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A Nonsense Mutation In *MYO7A*: The Cause Of Non-Syndromic Hearing Loss In An Indian Family

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Abstract
The MYO7A gene encodes the protein myosin VIIA, sometimes referred to as MYO7A. Non-syndromic hearing loss, in which the deafness develops without any other symptoms, has been associated with a number of mutations in the MYO7A gene. Mutations in this gene may result in two forms of non-syndromic hearing loss: DFNA11 and DFNB2. We attempted to find MYO7A mutations from a few Indian families with non-syndromic hearing loss after taking into account their substantial impact. Four members of an Indian family were found to have inherited hearing loss based on the findings of the current inquiry. The investigation of this family indicates that MYO7A has the homozygous stop gain variant p.Arg1373Stop; c.4117C>T; chr11:77,192,243C>T [hg 38]; p.Arg1373Stop. This premature stop codon (p.Arg1373Stop) in MYO7A increases the likelihood that this family will experience autosomal recessive non-syndromic hearing loss. The p.Arg1373Stop variation is the cause of MYO7A-related inherited hearing loss, which has been reported for the first time in India. This project will raise awareness of hereditary disorders in our community, potentially leading to better patient diagnosis and counseling in the future. The information this research project disseminates may also lead to the development of future treatment treatments for certain ailments.
Keywords: *Myosin VIIA; MYO7A; Mutation; Hearing loss; Genetic; Usher syndrome*

INTRODUCTION

Myosin VIIA (also known as MYO7A) is a protein that is encoded by the MYO7A. It is a member of the family of proteins known as unconventional myosins. Similar in structure, these proteins function in intracellular transport. Actin, a protein crucial to cell motility and shape, interacts with myosins. Long actin filaments are thought to serve as rails used by myosins to move other molecules (Zhang & Yu, 2020).

Both the inner ear and the retina (the light-sensitive tissue at the back of the eye) produce myosin VIIA. Myosin VIIA aids in the formation and maintenance of stereocilia, which are hair- like projections in the inner ear. Actin-rich stereocilia line the inner ear and deflect in response to vibrations in the air. Sound waves must undergo this bending motion in order to be transformed into nerve impulses and sent to the brain. The vestibular system, located in the inner ear, is responsible for helping the body maintain its balance and sense of spatial direction (Terziev & Vasileva, 2022). In order for the vestibular system to send signals to the brain, these stereocilia must bend. Retinal pigment epithelium (RPE) cells are where myosin VIIA is most concentrated in the eye. The growth and maintenance of this tissue, which is essential for the health of the retina, likely involves myosin VIIA. It has been hypothesized that myosin VIIA transports melanosomes, tiny sacs of pigment, around the RPE. This pigment is essential for healthy eyesight. There are other regions of the retina where myosin VIIA is present, suggesting that it transports other proteins and chemicals crucial to eye function (MedlinePlus, 2022).
Several mutations in the MYO7A have been linked to non-syndromic hearing loss, in which the deafness occurs independently of any other symptoms. DFNA11 and DFNB2 are two types of non-syndromic hearing loss that may be caused by mutations in this gene. Because of its autosomal dominant inheritance pattern, DFNA11 may be caused by the presence of even a single mutation MYO7A copy in any given cell. This kind of hearing loss manifests itself in early infancy, when a kid

has the ability to communicate verbally (post-lingual), and worsens with time (Hildebrand et al., 2010).

Usher syndrome type I is characterized by hearing loss, visual loss, and issues with balance and coordination, and more than 200 mutations in the *MYO7A* have been found in persons with this condition. More than half of all instances of Usher syndrome type I are due to mutations in the *MYO7A*, which causes Usher syndrome type IB (USH1B). Many of these mutations modify only one amino acid in key spots in the myosin VIIA protein. Other mutations alter the instructions for synthesizing myosin VIIA by adding a premature stop codon. Still other changes to the *MYO7A* include deletions or insertions of very small fragments of DNA. All of these modifications either cause the development of a myosin VIIA variant that is dysfunctional or completely eliminate its production. Myosin VIIA deficiency causes hearing loss, imbalance, and coordination issues because it prevents stereocilia from developing and functioning normally in the inner ear. Progressive vision loss is the outcome of retinitis pigmentosa, a disorder caused by a deficiency of myosin VIIA in the retina (Lenassi et al., 2014; Liu et al., 1997; Riazuddin et al., 2008; Rong et al., 2014). After considering the significant impact of *MYO7A* mutation, we tried to identify the same from some Indian families suffering from non-syndromic hearing loss.

MATERIALS AND METHODS

Ethical Approval

All the samples were collected after collecting duly filled and signed consent forms from each individual. Identity of each individual was concealed to comply with confidentiality norms. Photographs were taken with patients' or their guardians' permission wherever required.

Subjects

The affected family members from Maharashtra, India were underwent this study. Four family members were identified and found affected with non-syndromic hearing loss. Blood samples were obtained from affected children, parents and unaffected family members. All samples were obtained with approved informed consent.

DNA extraction

DNA was extracted from the blood samples obtained from the family members of the affected individuals using ReliaPrep Blood gDNA Miniprep Sytem.

Whole Exome Sequencing

The SureSelect Target Enrichment method is a solution-based approach that captures areas of interest using ultra-long - 120 merbiotinylatedcRNA baits - and enriches them from an NGS genomic fragment pool.

Captured Library Construction

We employ the Agilent SureSelectXT Low Input Target Enrichment procedure for Illumina paired-end sequencing libraries with 1ug of input gDNA to build standard exome capture libraries. PicoGreen and agarose gel electrophoresis are used to determine the amount and quality of DNA. We utilise 1 g of genomic DNA from each cell line diluted in EB Buffer and sheared to a desired peak size of 150–200 bp using the Covaris LE220 focused-ultrasonicator (Covaris, Woburn, MA) according to the manufacturer's instructions. End-repair and the addition of a 'A' tail follow fragmentation. The fragments are subsequently ligated to Agilent adapters.

The adapter ligated product is PCR amplified after the ligation efficiency is assessed. TapeStation DNA screentape D1000 is used to measure the final purified product (Agilent). According to the Agilent SureSelect Target Enrichment technique, 250 ng of DNA library is combined with hybridization buffers, blocking mixes, RNase block, and 5l of SureSelect all exon capture library for exome capture. The DNA is extracted, washed, and amplified. The resulting purified product is then quantified using qPCR (KAPA Library Quantification kits for Illumina Sequecing platforms) and validated using the TapeStation DNA screentape D1000 according to the qPCR Quantification Protocol Guide (Agilent).

Clustering & Sequencing

Illumina employs a one-of-a-kind amplification process that takes place on the flow cell's surface. The Illumina platform is filled with a flow cell holding millions of distinct clusters for automatic extension and imaging cycles. Sequencing-by-four proprietary nucleotides with reversible fluorophore and termination features are used in the synthesis. Each sequencing cycle happens with all four nucleotides present, resulting in better accuracy than approaches in which only one nucleotide is present in the reaction mix at a time. This cycle is repeated one base at atime, resulting in a sequence of pictures that each represent a single base expansion at a particular cluster.

Generation of Raw data

RTA, the Illumina platform's integrated primary analysis programme, generates raw pictures and base calling (Real Time Analysis). The binary base calling files are translated into FASTQ using the Illumina programme bcl2fastq v2.20.0. The value of the demultiplexing option (— barcode-mismatches) is 0 (Fu et al., 2012; Logan et al., 2022; Witten, 2011; Yang & Xu, 2020).

Results and Discussion

MYO7A information is tabulated in Table 1. Family pedigree indicating affected and unaffected individuals are depicted in Fig. 1. The clinical details of affected individuals from the family are exemplified in Table 2. The Sanger sequencing results are illustrated in Table 3.

Table 1. *MYO7A* gene information.

Gene name	MYO7A
Code protein	Myosin protein VIIA
Site of expression	Expressed in epithelial tissue of retina and inner ear

Table 2. The clinical details of affected individuals from the family.

Clinical Features	**Individual**			
	II:1	**II:3**	**II:4**	**II:5**
Hearing	No	No	No	No
Vision	Normal	Normal	Normal	Normal
Birth/Birth related issues, if any	Normal birth	Normal birth	Normal birth	Normal birth
Spoken communication	No word, use sign language	No word, use sign language	No word, use sign language	No word, use sign language
Weight at the time of examination	60 Kg	62 Kg	65 Kg	64 Kg
Age at the time of examination	45 years	43 years	40 years	38 years
Head circumference	Normal	Normal	Normal	Normal

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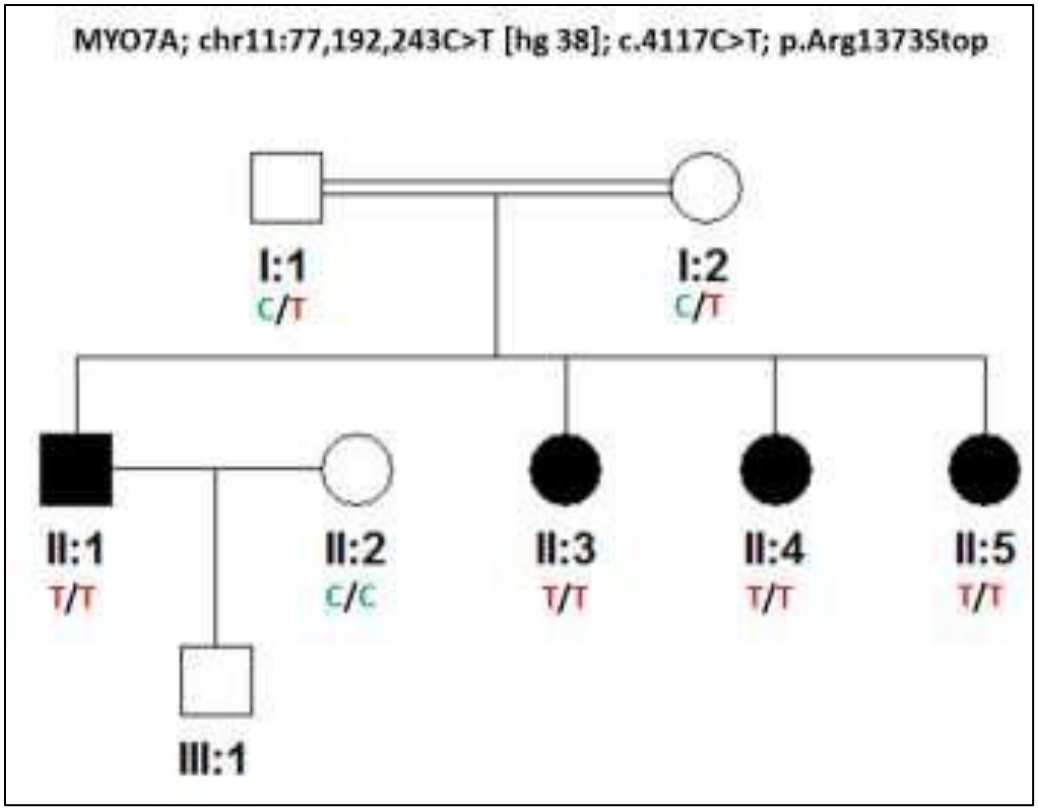

Fig. 1. The family pedigree indicating affected and unaffected individuals from studied cohort. Empty squares and circles indicate unaffected male and females from this family, respectively. Whereas filled in squares and circles indicate affected individuals suffering from autosomal recessive non-syndromic hearing loss.

Table 3. The Sanger sequencing results of the study

Individual	Genotype	Zygosity	Affectation Status	Gene	Variant
I:1	C/T	Heterozygous	Unaffected	MYO7A	c.4117C>T; p.Arg1373*
I:2	C/T	Heterozygous	Unaffected	MYO7A	c.4117C>T; p.Arg1373*
II:1	T/T	Homozygous	**Affected**	MYO7A	c.4117C>T; p.Arg1373*
II:3	T/T	Homozygous	**Affected**	MYO7A	c.4117C>T; p.Arg1373*
II:4	T/T	Homozygous	**Affected**	MYO7A	c.4117C>T; p.Arg1373*
II:5	T/T	Homozygous	**Affected**	MYO7A	c.4117C>T; p.Arg1373*
II:2	C/C	Wild type	Unaffected	MYO7A	c.4117C>T; p.Arg1373*

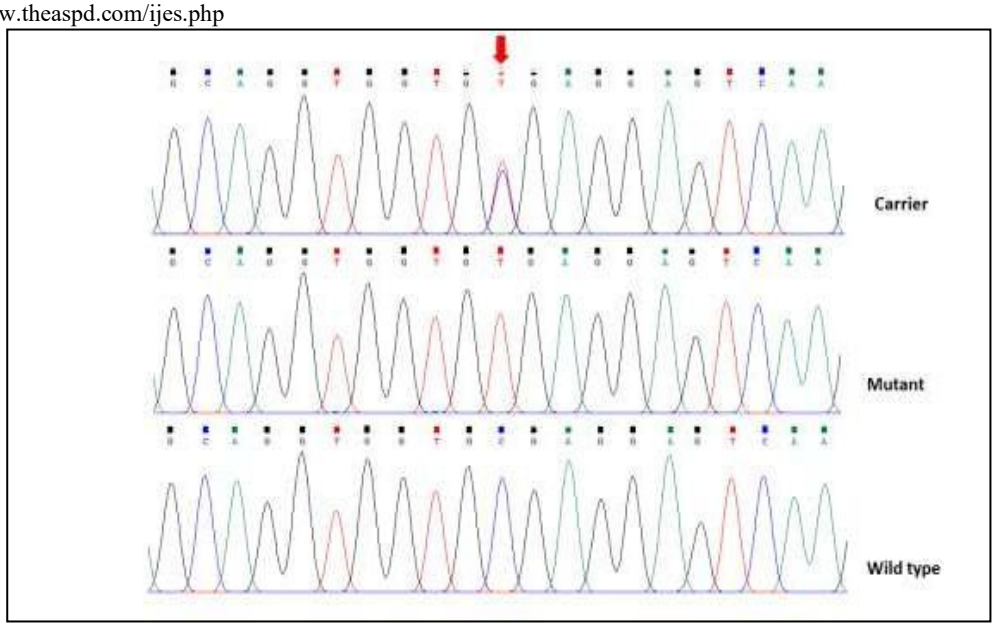

Fig. 2. Sequence chromatograms for carrier, mutant and WT

The *MYO7A* is found on chromosome 11q13.5 and encodes for an unusual myosin that is found in the inner ear, lung, kidney, testis, and retina. p.Arg1373Stop variant identified in this family has been reported in the French and Spanish families in the past. Sanger sequencing of all the affected and unaffected individuals from this family was performed for this specific variant to corroborate the fact this variation, p.Arg1373Stop in MYO7A is the underlying cause of this disease (autosomal recessive non-syndromic hearing loss) in this family. p.Arg1373Stop homozygous variant in MYO7A co-segregates completely with disease phenotype in this family.

During the course of the present research, a family from Maharashtra was uncovered that had four afflicted individuals who suffered from inherited hearing loss. Results of this study confirm that MYO7A homozygous stop gain variant chr11:77,192,243C>T [hg 38]; c.4117C>T; p.Arg1373Stop is the underlying cause of inherited non-syndromic hearing loss in this family.. This is the first study that describes this form of inherited hearing loss in India that is caused by this variant (p.Arg1373Stop) in MYO7A. In conclusion, this study helps to improve understanding about inherited illnesses in our community, which may in future contribute towards accurate diagnosis and counseling of similarly affected individuals as well as their family members. This research could also improve the prospects of developing a potential treatment therapy for inherited hearing loss in future.

CONCLUSION

A family from Maharashtra with four members who had inherited hearing loss was chosen for the current study. According to research done on this family, autosomal recessive non-syndromic hearing loss in this family is most likely caused by the homozygous stop gain variant chr11:77,192,243C>T [hg 38]; c.4117C>T; p.Arg1373Stop in MYO7A. This is the first account of this type of hereditary hearing loss in India caused by the variant (p.Arg1373Stop) in MYO7A. To sum up, this study increases knowledge about hereditary illnesses in our society and could help future diagnoses and counseling for patients and their families that are similarly impacted. Additionally, this study may improve the likelihood that a therapy for these kinds of illnesses may be developed in the future. Researchers, medical professionals, and the community may all benefit from this study.

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CONFLICTS OF INTERESTS

Declared none

REFERENCES

Fu, L., Niu, B., Zhu, Z., Wu, S., & Li, W. (2012). CD-HIT: Accelerated for clustering the next- generation sequencing data. *Bioinformatics*,28(23),3150–3152. https://doi.org/10.1093/bioinformatics/bts565.

Hildebrand, M. S., Thorne, N. P., Bromhead, C. J., Kahrizi, K., Webster, J. A., Fattahi, Z., Bataejad, M., Kimberling, W. J., Stephan, D., Najmabadi, H., Bahlo, M., & Smith, R. J. H. (2010). Variable hearing impairment in a DFNB2 family with a novel MYO7A missense mutation. *Clinical Genetics*, *77*(6), 563–571. https://doi.org/10.1111/j.1399- 0004.2009.01344.x.

Lenassi, E., Saihan, Z., Cipriani, V., Le Quesne Stabej, P., Moore, A. T., Luxon, L. M., Bitner Glindzicz, M., & Webster, A. R. (2014). Natural history and retinal structure in patients with usher syndrome type 1 owing to MYO7A mutation. *Ophthalmology*, *121*(2), 580–587. https://doi.org/10.1016/j.ophtha.2013.09.017.

Liu, X. Z., Walsh, J., Mburu, P., Kendrick-Jones, J., Cope, M. J. T. V., Steel, K. P., & Brown, S.D. M. (1997). Mutations in the myosin VIIA gene cause non-syndromic recessive deafness. *Nature Genetics*, *16*(2), 188–190. https://doi.org/10.1038/ng0697-188.

Logan, R., Fleischmann, Z., Annis, S., Wehe, A. W., Tilly, J. L., Woods, D. C., & Khrapko, K. (2022). 3GOLD: optimized Levenshtein distance for clustering third-generation sequencing data. *BMC Bioinformatics*, *23*(1). https://doi.org/10.1186/s12859-022-04637-7

MedlinePlus. (2022). *MedlinePlus: Genetics*. MedlinePlus.

Riazuddin, S., Nazli, S., Ahmed, Z. M., Yang, Y., Zulfiqar, F., Shaikh, R. S., Zafar, A. U., Khan, S. N., Sabar, F., Javid, F. T., Wilcox, E. R., Tsilou, E., Boger, E. T., Sellers, J. R., Belyantseva, I. A., Riazuddin, S., & Friedman, T. B. (2008). Mutation spectrum of MYO7A and evaluation of a novel non-syndromic deafness DFNB2 allele with residual function. *Human Mutation*, *29*(4), 502–511. https://doi.org/10.1002/humu.20677.

Rong, W., Chen, X., Zhao, K., Liu, Y., Liu, X., Ha, S., Liu, W., Kang, X., Sheng, X., & Zhao, C. (2014). Novel and recurrent MYO7A mutations in Usher syndrome type 1 and type 2. *PLoS ONE*, *9*(5). https://doi.org/10.1371/journal.pone.0097808.

Terziev, V., & Vasileva, S. (2022). The Public Library As Health Information Resource. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3948623.

Witten, D. M. (2011). Classification and clustering of sequencing data using a poisson model. *Annals of Applied Statistics*, *5*(4), 2493–2518. https://doi.org/10.1214/11-AOAS493.

Yang, D., & Xu, W. (2020). Clustering in human microbiome sequencing data: A distance-based unsupervised learning model. *Microorganisms*, *8*(10), 1–18. https://doi.org/10.3390/microorganisms8101612.

Zhang, Z., & Yu, P. (2020). MedlinePlus. In *Encyclopedia of Gerontology and Population Aging* (pp. 1–7). https://doi.org/10.1007/978-3-319-69892-2_450-2.