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Novel variant in *OTOG* gene in consanguineous family with sensorineural hearing loss

Yu An ,[1] Dylan Chan ,[2] Robert Wallerstein[1]

[1]Medical Genetics, Department of Pediatrics, UCSF Medical Center, San Francisco, California, USA
[2]Department of Otolaryngology-Head and Neck Surgery, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Robert Wallerstein;
Robert.wallerstein@ucsf.edu

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SUMMARY

The case report investigates sensorineural hearing loss (SNHL) in three siblings from a consanguineous Afghani family, with a particular focus on the novel variant in the *OTOG* gene, c.1644+5 G>C. The homozygous *OTOG* variant is consistently observed in all three siblings. This intronic+5 splice site variant is rare and predicted to have a deleterious effect, suggesting a potential role in SNHL pathogenesis. The study highlights the significance of *OTOG* variants in autosomal recessive non-syndromic hearing loss and the challenges in variant interpretation. While further research is needed to fully elucidate the functional consequences of *OTOG* variants, this finding emphasises the importance of genetic testing in consanguineous families and under-represented populations and underscores the heterogeneous nature of SNHL.

BACKGROUND

Otogelin, an N-glycosylated protein encoded by the *OTOG* gene, is a component of the acellular membranes of the inner ear. The acellular membranes cover the six sensory epithelial patches of the inner ear: the cochlea, the organ of Corti, vestibule, utricle, saccule and semicircular canals. These membranes are involved in the mechanotransduction process. Their movement is induced by sound in the cochlea or acceleration in the vestibule, resulting in the deflection of the stereocilia bundle at the apex of the sensory hair cells. In a mouse model study conducted by Simmler *et al*,[1] disruption of the *OTOG* gene impaired vestibular and auditory function in *OTOG* −/− mice. These results suggested that *OTOG* is a candidate gene for a human non-syndromic form of deafness. The *OTOG* gene is located at 11p15.1. Homozygous and compound heterozygous variants including missense, nonsense and frameshift variants in this gene have been reported in association with autosomal recessive non-syndromic deafness or deafness, autosomal recessive 18B.[2 3]

CASE PRESENTATION

Three patients who are full siblings (female in her late adolescence (patient 1), younger male in his late adolescence (patient 2) and youngest male in his middle childhood (patient 3)) from a consanguineous marriage of parents presented with bilateral sensorineural hearing loss (SNHL) and were otherwise healthy. No other otological symptoms, including vertigo, disequilibrium, Eustachian tube dysfunction, otalgia or aural fullness, were noted. The severity of hearing loss varied among the three siblings, with the two older children having mild to moderate SNHL and the youngest with mild SNHL. Sister also had a history of speech delay. There is no known hearing loss in either the maternal or paternal family and four other full siblings. Parents of the three patients are first cousins. Family history is otherwise unremarkable.

INVESTIGATIONS

Patient 1 had bilateral normal downsloping to moderate SNHL with speech reception thresholds (SRTs) and word recognition scores (WRS) of 25 dB HL and 84%, and 20 dB HL and 84% in the right and left ears, respectively. Age of onset of hearing loss is unknown; newborn hearing screening was not performed and hearing loss was first confirmed after routine hearing screening in early adolescence, though hearing loss was suspected for years previously. Hearing was stable over the 4 years of documented serial audiograms (figure 1). MRI revealed normal anatomy of the temporal bone, inner ear, seventh and eighth cranial nerves, and brain.

Patient 2 had bilateral symmetric mild downsloping to moderate SNHL, with SRT/WRS of 25 dB HL/100% and 25 dB HL/100% in the right and left ears, respectively. Age of onset was also unknown, with hearing loss identified on routine school hearing screening in early adolescence. Hearing was stable over 3 years of serial audiometry (figure 1).

Patient 3 had mild SNHL at mid frequencies only, with SRT/WRS of 20 dB HL/100% and 20 dB HL/97% in the right and left ears, respectively. Age of onset was unknown, with hearing loss identified on routine school hearing screening in middle childhood. As only one audiogram was documented, progression could not be ascertained (figure 1).

None of the patients had any phenotype other than hearing loss. Clinical genetic testing consisting of a hearing loss multigene panel was performed in the three patients with hearing loss with results as follows:

Patient 1

OTOG c.1644+5 G>C homozygous variant of uncertain significance.
MCM2 c.442 G>Ap.A148T homozygous variant of uncertain significance.
MYH14 c.4315G>Ap.Glu1439Lys heterozygous variant of uncertain significance.

Patient 2

OTOG c.1644+5 G>C homozygous variant of uncertain significance.

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MCM2 c.442 G>Ap.A148T heterozygous variant of uncertain significance.
MYH14 c.4315G>A p.Glu1439Lys heterozygous variant of uncertain significance.

Patient 3

OTOG c.1644+5 G>C homozygous variant of uncertain significance.
MCM2 c.442 G>Ap.A148T homozygous variant of uncertain significance.
MYH14 c. 4315G>A p.Glu1439Lys heterozygous variant of uncertain significance.

The *OTOG* variant was initially classified as a variant of uncertain significance due to (1) Intronic+5 splice site variant in a gene for which loss-of-function is a known mechanism of disease, and both splice predictors and evolutionary conservation support a deleterious effect, although in the absence of functional evidence; (2) The actual effect of this sequence change is unknown; (3) Observed in apparent homozygous state in this patient and an affected sibling and not reported to be observed in homozygous state in controls and (4) Has not been previously published as pathogenic or benign to our knowledge.

Targeted variant testing of the *OTOG* gene and the *MYH14* gene was performed in parents and confirmed that both parents are heterozygous for the *OTOG* variant. The father is heterozygous for the MYH14 variant. In total, nine individuals from this family were studied, only the three individuals mentioned in this report were the only ones homozygous for the OTOG c.1644+5G>C variant and were the only ones with clinical hearing loss.

DIFFERENTIAL DIAGNOSIS

Based on the family history of hearing loss and consanguinity, a genetic form of hearing loss was highly suspected. The three variants of uncertain significance in the *OTOG, MCM2 and MYH14* genes detected in the three patients were evaluated in detail.

The variant of uncertain significance in the *OTOG* gene detected in homozygous state in all three patients and heterozygous state in both parents is an intronic+5 splice site variant. Although this variant has not been previously published regarding its possible pathogenicity, it has extremely low frequency (0.044%) in gnomAD population databases and has been observed in 0.0067% (10/148 878 alleles) in large population cohorts as part of the Exome Aggregation Consortium,[4] which supports an increased pathogenicity. The specific tools spliceAI and Pangolin indicate a moderate probability that the c.1644+5C variant affects gene splicing. As loss-of-function is a known mechanism of the *OTOG* gene, both the splice predictors and the evolutionary conservation support a deleterious effect of this variant. Considering the lack of family history of hearing loss, especially in their parents, and parents being both in heterozygous state of the *OTOG* variant in the three patients, the hearing loss in this family is likely caused by an autosomal recessive condition that fits the inheritance pattern of the OTOG-related autosomal recessive non-syndromic hearing loss. The ACMG algorithm of sequence variants PM2+PM3+PP1+PP3=likely pathogenic status.

The *MCM2* gene encodes the minichromosome maintenance (MCM) complex component 2 protein, which plays a role in DNA replication and cell division. Gao *et al*[5] reported a heterozygous missense variant in the *MCM2* associated with autosomal dominant nonsyndromic deafness in a Chinese family. Both intrafamilial variability and complete penetrance were reported among all affected family members harbouring the *MCM2* variant, which was absent in unaffected relatives and unrelated controls. The condition is characterised by postlingual, symmetric sensorineural hearing with onset ranging from teens to adulthood, which does not fit the presentation in our patients especially the sister with speech delay. Although no family testing was performed in unaffected family members in our case, having all three patients harbour the same variant in MCM2 makes it more likely to be inherited from their parents instead of de novo. The c.442G>Ap.Ala148Thr is common and predicted to be 'likely benign' by AlphaMissense. Considering the reported full penetrance and the unaffected parents of the three patients, the variant of uncertain significance found in the *MCM2* gene in them is less likely the cause of their hearing loss.

The *MYH14* gene encodes a conventional non-muscle myosin. Myosins are actin-dependent motor proteins with diverse functions including regulation of cytokinesis, cell motility and cell polarity. Shearer *et al*[6] and Kim *et al*[7] reported that disrupted *MYH14* gene can cause autosomal dominant non-syndromic SNHL (DFNA4). As the *MYH14* variant has been detected in the father without hearing loss, it is also not likely the cause of the hearing loss in this family. The 4315G>A p.Glu1439Lys variant is predicted to be 'ambiguous' by AlphaMissense.

OUTCOME AND FOLLOW-UP

The three patients were managed with bilateral hearing aids and educational services to support their hearing needs. They responded well to augmented hearing and are making satisfactory academic progress.

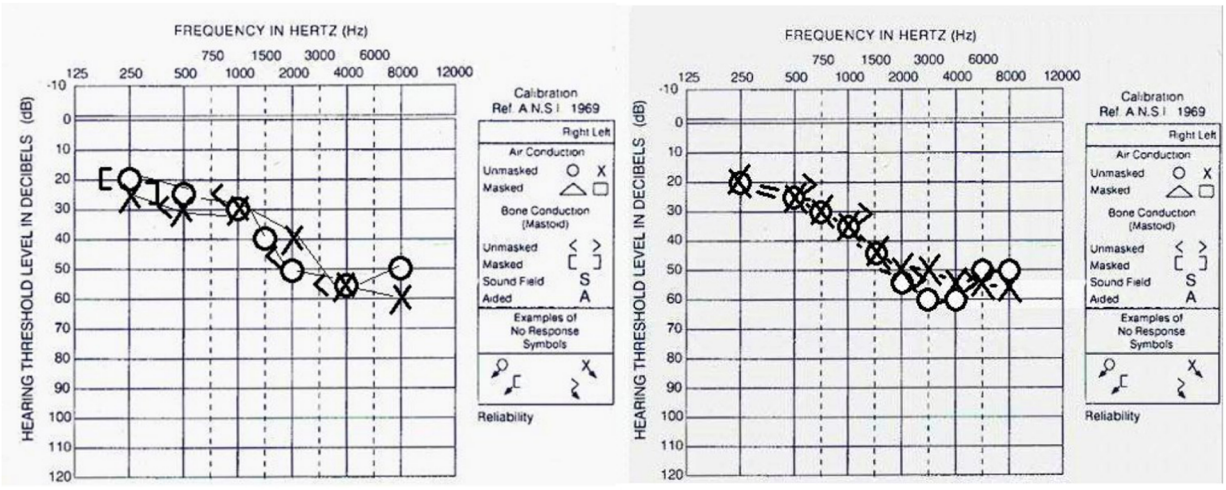
DISCUSSION

Hearing loss has a high likelihood of a genetic aetiology. Approximately 80% of prelingual deafness is genetic, most often autosomal recessive and non-syndromic. The most common cause of severe-to-profound autosomal recessive non-syndromic hearing loss in most populations is mutation of GJB2. The most common cause of mild-to-moderate autosomal recessive hearing loss is mutation of STRC; of note, there is ethnic-based variability.[8] Racial/ethnic disparities in the diagnostic efficacy of genetic testing for hearing loss relate to differences in variant classification between different racial/ethnic groups, which may, in turn, derive from disparate representation of these groups in the published literature.[9] We present the current case in an underrepresented group with a novel variant. The variant was initially classified as uncertain clinical significance, which may be related to the incidence of this variant in individuals with deafness and/or the limited genetic analysis of the patients' population.

Identifying the specific cause of deafness is also important for considering treatment options. Gene therapy is a promising new approach for hereditary deafness. AAV1-hOTOF gene therapy with dual adeno-associated virus serotype 1 carrying human *OTOF* transgene is under investigation, with preliminary data showing that this is a safe procedure with restoration of hearing in all subjects to date.[10]

Genetic testing can be complex to interpret, and often family studies are necessary for clarification and interpretation of variants. This case highlights the complexities of such testing and the need for variant interpretation. Consanguinity is a risk factor for recessive disorders. Study of under-represented ethnicities will help to provide additional information on genetic origins of deafness in different populations to hopefully lead to improved management.

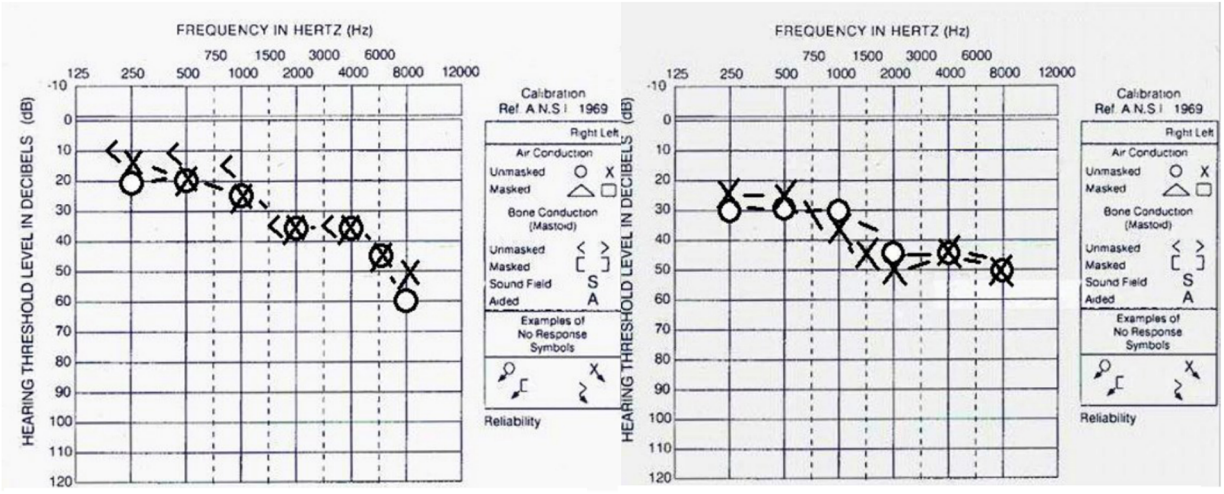
Patient 1



Early Adolescence

Late Adolescence

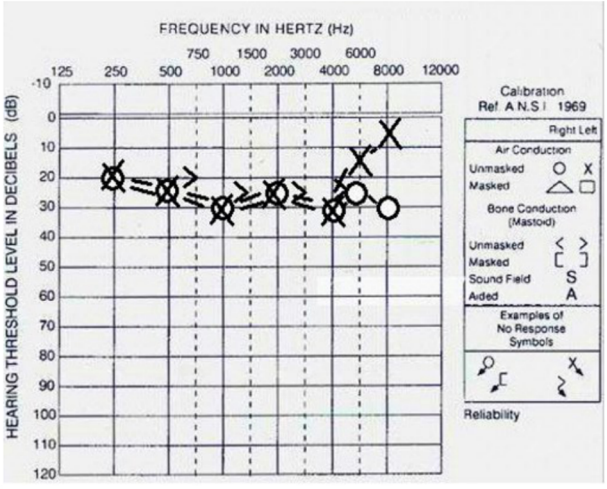
Patient 2



Early Adolescence

Early to Late Adolescence

Patient 3



Middle Childhood

Figure 1 Audiograms in three patients indicate mild to moderate hearing loss in patients 1 and 2 and mild hearing loss in patient 3. Hearing loss was stable without apparent progression in patients 1 and 2.

Learning points

- Genetic evaluation is important for determining the aetiology of hearing loss.
- The *OTOG* gene is associated with autosomal recessive hearing loss, and the c.1644+5 G>C variant is proposed to be a pathogenic variant.
- Genetic testing can reveal variants in multiple genes associated with sensorineural hearing loss (SNHL), but interpreting the clinical significance of these variants can be complex. Family studies and detailed variant analysis are often necessary for accurate interpretation.
- Consanguinity increases the risk of autosomal recessive disorders, including SNHL. This highlights the importance of genetic counselling and testing in consanguineous families, especially when SNHL is suspected.
- Racial and ethnic disparities in variant classification and representation in the literature can affect the diagnostic efficacy of genetic testing for SNHL. Studying under-represented populations is crucial for gaining insights into the genetic basis of hearing loss across different populations, as different mechanisms such as founder effect, genetic drift and genetic isolation may affect the incidence of genetic variations and, therefore, treatment resources needed in these populations.

Contributors All listed authors provided and cared for study patients. YA drafted the manuscript. DC and RW critically reviewed the case report. RW is the guarantor and obtained study consent.

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ORCID iDs
Yu An http://orcid.org/0009-0004-5788-2996
Dylan Chan http://orcid.org/0000-0003-0836-3730

REFERENCES

1 Simmler MC, Cohen-Salmon M, El-Amraoui A, *et al*. Targeted disruption of otog results in deafness and severe imbalance. *Nat Genet* 2000;24:139–43.
2 Schraders M, Ruiz-Palmero L, Kalay E, *et al*. Mutations of the gene encoding otogelin are a cause of autosomal-recessive nonsyndromic moderate hearing impairment. *Am J Hum Genet* 2012;91:883–9.
3 Ganaha A, Kaname T, Yanagi K, *et al*. Clinical characteristics with long-term follow-up of four Okinawan families with moderate hearing loss caused by an *OTOG* variant. *Hum Genome Var* 2019;6:37.
4 Lek M, Karczewski KJ, Minikel EV, *et al*. Analysis of protein-coding genetic variation in 60,706 humans. *Nature New Biol* 2016;536:285–91.
5 Gao J, Wang Q, Dong C, *et al*. Whole Exome Sequencing Identified MCM2 as a Novel Causative Gene for Autosomal Dominant Nonsyndromic Deafness in a Chinese Family. *PLoS ONE* 2015;10:e0133522.
6 Shearer AE, DeLuca AP, Hildebrand MS, *et al*. Comprehensive genetic testing for hereditary hearing loss using massively parallel sequencing. *Proc Natl Acad Sci USA* 2010;107:21104–9.
7 Kim BJ, Kim AR, Han JH, *et al*. Discovery of MYH14 as an important and unique deafness gene causing prelingually severe autosomal dominant nonsyndromic hearing loss. *J Gene Med* 2017;19.
8 Florentine MM, Rouse SL, Stephans J, *et al*. Racial and ethnic disparities in diagnostic efficacy of comprehensive genetic testing for sensorineural hearing loss. *Hum Genet* 2022;141:495–504.
9 Rouse SL, Florentine MM, Taketa E, *et al*. Racial and ethnic disparities in genetic testing for hearing loss: a systematic review and synthesis. *Hum Genet* 2022;141:485–94.
10 Wang H, Chen Y, Lv J, *et al*. Bilateral gene therapy in children with autosomal recessive deafness 9: single-arm trial results. *Nat Med* 2024;30:1898–904.