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Review Article

Pathogenesis and research progress of OTOF gene related auditory neuropathy: a retrospective review

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Abstract: Auditory Neuropathy (AN) is a disorder of auditory information processing caused by dysfunction in inner hair cells, synapses, spiral ganglion cells, and auditory nerves. Patients with AN typically have normal sound detection abilities but struggle with speech comprehension. Representing 10% of cases of permanent hearing loss in children, AN is a significant contributor to hereditary deafness. The otoferlin protein, encoded by the OTOF gene, is involved in the fusion of Ca^{2+}-dependent synaptic vesicles in inner hair cells and neurotransmitter release. Mutations in the OTOF gene are a major cause of AN. Patients with OTOF mutations exhibit distinct cochlear microphonic waveforms compared to other AN patients and may experience temperature-sensitive AN. Although most individuals with OTOF mutations present with stable, congenital, or prelingual onset of severe to profound hearing loss, some show atypical clinical phenotypes. The genotype-phenotype correlation in OTOF-related AN is still not fully understood. This review aims to explore the pathogenic mechanisms and the latest research progress in otoferlin-related AN based on current findings.

Keywords: Auditory neuropathy, gene, mutations, OTOF, hearing loss, congenital

Introduction

Outer hair cells primarily serve as amplifiers, enhancing the perception of low-to-medium intensity sounds by inner hair cells [1, 2]. Damage to outer hair cells impairs this amplification, leading to hearing loss. In auditory neuropathy (AN), although outer hair cells remain functionally intact and can still amplify sounds, pathologies occur along the auditory pathway, affecting the inner hair cells, auditory nerve, or higher-level auditory structures [3, 4]. These pathologies disrupt neurotransmitter and nerve impulse transmission, impair auditory processing and discrimination, and degrade temporal processing, resulting in the ability to hear sounds but not understand speech.

Audiological manifestations of AN include the presence of otoacoustic emissions (OAE) and/or cochlear microphonics (CM), reflecting outer hair cell function, while the auditory brainstem response (ABR), which reflects the function of the entire auditory pathway, may be absent or abnormal [5-7]. Additional symptoms include difficulty with speech recognition in noisy environments and a disproportionate decline in speech recognition compared to pure tone thresholds.

The etiology of AN may involve both environmental and genetic factors. Environmental factors include neonatal hyperbilirubinemia, hypoxia or asphyxia, infections, drugs, and noise exposure [3, 8-10]. However, research indicates that over 40% of AN cases have a genetic component, with inheritance patterns including autosomal recessive, autosomal dominant, X-linked, and mitochondrial mutations with maternal inheritance [3, 11, 12]. Several pathogenic genes are associated with different forms of AN, including SLC17A8, OTOF, PJVK, and DIAPH3. Among these, mutations in the OTOF gene are considered one of the primary genetic causes [13-15].

Sadaf Naz and colleagues conducted a study on 92 families with stable or progressive hearing impairment of moderate to severe degree

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and autosomal recessive inheritance [4]. Using homozygosity mapping, Sanger sequencing, massively parallel sequencing, and whole-exome sequencing, they identified mutations in eight genes, including OTOF, which accounted for hearing loss in 54% of the families [4]. These findings suggest that modifier factors may influence phenotypic severity.

Due to the unclear genetic mechanisms underlying AN, treatment options remain limited. Current primary interventions include hearing aids, cochlear implants, assistive listening devices, and pharmacological therapies. Cochlear implantation outcomes vary widely among patients with AN. For patients with specific inner hair cell and synapse pathologies, such as presynaptic or synaptic AN caused by OTOF gene mutations, cochlear implants often yield better results. This is because cochlear implants bypass the damaged inner hair cells and synapses, directly stimulating the auditory nerve.

Based on current research, this article further explores the pathogenic mechanisms of OTOF gene-related AN, offering insights for clinical treatment selection.

AN

Etiology and pathogenesis

AN is a disorder of auditory information processing caused by dysfunction in inner hair cells, synapses, spiral ganglion cells, and the auditory nerve [16, 17]. Patients typically have the ability to hear sounds but struggle with speech comprehension. AN can be classified into two types based on lesion location: Type I, where the lesion is in the auditory nerve, and Type II, where the lesion affects the inner hair cells, terminal dendrites, and synapses. Recent studies have shown that patients with Type II AN tend to have more favorable outcomes after cochlear implantation compared to those with Type I. Among children with a genetic history, those carrying mutations in the OTOF gene, expressed in the inner hair cells of the cochlea, achieve the most successful results with cochlear implantation.

The etiology of AN involves both environmental and genetic factors. Environmental causes include neonatal hyperbilirubinemia, hypoxia or asphyxia, infections, medications, and noise exposure. Genetic factors primarily involve autosomal recessive inheritance, autosomal dominant inheritance, X-linked inheritance, and mitochondrial mutations with maternal inheritance [1, 18, 19]. Various pathogenic genes are associated with different types of AN, with common examples being SLC17A8, OTOF, PJVK, and AUNA2 [8, 12, 13, 20].

Sadaf Naz and colleagues investigated the genetic causes of moderate to severe hearing loss, focusing on modifiers. Using homozygosity mapping, Sanger sequencing, large-scale parallel sequencing, and whole-exome sequencing to target known deafness genes, they identified genetic variations in 69% of the families studied. Among these, variations in SLC26A4, GJB2, MYO15A, TMC1, TMPRSS3, OTOF, MYO7A, and CLDN14 were found in 54% of the families (**Table 1**). In total, 20 reported and 21 novel variations across 21 known deafness genes were identified. These findings suggest that both genetic factors and environmental influences significantly contribute to the severity of hearing loss in humans [4].

Clinical manifestations

AN can manifest at any age, though it often appears in adolescence or infancy, with no significant gender differences. The onset is typically insidious, characterized by slow and progressive bilateral hearing loss. The most prominent feature is impaired sound discrimination, which makes speech comprehension, especially in noisy environments, difficult. In some cases, tinnitus, dizziness, and a family history of hearing loss may also be present [3, 21].

Diagnostic criteria

Given the diverse clinical manifestations of AN across different age groups - infants, children, and adolescents - the diagnostic criteria can vary. The etiology, lesion location, and clinical presentation of AN are highly heterogeneous. In addition to audiological assessments, a comprehensive evaluation involving multidisciplinary collaboration (e.g., pediatrics, neurology, radiology, genetics, and ophthalmology) is crucial for developing individualized auditory rehabilitation plans and interventions. The current clinical diagnostic criteria for AN include

Table 1. Pathogenic genes associated with acoustic neuropathy

Pathogenic gene	Article	First Author
OTOF	A Multicenter Study on the Prevalence and Spectrum of Mutations in the Otoferlin Gene (OTOF) in Subjects With Nonsyndromic Hearing Impairment and Auditory Neuropathy	Montserrat Rodríguez-Ballesteros [36]
SLC17A8/ SLC26A4	The genetic load for hereditary hearing impairment in Chinese population and its clinical implication	Qiuju Wang [6]
PJVK	Genetic analysis of auditory neuropathy spectrum disorder in the Korean population	SH Bae
AUNA2	AUNA2: A Novel Type of Non-Syndromic Slowly Progressive Auditory Synaptopathy/Auditory Neuropathy with Autosomal-Dominant Inheritance	R Lang-Roth [20]
GJB2	Hereditary deafness and phenotyping in humans	M Bitner-Glindzicz [53]
MYO15A/ MYO7A	Unexpected genetic heterogeneity in a large consanguineous Brazilian pedigree presenting deafness	K Lezirovitz [54]
TMC1	Advances in treatment of OTOF-related auditory neuropathy	Han L [51]
CLDN14	The natural history, clinical outcomes, and genotype-phenotype relationship of otoferlin-related hearing loss: a systematic, quantitative literature review	Ford CL [50]

the following six aspects: 1) absence or severe abnormality of the ABR from wave I; 2) normal EOAE or CM; 3) disproportionately poor speech discrimination relative to pure tone thresholds; 4) audiogram showing predominantly elevated low-frequency thresholds; 5) absent or elevated acoustic stapedius reflex thresholds; 6) absent contralateral sound suppression of EOAE [2].

OTOF gene and AN

OTOF gene

The OTOF gene (Otoferlin), located on chromosome 2p23.3, encodes otoferlin, a member of the ferlin family of large transmembrane proteins involved in cell membrane fusion and vesicle formation. Otoferlin is expressed exclusively in the cochlear hair cells, vestibular hair cells, and central nervous system [8, 14, 22]. It plays a critical role in Ca^{2+}-dependent neurotransmitter exocytosis in inner ear hair cells and is essential for auditory signal transmission. Otoferlin serves two key functions: auditory signal transmission and calcium ion sensing. In inner hair cells, otoferlin is involved in synaptic vesicle release, facilitating the conversion of sound signals into neural signals. Additionally, otoferlin senses changes in calcium ion concentrations, which triggers neurotransmitter release [23, 24]. Mutations in the OTOF gene are one of the leading causes of congenital deafness and autosomal recessive hearing loss, with patients typically presenting with severe to profound hearing loss at birth [11, 15, 25-29].

AN caused by OTOF gene mutation

Mutations in the OTOF gene are a common cause of inherited hearing loss and a leading factor in acoustic neuropathy spectrum disorder [30, 31]. While most patients with OTOF mutations experience stable, congenital, or preverbal severe to profound hearing loss, some exhibit atypical clinical phenotypes. The genotypic-phenotypic relationship in OTOF mutation carriers remains incompletely understood [3]. Pathogenic variations in the OTOF gene are associated with autosomal recessive nonsyndromic ANSD and temperature-sensitive ANSD [32, 33]. In nonsyndromic ANSD patients, the severity of hearing loss ranges from mild to severe [11, 15, 34].

Mutations in the OTOF gene, especially those affecting highly conserved domains, disrupt the structure or function of the otoferlin protein. For example, the novel mutation p.Lys896AsnfsTer104 lies between the C2C and C2D domains, while p.Gln994ValfsTer7, previously reported in familial temperature-sensitive nonsyndromic AN (TS-NSRAN), is located in

the C2D domain [35]. Three identified missense mutations - c.4960G>A, c.1469C>G, and c.2675A>G - result in the substitution of highly conserved amino acids: glycine to serine (p.Gly1654Ser), proline to arginine (p.Pro490Arg), and lysine to arginine (p.Lys892Arg), respectively [36, 37]. Among these, the G>A nucleotide change at position 4960 occurs at the exon/intron junction and likely causes abnormal splicing, leading to a defective otoferlin protein. The c.1469C>G missense mutation, located in the C2C domain, has been shown to impair protein function [38].

OTOF gene mutations cause presynaptic ANSD, with varying prevalence and hotspot mutations across different ethnic groups. In the Spanish population, OTOF mutations account for 87% of nonsyndromic ANSD cases, with a hotspot mutation at c.2485C>T (p.LN829ter). In the Japanese population, the prevalence is 57%, with a hotspot mutation at c.5816G>A (p.Arg1939Gln) [39, 40]. In mainland China, the prevalence exceeds 41%, though no specific hotspot mutations have been identified.

Gene sequencing of OTOF: Gene sequencing is currently the primary method for detecting AN caused by OTOF gene mutations [34, 41]. Deng et al. used whole exome sequencing (WES) to analyze a pair of preverbal deaf sisters, identifying a nonsense mutation c.4030C>T (p.R1344X) and a missense mutation c.5000C>A (p.A1667D) in the OTOF gene [42]. The parents were found to be heterozygous carriers of the mutations (c.5000C>A in the father and c.4030C>T in the mother). Their study expanded the spectrum of OTOF mutations associated with AN and demonstrated the effectiveness of WES in diagnosing AN [42]. Mohammad Amin Tabatabaiefar et al., using next-generation sequencing (NGS) and genetic linkage analysis of DFNB1A/B, highlighted the combined effectiveness of targeted NGS and preimplantation genetic diagnosis (PGD) in diagnosing and preventing hereditary hearing loss [43]. To determine the frequency and genetic context of hearing loss in the Japanese population, Yoh-Ichiro Iwasa et al. performed OTOF mutation analysis using large-scale parallel DNA sequencing (MPS). They found that 39 of 2,265 patients (1.72%) carried homozygous or complex heterozygous mutations in the OTOF gene, and most patients with biallelic OTOF mutations had severe to profound hearing loss [34].

Clinical features of OTOF gene-associated AN: The clinical features of AN are partially influenced by OTOF genotype-phenotype correlations, with the severity of hearing loss varying across different genotypes. OTOF encodes otoferlin, a calcium-binding protein, and its mutations account for 1-8% of congenital nonsyndromic hearing loss, making it a major cause of AN spectrum disorder (ANSD) [10, 22, 44]. However, due to the limited number of homogeneous OTOF genotype cases reported, the natural progression of otoferlin-associated hearing loss and the relationship between OTOF mutations and hearing loss phenotypes remain poorly understood [8, 15, 45].

Yoh-Ichiro Iwasa et al. studied clinical features and genotypic associations in a cohort of OTOF-associated hearing loss patients in Japan [22]. They found that 90.6% of patients exhibited a “typical” phenotype of prespeech onset and severe-to-profound hearing loss. Notably, truncation mutations and the p.Arg1939Gln variant were strongly associated with severe phenotypes. However, nearly half of the patients with non-truncating mutations displayed mild to moderate hearing loss. Interestingly, patients with mutations such as p.Ile513Arg, p.Ile1573Thr, and p.Leu1910Lys presented with clinical features resembling “true” AN, suggesting that the OTOF genotype can influence clinical outcomes.

Previous research has demonstrated that OTOF mutations can lead to nonsyndromic prespeech deafness and acoustic neuropathy/dyssynchronization [3, 46, 47]. Fedick et al. identified a novel OTOF variant, c.5332G>T (p.Val1778Phe), responsible for high-frequency nonsyndromic hearing loss in the Ashkenazi Jewish population [48]. In this study, the variant was found in four siblings with hearing loss in an extended family. This mutation did not correlate with acoustic neuropathy, as otoacoustic emissions were still detectable. However, other studies report opposing findings. For example, Young Ju Jin et al. found a novel OTOF splice site variant in a Korean cohort, noting that OTOF mutations had a minimal impact on autosomal recessive nonsyndromic sensorineural hearing loss and AN/AD in South Korea, suggesting the need to explore other genetic causes [49].

Ford et al. conducted a systematic literature review to assess the natural history, clinical

Table 2. Treatment methods of auditory neuropathy

Treatment method	Indications	Curative effect
Wear hearing AIDS	Patients with mild to moderate deafness	It can effectively amplify the sound, but does not change the problem of asynchronous sound processing in AN patient
Cochlear implant	Severe to severe AN patient	Patients with presynaptic and synaptic type of AN can achieve hearing and speech recovery after implantation comparable to other SNHL patients, while some patients with postsynaptic type of AN have poor hearing recovery after cochlear implantation
Gene therapy (Gene overexpression, gene editing, RNA interference)	Hereditary AN	Gene therapy is expected to be a new strategy for the clinical treatment of hereditary AN in the future

AN: auditory neuropath; SNHL: sensorineural hearing loss.

outcomes, and genotypic-phenotypic relationships of otoferlin-associated hearing loss [50]. Their findings indicated that most patients exhibited severe to profound hearing loss with a preverbal onset, while 10-15% showed atypical phenotypes, such as mild-to-moderate, progressive, and temperature-sensitive hearing loss. Phenotypic variation appears to be genotype-dependent; non-truncating variants located in and downstream of the C2E calcium-binding domain are more likely to result in atypical phenotypes. Furthermore, the prevalence of specific sequence variants and associated phenotypes varies across populations, potentially due to the founder effect. Ryan K. Thorpe et al. collected audiograms and distortion product otoacoustic emissions (DPOAE) data from various populations diagnosed with deafness-associated ANSD through comprehensive genetic testing [3]. They observed significant differences in hearing thresholds across frequency ranges between different genotype groups, with LoF/LoF genotypes showing significantly poorer hearing. Among individuals who underwent testing, DPOAE frequency loss occurred at a rate of 8.5% per year.

Treatment status of OTOF gene-related AN: Currently, clinical treatments for OTOF gene-related AN primarily include hearing aids, cochlear implants, assistive hearing technologies, and pharmacological therapies. Among these, cochlear implants have shown relatively better efficacy in treating OTOF gene-related AN [49, 51, 52]. Longlong Zhang et al. conducted preclinical evaluations of the efficacy and safety of AAV1-hOTOF in mice and non-human primates [7]. Their study developed a gene therapy agent based on adeno-associated virus 1 (AAV1), which carries the human OTOF coding sequence. The results showed that AAV1-hOTOF was well tolerated and effective in animals, providing strong support for its potential clinical application.

Iwasa et al. examined clinical features and genotypic associations in a cohort of OTOF-associated hearing loss patients in Japan [22]. They found that 90.6% of patients exhibited a "typical" phenotype of prespeech onset and severe-to-profound hearing loss. Among 47 patients (73.4%) who underwent cochlear implantation, the procedure was successful. Approximately 85-90% of cochlear implant recipients achieved a hearing level of 20-39 dB, with a Communication Ability Profile (CAP) grade of 6 or higher. Thorpe et al. found that patients with LoF-associated ANSD had significantly poorer hearing, particularly those with the LoF/LoF genotype [3]. The unique pattern of autosomal recessive acoustic neuropathy associated with OTOF mutations may make certain cases suitable for gene therapy in specific clinical settings.

We propose that cochlear implants are most effective in patients with presynaptic or synaptic AN, such as that caused by OTOF gene mutations, because the implants can bypass the damaged inner hair cells and their synapses to directly stimulate the auditory nerve. In contrast, cochlear implants in patients with postsynaptic AN typically yield poorer results. It is generally recommended that cochlear implantation be performed around 2 years of age, except for children with extremely severe hearing loss due to genetic factors (e.g., OTOF-related AN), for whom earlier implantation can be beneficial (**Table 2**).

Conclusion

OTOF gene mutations are a common cause of inherited hearing loss and a leading factor in ANSD. Otoferlin, encoded by the OTOF gene, plays a crucial role in Ca^{2+}-mediated synaptic vesicle fusion and neurotransmitter release. Advances in the understanding of the pathogenesis of OTOF gene mutations and developments in gene therapy have made significant progress in treating AN. However, most studies report small cohorts with homogeneous OTOF genotypes, and thus, the natural history of Otoferlin-associated hearing loss, the relationship between OTOF genotypes and hearing loss phenotypes, and clinical outcomes remain unclear. Identifying the genetic phenotype in patients with auditory neuropathy is essential for improving clinical diagnosis and treatment.

As this study is a review of existing literature, it has limitations such as sample heterogeneity (due to different study populations). Future research with larger sample sizes and multicenter studies is needed to further elucidate the association between OTOF mutations and AN, as well as to refine treatment strategies. Additionally, the specific pathogenic molecular mechanisms underlying these mutations require further investigation.

Disclosure of conflict of interest

None.

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