early intervention via hearing aids or cochlear implants. This is crucial for normal speech and language development and for reducing the impact of SNHL on learning. Affordable access to genetic testing simplifies the diagnosis of NSHL. In this study, a novel variant was identified using targeted exome sequencing. Identifying the causative variant could help the family consider IVF in the future.

Several genes have been identified to cause NSHL worldwide, including in Saudi Arabia (3–5,14). Furthermore, several hundred variants within the same genes were reported. The most common gene causing NSHL worldwide is the gap junction protein, beta-2 (*GJB2*); however, the Otoferlin (*OTOF*) gene is the most common gene causing NSHL in Saudi Arabia (4,12). The *MYO15A* gene is the third most common gene causing NSHL worldwide (3–5). However, in Saudi Arabia, only a single family was reported that has a frameshift variant on *MYO15A* (NM_016239.4:c.1047C>T) (14,22). Variants of the *MYO15A* gene are common in Brazil and Turkey (Val1400Met (c.4198G>A)) (23,24). Several different variants were found in Iran (p.Tyr1392* and c.4596+1G>A), and Pakistan (p.D2720H) (25–27). Several other coding and noncoding variants were reported in the NSHL Palestine families (28). An indel variant was found in Qatar, and another single nucleotide deletion was reported in the Yemen (29,30).

The two-bp duplication variant ((NM_016239.4:c.8813_8814dup(p.Arg2939Glyfs*96)) is located at the exon 51, which is part of the SH3 domain of the MYO15A protein (*i.e.* amino acids 2865–2959) (6). The SH3 domain is part of the tail region of the MYO15A protein. It functions in conjunction with two myosin tail homology 4 domains and two four-point-one ezrin-radixin-moesin homology domains to develop and elongate the stereocilia (6). This process occurs when the Whirlin protein interacts with these domains to regulate the elongation of actin filaments in stereocilia, forming a staircase-like arrangement in hair bundles (31). The length of the stereocilia and the structure of

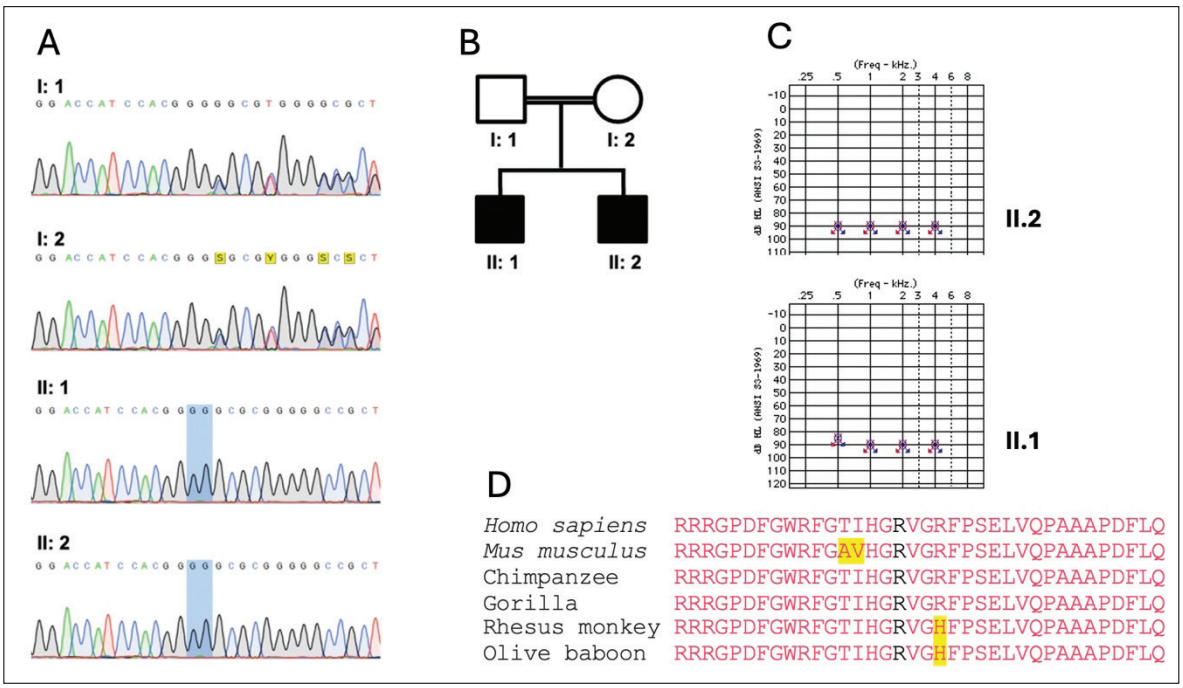

Figure 1. *The family pedigree, Sanger sequencing for the family, the ABR results for the affected children, and evolution analysis. A. Sanger sequencing data for the affected children and their parents. The highlighted region shows the duplicated region in heterozygous status for the parents (I-1 and I-2) and homozygous status for the affected children (II-1 and II-2). The yellow highlight represents the positions where amino acid differences occur. B. The family pedigree shows the consanguinity and the affected children. C. The plotted audiogram for both affected children showed profound hearing loss. D. The protein evolutionary alignment between species highlighted the arginine (R) amino acid shown in black.*

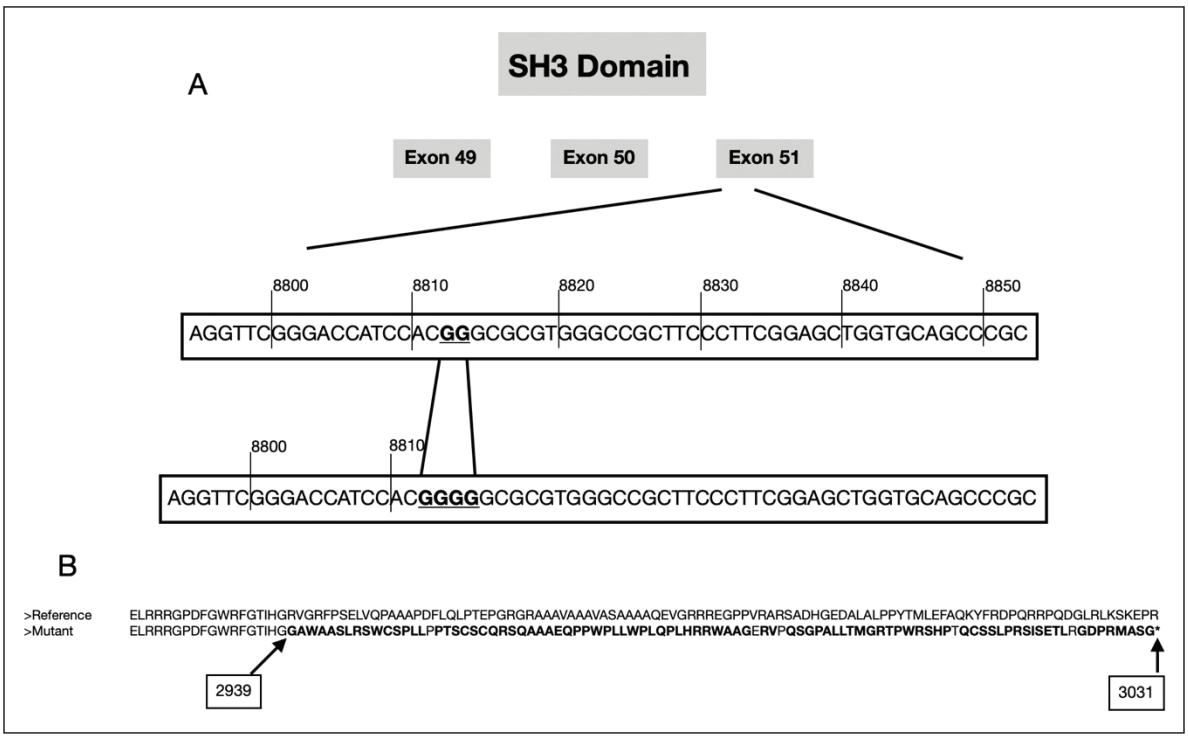

Figure 2. *The location of the two-bp duplicate variant and its effect on the protein level. A. Location of the two-bp duplication variant at the domain level to the sequence level. B. Amino acid sequence alignment for the reference and the mutated sequence. This shows the changes at the amino acid level and location of the stop codon.*

hair bundles in the inner ear are essential for maintaining normal hearing function (31). The variant in this domain is crucial to the inner ear function. Several variants in this domain have been reported in different populations and are known to cause NSHL (32).

This study identified a novel two-base pair homozygous duplication variant in a known gene (*MYO15A*) causing NSHL that was predicted to cause frameshift with nonsense-mediated decay. Additionally, the variant occurs in exon 51, which is part of the SH3 functional

domain. This variant will be classified as pathogenic with strong support (PSV1). Furthermore, the variant is not identified in the control population, the gnomeAD, and local databases; therefore, it is classified as PM2 (supporting). Variant segregated in the family member and two affected members in the family; thus, classified as PP1 supporting. Based on ACMG guidelines, this variant is considered a pathogenic variant (15).

Private and rare variants could shape the genetic inheritance of a population. This is because of the founder effect arising from the consanguineous marriage in that population. A notable example of this is an isolated seven-bp duplication at the *MYO15A* in the Omani families. This duplication has been detected in a third of the NSHL Omani patient cohort and has a significant allele carrier frequency of 0.3% of the cohort (33). This high allele carrier frequency is evidence of a private and founder variant. The variant was found to occur in recent centuries due to the low homozygous region around the variant (33). In the current study, the two-bp duplication variant is private to the Saudi population and very rare. It has not been reported in the international database or the local or nearby database population. As part of the limitations of this current study and it would be interesting to be carried out for further investigation is the following. Identify the regions of homozygosity for the current rare duplication variant. This would provide further insights into the complexities of inbreeding in the Saudi population. Additionally, investigating the carrier status of extended family members and hearing loss cohort could be valuable for future studies. The last limitation, and it would be considered an important element for future research, is finding another affected family that has the current variant.

Conclusion

A biallelic two-bp duplication in the *MYO15A* gene was identified in two Saudi siblings with NSHL. This variant is predicted to cause a frameshift, leading to the disruption of protein function. The variant is private to the Saudi population, very rare, and isolated. This phenomenon is probably due to the high consanguinity rate in the population. Further genotype-phenotype correlation studies on NSHL patients may confirm this finding and lead to the discovery of additional novel variants.

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Conflict of interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for participate
Written consent was obtained from all the participants

Ethical approval
The research study was approved by the institutional review board of Taibah University via reference/letter number (2023/146/103 MLT), dated: 11/10/2022.

Data availability statement
Data sharing is available upon request to the author.

Author contributions
Almalki F. and Halawani R. designed and directed the project; Halawani R., Wali H., and Alshamani M. recruited the family and carried out the hearing assessment test; Almalki F., and Balahmar R., performed the experiments; Almalki F., and Alshareef A., analyzed the data; all authors wrote and revised the manuscript.

Author details
Faisal Almalki[1], Hamzah Wali[2], Reham M. Balahmar[3], Abdularaheem Alshareef[1], Mansour Rabeh Alshamani[2], Roa Talal Halawani[2]

1. Clinical Laboratory Sciences, Applied Medical Science, Taibah University, Medina, Saudi Arabia
2. Ohud General Hospital, Ministry of Health, Medina, Saudi Arabia
3. Center for Genetics and Inherited Diseases, Taibah University, Medina, Saudi Arabia

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