U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Azaiez H, Thorpe RK, Smith RJH. *OTOF*-Related Deafness. 2008 Feb 29 [Updated 2021 Jan 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

OTOF-Related Deafness

Synonyms: DFNB9, DFNB9 Nonsyndromic Hearing Loss

Hela Azaiez, PhD,[1] Ryan K Thorpe, MD,[1] and Richard JH Smith, MD[2]

Created: February 29, 2008; Updated: January 21, 2021.

Summary

Clinical characteristics

OTOF-related deafness is characterized by two phenotypes: prelingual nonsyndromic auditory neuropathy spectrum disorder (ANSD) and, less frequently, temperature-sensitive auditory neuropathy spectrum disorder (TS-ANSD).

- *OTOF*-related ANSD is characterized by congenital or prelingual, typically severe-to-profound bilateral deafness without inner-ear anomalies on MRI or CT examination of the temporal bones. Otoacoustic emissions (OAEs) are present and auditory brain stem response is abnormal at birth. Newborn hearing screening testing of OAEs only will fail to detect this disorder in most individuals. OAEs may decrease or disappear with age in 20%-80% of individuals.
- TS-ANSD typically presents with normal-to-moderate hearing loss (0-55 dB) at baseline body temperature. An elevation of body temperature (approximately 0.5°C or more) triggers significant bilateral hearing loss ranging from severe to profound, with resolution of hearing loss typically occurring within hours of a return to baseline body temperature.

Diagnosis/testing

The diagnosis of *OTOF*-related deafness is established in a proband with suggestive findings and biallelic pathogenic variants in *OTOF* identified by molecular genetic testing.

Management

Treatment of manifestations: Hearing aids should be fitted as soon as possible after hearing loss is identified. Consideration of cochlear implants (CIs) as soon as possible if hearing aids are not beneficial, as CIs have been

Author Affiliations: 1 Molecular Otolaryngology Research Laboratories, Department of Otolaryngology – Head & Neck Surgery Carver College of Medicine, University of Iowa, Iowa City, Iowa; Email: hela-azaiez@uiowa.edu; Email: ryan-thorpe@uiowa.edu. 2 Director, Molecular Otolaryngology Research Laboratories, Sterba Hearing Research Professor of Otolaryngology, Department of Otolaryngology – Head & Neck Surgery Carver College of Medicine, University of Iowa, Iowa City, Iowa; Email: richard-smith@uiowa.edu.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

shown to be effective for both phenotypes associated with *OTOF*-related deafness. Educational programs designed for individuals with hearing impairment should start as early as possible.

Prevention of primary manifestations: For individuals with TS-ANSD, prevent fevers and other activities/ambient conditions that would cause body temperature to rise; treat febrile episodes as quickly as possible.

Surveillance: Audiometry and speech discrimination testing every six months until age 18 years, then annually.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic sibs of a proband shortly after birth by molecular genetic testing for the pathogenic variants found in the proband so that appropriate early support and management can be provided to the child and family.

Genetic counseling

OTOF-related deafness is inherited in an autosomal recessive manner. If both parents are known to be carriers, each sib of an individual with *OTOF*-related deafness has at conception a 25% chance of being deaf, a 50% chance of having normal hearing and being a carrier, and a 25% chance of having normal hearing and not being a carrier. Once the *OTOF* pathogenic variants have been identified in the family, carrier testing, prenatal testing, and preimplantation genetic testing for *OTOF*-related deafness are possible.

GeneReview Scope

OTOF-Related Deafness: Included Phenotypes [1]	
Primary designation used in this *GeneReview*	Other designations
Auditory neuropathy spectrum disorder (ANSD)	• Auditory synaptopathy • Auditory dyssynchrony
Temperature-sensitive auditory neuropathy spectrum disorder (TS-ANSD)	• Temperature-sensitive nonsyndromic auditory neuropathy • Temperature-sensitive nonsyndromic auditory synaptopathy • Temperature-sensitive nonsyndromic auditory dyssynchrony

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

OTOF-related deafness **should be suspected** in individuals with:

- Congenital auditory neuropathy/synaptopathy without a history of causative environmental factors (e.g., neonatal hyperbilirubinemia and neonatal hypoxia), with or without progression of hearing loss;
- Temperature-sensitive nonsyndromic auditory neuropathy or synaptopathy.

  Note: *OTOF*-related deafness can appear to be an auditory neuropathy based on electrophysiologic testing in which auditory brain stem responses (ABRs) are absent and otoacoustic emission (OAEs) are present. However, in some individuals, OAEs disappear and electrophysiologic testing becomes more consistent with a cochlear defect by several years of age [Chiu et al 2010]. *OTOF*-related deafness will be identified with physiologic newborn hearing screening if automated ABR is used as part of the screen. If the program uses OAE testing only, the diagnosis may be missed.
- Family history consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *OTOF*-related deafness **is established** in a proband with suggestive findings and biallelic pathogenic variants in *OTOF* identified by molecular genetic testing (see Table 1).

Note: Identification of biallelic *OTOF* variants of uncertain significance (or identification of one known *OTOF* pathogenic variant and one *OTOF* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Because the phenotype of *OTOF*-related deafness may be indistinguishable from many other inherited disorders with deafness, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *OTOF*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A hearing loss multigene panel** that includes *OTOF* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *OTOF*-Related Deafness

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
OTOF	Sequence analysis [3]	98% [4]
	Gene-targeted deletion/duplication analysis [5]	~2% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017], the Deafness Variation Database [Azaiez et al 2018], ClinVar, and Leiden Open Variation Database
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. There have been three reports of a deletion involving *OTOF* [Zadro et al 2010, Tsai et al 2013, Chang et al 2015]. Two additional deletions were identified at the Molecular Otolaryngology and Renal Research Laboratories [Authors, unpublished observation].

Clinical Characteristics

Clinical Description

The two phenotypes observed in *OTOF*-related deafness are prelingual nonsyndromic auditory neuropathy spectrum disorder (ANSD) and, less frequently, temperature-sensitive auditory neuropathy spectrum disorder (TS-ANSD), also referred to as auditory synaptopathy, as it is related to a defect in synaptic transmission.

***OTOF*-related ANSD** is characterized by congenital or prelingual, typically severe-to-profound bilateral deafness without inner-ear anomalies on MRI or CT examination of the temporal bones. Otoacoustic emissions (OAEs) are present and auditory brain stem response (ABR) is abnormal at birth. Newborn hearing screening testing only for OAEs will fail to detect this disorder in most individuals. OAEs may decrease or disappear with age in 20%-80% of individuals [Kitao et al 2019].

The hearing loss can range from moderate to profound. (Moderate deafness is defined as hearing loss of 41-55 dB, moderately severe deafness as hearing loss of 56-70 dB, severe deafness as hearing loss of 71-90 dB, and profound deafness as hearing loss of >90 dB.) In some individuals, hearing loss may progress throughout early childhood and adolescence [Chiu et al 2010].

As is typical of auditory neuropathy spectrum disorders, individuals with *OTOF*-related deafness have poor speech discrimination, and derive significant benefit from cochlear implantation.

TS-ANSD typically presents with normal-to-moderate hearing loss (0-55 dB) at baseline body temperature. An elevation of body temperature (~0.5°C or more) in persons with TS-ANSD triggers significant bilateral hearing loss ranging from severe to profound.

Resolution of hearing loss typically occurs within hours of a return to baseline body temperature. Baseline hearing in children with TS-ANSD has been reported to improve with age in some individuals [Zhang et al 2016b].

Speech discrimination has been described as normal to slightly decreased at baseline with significant worsening during febrile periods. Speech development in these children is dependent on their baseline level of hearing, and benefit has been described from cochlear implantation.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified among the individuals with the *OTOF*-related ANSD phenotype. Regardless of variant type – truncating versus nontruncating – pathogenic variants in *OTOF* typically cause severe-to-profound hearing loss (see Figure 1B).

However, individuals with TS-ANSD are found to have certain pathogenic variants in *OTOF*, including p.Arg1939Gln, p.Ile515Thr, p.Gly541Ser, p.Arg1607Trp, and p.Glu1804del (see Table 6).

Nomenclature

Auditory neuropathy can be caused by a number of different defects in the auditory system, including the synaptic region (synaptopathy) or the auditory nerve (neuropathy). Because *OTOF*-related hearing loss is due to lesions at the presynaptic region of inner hair cells, the terms auditory synaptopathy or auditory neuropathy spectrum disorder are preferred.

Auditory dyssynchrony is a historical term used to describe the mismatch between outer and inner hair cell activity reflected by the difference between ABR and OAE testing.

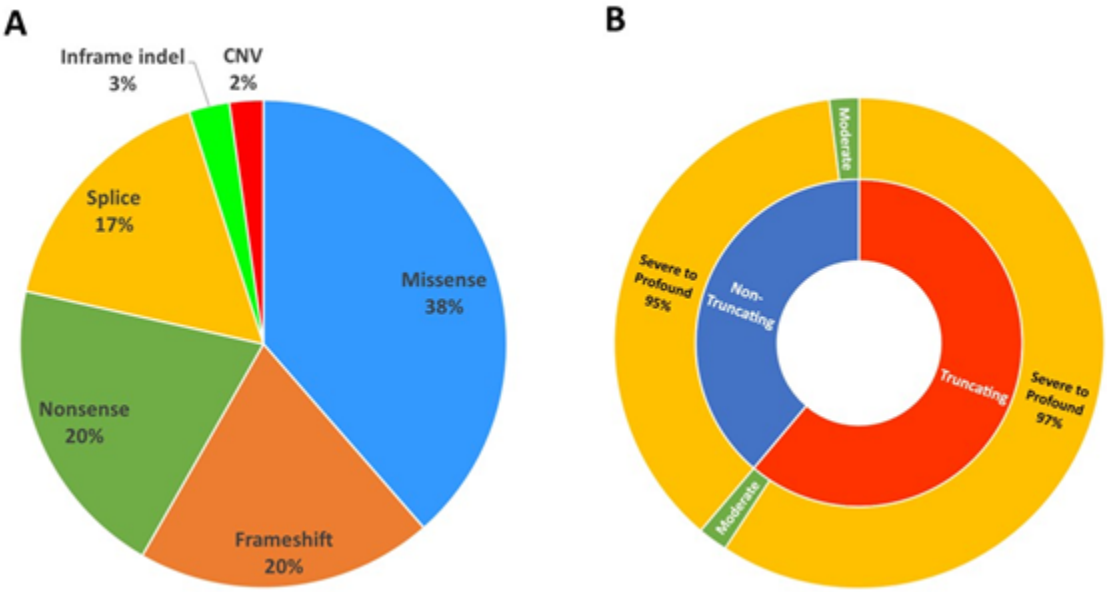

Figure 1: Genetic spectrum of *OTOF*-related hearing loss

A. Different types of pathogenic variants have been identified in *OTOF*, including missense, nonsense, frameshift, splice, inframe indels, and copy number variants (CNV).

B. Regardless of variant type – truncating versus nontruncating – pathogenic variants in *OTOF* typically cause severe-to-profound hearing loss. Only a few reported individuals exhibit moderate hearing loss.

Prevalence

The prevalence of *OTOF* pathogenic variants in persons with congenital autosomal recessive nonsyndromic deafness varies depending on ethnic origins. Among individuals with congenital/prelingual autosomal recessive hearing loss, biallelic *OTOF* pathogenic variants have been found in:

- 1%-2% in a Japanese cohort [Iwasa et al 2019];
- 2%-3% in both a Pakistani population [Choi et al 2009] and in a cohort of individuals tested in an American clinical laboratory [Sloan-Heggen et al 2016];
- 5%-8% in Spanish populations [Rodríguez-Ballesteros et al 2008].

Among individuals with auditory neuropathy spectrum disorder (ANSD), *OTOF* is a common genetic cause, found in 41%-91% of those tested [Zhang et al 2016a, Kim et al 2018].

The prevalence of temperature-sensitive auditory neuropathy is unknown.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *OTOF*.

Differential Diagnosis

Congenital (or prelingual) inherited hearing impairment affects approximately one in 1,000 newborns; 30% of these infants have additional anomalies, making the diagnosis of a syndromic form of hearing impairment possible (see Hereditary Hearing Loss and Deafness Overview). In developed countries, approximately half of

the remaining children (i.e., the 70% with nonsyndromic hearing impairment) have pathogenic variants in *GJB2* [Smith et al 2005, Angeli 2008]. Variants in at least 72 genes (including *OTOF*) have been implicated in congenital autosomal recessive nonsyndromic deafness.

Differential diagnosis of *OTOF*-related auditory neuropathy spectrum disorder. Other nonsyndromic hereditary auditory neuropathies include those summarized in Table 2.

Table 2. Other Nonsyndromic Hereditary Auditory Neuropathy Spectrum Disorders

Gene	Phenotype	MOI	OMIM Entry/Reference
AIFM1	DFNX5	XL	Zong et al [2015]
DIAPH3	AUNA1	AD	609129
PJVK [1]	DFNB59	AR	610220
ROR1	DFNB108	AR	617654

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Delmaghani et al [2006], Schwander et al [2007]

Note: *OTOF* pathogenic variants are extremely unlikely in a child with severe-to-profound hearing loss in only one ear and electrophysiologic responses consistent with auditory neuropathy. Instead, a cochlear defect should be considered; MRI is indicated [Buchman et al 2006].

Differential diagnosis of temperature-sensitive auditory neuropathy spectrum disorder. Other syndromes, such as Muckle-Wells syndrome (cryopyrin-associated periodic syndrome) (OMIM 191900), are associated with progressive deafness and intermittent fevers, but the fever itself does not cause a fluctuating hearing loss [Kuemmerle-Deschner et al 2013].

Management

No clinical practice guidelines for *OTOF*-related deafness have been published.

Evaluations Following Initial Diagnosis

To establish the extent of involvement in an individual diagnosed with *OTOF*-related deafness, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *OTOF*-Related Deafness

System/Concern	Evaluation	Comment
Hearing loss / Deafness	Assessment of auditory acuity (ABR emission testing, pure tone audiometry)	
Speech delay	By speech therapist / speech pathologist	
Speech discrimination	By audiologist	Tested when audiometry obtained
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *OTOF*-related deafness to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support.	

ABR = auditory brain stem response; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *OTOF*-Related Deafness

Manifestation/Concern	Treatment	Considerations/Other
Hearing loss / Deafness	Hearing aids (HAs)	HAs should be fitted as soon as possible after hearing loss is identified. However, based on severity of hearing loss & underlying pathophysiology, HAs are unlikely to be beneficial in many persons.
	Cochlear implantation	• CIs should be considered as soon as possible if hearing aids are not beneficial. • Case reports have shown good outcomes w/CIs in persons w/ *OTOF*-related deafness. [1] • CIs have also been used in TS-ANSD w/beneficial results. [2]
	Educational programs designed for persons w/hearing impairment	Start as early as possible.
Speech delay	Individualized speech therapy	

CIs = cochlear implants
1. Yawn et al [2019], Zheng & Liu [2020]
2. Zhang et al [2016b]

See Hereditary Deafness and Hearing Loss Overview for additional details.

Prevention of Primary Manifestations

For individuals with TS-ANSD:

- Prevent febrile episodes.
- Avoid the level of exercise and/or ambient conditions that would cause body temperature to rise.
- Treat febrile episodes as quickly as possible to return body temperature to normal.
- Inform individuals and their caregivers that the onset of hearing loss may be the first sign of a pyretic/ infectious event requiring treatment [Starr et al 1998].

Surveillance

Table 5. Recommended Surveillance for Individuals with *OTOF*-Related Deafness

System/Concern	Evaluation	Frequency
Hearing loss / Deafness	Audiometry to determine whether hearing loss is progressive or fluctuant	Every 6 mos until age 18 yrs, then annually
Speech recognition	Speech discrimination test	Done w/audiometry

Agents/Circumstances to Avoid

Avoid the following:

- Noisy environments
- Excessive body temperatures whenever possible for individuals with TS-ANSD (See Prevention of Primary Manifestations.)

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic sibs of a proband shortly after birth by molecular genetic testing for the pathogenic variants found in the proband so that appropriate early support and management can be provided to the child and family.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Several studies have shown the effectiveness of adeno-associated viral gene therapy to treat *OTOF*-related hearing loss in animal models [Akil et al 2019, Al-Moyed et al 2019]. Several companies are preparing for clinical trials using this methodology.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

OTOF-related deafness is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of a child with *OTOF*-related deafness are obligate heterozygotes (i.e., presumed to be carriers of one *OTOF* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *OTOF* pathogenic variant and to allow reliable assessment of recurrence probability. (In rare families, only one parent of a proband with an autosomal recessive disorder is heterozygous and the proband is affected as the result of either (1) one pathogenic variant inherited from the heterozygous parent and a second pathogenic variant that occurred *de novo* in the proband or (2) uniparental isodisomy and consequent homozygosity for the pathogenic variant transmitted by a heterozygous parent [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and do not develop *OTOF*-related deafness.

Sibs of a proband

- If both parents are known to be heterozygous for an *OTOF* pathogenic variant, each sib of the proband has at conception a 25% chance of being deaf, a 50% chance of being a carrier, and a 25% chance of not having a deafness-related variant in *OTOF*.
- Heterozygotes (carriers) are asymptomatic and do not develop *OTOF*-related deafness.

Offspring of a proband. The offspring of an individual with *OTOF*-related deafness are obligate heterozygotes (carriers of a pathogenic variant in *OTOF*).

Other family members. For each sib of the proband's parents, the probability of being a carrier of an *OTOF* pathogenic variant is 50%.

Carrier Detection

Carrier testing for relatives requires prior identification of the *OTOF* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing relatives for the purpose of early diagnosis and treatment.

The following points are noteworthy:

- Communication with individuals who are members of the Deaf community and sign requires the services of a skilled interpreter.
- Members of the Deaf community may view deafness as a distinguishing characteristic and not as a handicap, impairment, or medical condition requiring a "treatment" or "cure," or to be "prevented."
- Many deaf people are interested in obtaining information about the cause of their own deafness, including information on medical, educational, and social services, rather than information about prevention, reproduction, or family planning. It is, therefore, important to ascertain and address the questions and concerns of the family/individual.
- The use of certain terms is preferred: probability or chance vs risk; deaf and hard-of-hearing vs hearing impaired. Terms such as "abnormal" should be avoided.

Family planning

- The optimal time for determination of genetic status and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of the probability that offspring will be deaf and reproductive options) to young adults who have *OTOF*-related deafness, are carriers, or may be carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and deafness will improve in the future, consideration should be given to banking DNA of deaf individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *OTOF* pathogenic variants have been identified in a deaf family member, prenatal testing and preimplantation genetic testing for *OTOF*-related deafness are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **BabyHearing.org**
  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
  www.babyhearing.org
- **MedlinePlus**
  Nonsyndromic hearing loss
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. OTOF-Related Deafness: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

OTOF	2p23.3	Otoferlin	Hereditary Hearing Loss Homepage (OTOF) CCHMC - Human Genetics Mutation Database (OTOF) Deafness Variation Database (OTOF)	OTOF	OTOF

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for OTOF-Related Deafness (View All in OMIM)

601071	DEAFNESS, AUTOSOMAL RECESSIVE 9; DFNB9
603681	OTOFERLIN; OTOF

Molecular Pathogenesis

OTOF encodes otoferlin, a member of the FER-1 family of transmembrane proteins characterized by the presence of C2 domains [Yasunaga et al 1999]. Otoferlin contains six C2 domains (C2A-F), a transmembrane domain, and two Fer domains [Roux et al 2006, Lek et al 2010]. In the ear, otoferlin is expressed in cochlear inner hair cells. Otoferlin is a Ca^{2+} sensor that plays a significant role in the synaptic transmission in inner hair cells by tethering glutamatergic synaptic vesicles to the plasma membrane and triggering their fusion and pool replenishment at ribbon synapses [Strenzke et al 2016, Michalski et al 2017].

Normal hearing relies on a temporally precise and sustained glutamate release at these ribbon synapses. Defects in otoferlin affect this process by compromising exocytosis of synaptic vesicles and their reformation leading to impaired signal transmission to the auditory nerve. Consequently, individuals with biallelic pathogenic variants in *OTOF* have congenital severe-to-profound hearing loss characterized by normal otoacoustic emission (OAE), indicating normal cochlear function, and abnormal auditory brain stem responses (ABRs), indicating altered transmission of auditory signal from the synapse to the brain and impaired speech discrimination.

To date, more than 220 pathogenic variants have been reported in *OTOF* [Azaiez et al 2018]. They are distributed all over the gene and affect all domains except C2A domain. Of these variants, 38% were missense, 20% nonsense, 20% frameshift, 17% splice, 3% inframe indel, and 2% copy number variants (CNV) (see Figure 1A). Truncating variants (nonsense, frameshift, splice, and CNV) in *OTOF* lead to absent or shortened nonfunctional protein. Missense variants impair protein folding, stability, or function. Both types of variants typically result in congenital or prelingual severe-to-profound hearing loss (see Figure 1B).

Certain pathogenic variants in *OTOF* cause temperature-sensitive auditory neuropathy spectrum disorder (see Table 6). Missense variants cause normal to mild hearing loss when homozygous or compound heterozygous with another missense variant, but when in compound heterozygosity with a truncating variant, the hearing loss is moderate. At normal body temperature, hearing ranges from normal to a moderate loss, while an elevation in body temperature severely worsens hearing loss and speech perception. When temperature decreases, hearing returns to baseline. Studies in mouse models showed that otoferlin is sensitive to heat and this instability is exacerbated by certain pathogenic variants such as Ile515Thr. At increased temperatures, mutated otoferlin undergoes faster degradation and loss from the plasma membrane [Strenzke et al 2016].

Mechanism of disease causation. *OTOF*-related deafness is caused by loss-of-function pathogenic variants.

***OTOF*-specific laboratory technical considerations.** Variants in *OTOF* should be annotated on transcript NM_001287489.2, the cochlea-specific transcript.

Table 6. Notable *OTOF* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001287489.2	c.2485C>T	p.Gln829Ter	Founder variant in Spanish population [Migliosi et al 2002, Rodríguez-Ballesteros et al 2008]
	c.5816G>A	p.Arg1939Gln	Founder variant in Japanese population [Matsunaga et al 2012]
	c.1544T>C	p.Ile515Thr	Assoc w/TS-ANSD [Varga et al 2006]
	c.1621G>A	p.Gly541Ser	Assoc w/TS-ANSD [Matsunaga et al 2012]
	c.4819C>T	p.Arg1607Trp	Assoc w/TS-ANSD [Wang et al 2010, Zhang et al 2016b]
	c.5410_5412delGAG	p.Glu1804del	Assoc w/TS-ANSD [Marlin et al 2010]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
TS-ANSD = temperature-sensitive auditory neuropathy spectrum disorder

Chapter Notes

Author Notes

The Hereditary Hearing Loss Homepage (hereditaryhearingloss.org) provides an up-to-date overview of the genetics of hereditary hearing impairment for researchers and clinicians, and lists data and links for all known gene localizations and identifications for monogenic nonsyndromic hearing impairment.

The Deafness Variation Database (DVD) [Azaiez et al 2018] collates, annotates, and classifies all genetic variants related to syndromic and nonsyndromic hearing loss. Data are collated from all major public databases and used to generate an evidence-based single classification for each variant, which is then curated by experts in hereditary hearing loss.

Acknowledgments

The work in this *GeneReview* was supported in part by grants R01s DC002842, DC012049, and DC017955 (RJHS) and grant 5T32DC000040 (RKT).

Author History

Hela Azaiez, PhD (2021-present)
Jose G Gurrola III, MD; University of Iowa (2007-2015)
Philip M Kelley, PhD; Boys Town National Research Hospital (2007-2015)
A Eliot Shearer, MD, PhD; University of Iowa (2015-2021)
Richard JH Smith, MD (2007-present)
Ryan K Thorpe, MD (2021-present)

Revision History

- 21 January 2021 (ha) Comprehensive update posted live
- 30 July 2015 (me) Comprehensive update posted live
- 14 June 2011 (cd) Revision: link to hearing loss/deafness panel listings in GeneTests Laboratory Directory provided

- 26 April 2011 (me) Comprehensive update posted live
- 29 February 2008 (me) Review posted live
- 15 October 2007 (rjhs) Original submission

References

Literature Cited

Akil O, Dyka F, Calvet C, Emptoz A, Lahlou G, Nouaille S, Boutet de Monvel J, Hardelin JP, Hauswirth WW, Avan P, Petit C, Safieddine S, Lustig LR. Dual AAV-mediated gene therapy restores hearing in a DFNB9 mouse model. Proc Natl Acad Sci U S A. 2019;116:4496–501. PubMed PMID: 30782832.

Al-Moyed H, Cepeda AP, Jung S, Moser T, Kügler S, Reisinger E. A dual-AAV approach restores fast exocytosis and partially rescues auditory function in deaf otoferlin knock-out mice. EMBO Mol Med. 2019;11:e9396. PubMed PMID: 30509897.

Angeli SI. Phenotype/genotype correlations in a DFNB1 cohort with ethnical diversity. Laryngoscope. 2008;118:2014–23. PubMed PMID: 18758381.

Azaiez H, Booth KT, Ephraim SS, Crone B, Black-Ziegelbein EA, Marini RJ, Shearer AE, Sloan-Heggen CM, Kolbe D, Casavant T, Schnieders MJ, Nishimura C, Braun T, Smith RJH. Genomic landscape and mutational signatures of deafness-associated genes. Am J Hum Genet. 2018;103:484–97. PubMed PMID: 30245029.

Buchman CA, Roush PA, Teagle HF, Brown CJ, Zdanski CJ, Grose JH. Auditory neuropathy characteristics in children with cochlear nerve deficiency. Ear Hear. 2006;27:399–408. PubMed PMID: 16825889.

Chang MY, Kim AR, Kim NK, Lee C, Park WY, Choi BY. Refinement of molecular diagnostic protocol of auditory neuropathy spectrum disorder: disclosure of significant level of etiologic homogeneity in Koreans and its clinical implications. Medicine (Baltimore). 2015;94:e1996. PubMed PMID: 26632695.

Chiu YH, Wu CC, Lu YC, Chen PJ, Lee WY, Liu AY, Hsu CJ. Mutations in the OTOF gene in Taiwanese patients with auditory neuropathy. Audiol Neurootol. 2010;15:364–74. PubMed PMID: 20224275.

Choi BY, Ahmed ZM, Riazuddin S, Bhinder MA, Shahzad M, Husnain T, Riazuddin S, Griffith AJ, Friedman TB. Identities and frequencies of mutations of the otoferlin gene (OTOF) causing DFNB9 deafness in Pakistan. Clin Genet. 2009;75:237–43. PubMed PMID: 19250381.

Delmaghani S, del Castillo FJ, Michel V, Leibovici M, Aghaie A, Ron U, Van Laer L, Ben-Tal N, Van Camp G, Weil D, Langa F, Lathrop M, Avan P, Petit C. Mutations in the gene encoding pejvakin, a newly identified protein of the afferent auditory pathway, cause DFNB59 auditory neuropathy. Nat Genet. 2006;38:770–8. PubMed PMID: 16804542.

Iwasa YI, Nishio SY, Sugaya A, Kataoka Y, Kanda Y, Taniguchi M, Nagai K, Naito Y, Ikezono T, Horie R, Sakurai Y, Matsuoka R, Takeda H, Abe S, Kihara C, Ishino T, Morita SY, Iwasaki S, Takahashi M, Ito T, Arai Y, Usami SI. OTOF mutation analysis with massively parallel DNA sequencing in 2,265 Japanese sensorineural hearing loss patients. PLoS One. 2019;14:e0215932. PubMed PMID: 31095577.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kim BJ, Jang JH, Han JH, Park HR, Oh DY, Lee S, Kim MY, Kim AR, Lee C, Kim NKD, Park WY, Choung YH, Choi BY. Mutational and phenotypic spectrum of OTOF-related auditory neuropathy in Koreans: eliciting reciprocal interaction between bench and clinics. J Transl Med. 2018;16:330. PubMed PMID: 30482216.

Kitao K, Mutai H, Namba K, Morimoto N, Nakano A, Arimoto Y, Sugiuchi T, Masuda S, Okamoto Y, Morita N, Sakamoto H, Shintani T, Fukuda S, Kaga K, Matsunaga T. Deterioration in distortion product otoacoustic emissions in auditory neuropathy patients with distinct clinical and genetic backgrounds. Ear Hear. 2019;40:184–91. PubMed PMID: 29688962.

Kuemmerle-Deschner JB, Koitschev A, Ummenhofer K, Hansmann S, Plontke SK, Koitschev C, Koetter I, Angermair E, Benseler SM. Hearing loss in Muckle-Wells syndrome. Arthritis Rheum. 2013;65:824–31. PubMed PMID: 23440695.

Lek A, Lek M, North KN, Cooper ST. Phylogenetic analysis of ferlin genes reveals ancient eukaryotic origins. BMC Evol Biol. 2010;10:231. PubMed PMID: 20667140.

Marlin S, Feldmann D, Nguyen Y, Rouillon I, Loundon N, Jonard L, Bonnet C, Couderc R, Garabedian EN, Petit C, Denoyelle F. Temperature-sensitive auditory neuropathy associated with an otoferlin mutation: deafening fever! Biochem Biophys Res Commun. 2010;394:737–42. PubMed PMID: 20230791.

Matsunaga T, Mutai H, Kunishima S, Namba K, Morimoto N, Shinjo Y, Arimoto Y, Kataoka Y, Shintani T, Morita N, Sugiuchi T, Masuda S, Nakano A, Taiji H, Kaga K. A prevalent founder mutation and genotype-phenotype correlations of OTOF in Japanese patients with auditory neuropathy. Clin Genet. 2012;82:425–32. PubMed PMID: 22575033.

Michalski N, Goutman JD, Auclair SM, Boutet de Monvel J, Tertrais M, Emptoz A, Parrin A, Nouaille S, Guillon M, Sachse M, Ciric D, Bahloul A, Hardelin JP, Sutton RB, Avan P, Krishnakumar SS, Rothman JE, Dulon D, Safieddine S, Petit C. Otoferlin acts as a Ca(2+) sensor for vesicle fusion and vesicle pool replenishment at auditory hair cell ribbon synapses. Elife. 2017;6:e31013. PubMed PMID: 29111973.

Migliosi V, Modamio-Hoybjor S, Moreno-Pelayo MA, Rodriguez-Ballesteros M, Villamar M, Telleria D, Menendez I, Moreno F, Del Castillo I. Q829X, a novel mutation in the gene encoding otoferlin (OTOF), is frequently found in Spanish patients with prelingual non-syndromic hearing loss. J Med Genet. 2002;39:502–6. PubMed PMID: 12114484.

Rodríguez-Ballesteros M, Reynoso R, Olarte M, Villamar M, Morera C, Santarelli R, Arslan E, Medá C, Curet C, Völter C, Sainz-Quevedo M, Castorina P, Ambrosetti U, Berrettini S, Frei K, Tedín S, Smith J, Cruz Tapia M, Cavallé L, Gelvez N, Primignani P, Gómez-Rosas E, Martín M, Moreno-Pelayo MA, Tamayo M, Moreno-Barral J, Moreno F, del Castillo I. A multicenter study on the prevalence and spectrum of mutations in the otoferlin gene (OTOF) in subjects with nonsyndromic hearing impairment and auditory neuropathy. Hum Mutat. 2008;29:823–31. PubMed PMID: 18381613.

Roux I, Safieddine S, Nouvian R, Grati M, Simmler MC, Bahloul A, Perfettini I, Le Gall M, Rostaing P, Hamard G, Triller A, Avan P, Moser T, Petit C. Otoferlin, defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. Cell. 2006;127:277–89. PubMed PMID: 17055430.

Schwander M, Sczaniecka A, Grillet N, Bailey JS, Avenarius M, Najmabadi H, Steffy BM, Federe GC, Lagler EA, Banan R, Hice R, Grabowski-Boase L, Keithley EM, Ryan AF, Housley GD, Wiltshire T, Smith RJ, Tarantino LM, Muller U. A forward genetics screen in mice identifies recessive deafness traits and reveals that pejvakin is essential for outer hair cell function. J Neurosci. 2007;27:2163–75. PubMed PMID: 17329413.

Sloan-Heggen CM, Bierer AO, Shearer AE, Kolbe DL, Nishimura CJ, Frees KL, Ephraim SS, Shibata SB, Booth KT, Campbell CA, Ranum PT, Weaver AE, Black-Ziegelbein EA, Wang D, Azaiez H, Smith RJH. Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016;135:441–50. PubMed PMID: 26969326.

Smith RJ, Bale JF Jr, White KR. Sensorineural hearing loss in children. Lancet. 2005;365:879–90. PubMed PMID: 15752533.

Starr A, Sininger Y, Winter M, Derebery MJ, Oba S, Michalewski HJ. Transient deafness due to temperature-sensitive auditory neuropathy. Ear Hear. 1998;19:169–79. PubMed PMID: 9657592.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Varga R, Avenarius MR, Kelley PM, Keats BJ, Berlin CI, Hood LJ, Morlet TG, Brashears SM, Starr A, Cohn ES, Smith RJ, Kimberling WJ. OTOF mutations revealed by genetic analysis of hearing loss families including a potential temperature sensitive auditory neuropathy allele. J Med Genet. 2006;43:576–81. PubMed PMID: 16371502.

Strenzke N, Chakrabarti R, Al-Moyed H, Müller A, Hoch G, Pangrsic T, Yamanbaeva G, Lenz C, Pan KT, Auge E, Geiss-Friedlander R, Urlaub H, Brose N, Wichmann C, Reisinger E. Hair cell synaptic dysfunction, auditory fatigue and thermal sensitivity in otoferlin Ile515Thr mutants. EMBO J. 2016;35:2519–35. PubMed PMID: 27729456.

Tsai EA, Berman MA, Conlin LK, Rehm HL, Francey LJ, Deardorff MA, Holst J, Kaur M, Gallant E, Clark DM, Glessner JT, Jensen ST, Grant SF, Gruber PJ, Hakonarson H, Spinner NB, Krantz ID. PECONPI: a novel software for uncovering pathogenic copy number variations in non-syndromic sensorineural hearing loss and other genetically heterogeneous disorders. Am J Med Genet A. 2013;161A:2134–47. PubMed PMID: 23897863.

Wang DY, Wang YC, Weil D, Zhao YL, Rao SQ, Zong L, Ji YB, Liu Q, Li JQ, Yang HM, Shen Y, Benedict-Alderfer C, Zheng QY, Petit C, Wang QJ. Screening mutations of OTOF gene in Chinese patients with auditory neuropathy, including a familial case of temperature-sensitive auditory neuropathy. BMC Med Genet. 2010;11:79. PubMed PMID: 20504331.

Yasunaga S, Grati M, Cohen-Salmon M, El-Amraoui A, Mustapha M, Salem N, El-Zir E, Loiselet J, Petit C. A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. Nat Genet. 1999;21:363–9. PubMed PMID: 10192385.

Yawn RJ, Nassiri AM, Rivas A. Auditory neuropathy: bridging the gap between hearing aids and cochlear implants. Otolaryngol Clin North Am. 2019;52:349–55. PubMed PMID: 30765091.

Zadro C, Ciorba A, Fabris A, Morgutti M, Trevisi P, Gasparini P, Martini A. Five new OTOF gene mutations and auditory neuropathy. Int J Pediatr Otorhinolaryngol. 2010;74:494–8. PubMed PMID: 20211493.

Zhang QJ, Han B, Lan L, Zong L, Shi W, Wang HY, Xie LY, Wang H, Zhao C, Zhang C, Yin ZF, Wang DY, Petit C, Guan J, Wang QJ. High frequency of OTOF mutations in Chinese infants with congenital auditory neuropathy spectrum disorder. Clin Genet. 2016a;90:238–46. PubMed PMID: 26818607.

Zhang Q, Lan L, Shi W, Yu L, Xie LY, Xiong F, Zhao C, Li N, Yin Z, Zong L, Guan J, Wang D, Sun W, Wang Q. Temperature sensitive auditory neuropathy. Hear Res. 2016b;335:53–63. PubMed PMID: 26778470.

Zheng D, Liu X. Cochlear implantation outcomes in patients with OTOF mutations. Front Neurosci. 2020;14:447. PubMed PMID: 32508568.

Zong L, Guan J, Ealy M, Zhang Q, Wang D, Wang H, Zhao Y, Shen Z, Campbell CA, Wang F, Yang J, Sun W, Lan L, Ding D, Xie L, Qi Y, Lou X, Huang X, Shi Q, Chang S, Xiong W, Yin Z, Yu N, Zhao H, Wang J, Wang J, Salvi RJ, Petit C, Smith RJ, Wang Q. Mutations in apoptosis-inducing factor cause X-linked recessive auditory neuropathy spectrum disorder. J Med Genet. 2015;52:523–31. PubMed PMID: 25986071.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii)

reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.