Review Article

The Genetic Basis of Auditory Neuropathy Spectrum Disorder

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Running title: Genetic Mutations and Auditory Neuropathy Syndromes

Abstract

Background: Auditory neuropathy spectrum disorder (ANSD) disrupts neural coordination despite normal outer hair cell function, impairing speech comprehension, especially in noisy environments.

Objectives: This review explores the genetic mechanisms underlying ANSD.
Methods: PubMed, Scopus, and Web of Science were searched from 2010 to 2023 for studies on ANSD genetics, excluding those focused on non-genetic causes or lacking relevant data.
Results: ANSD is associated with conditions such as Brown-Vialetto-Van Laere Syndrome and Charcot-Marie-Tooth disease, often resulting from mutations in the auditory nerve. Non-syndromic ANSD is associated with genes such as OTOF and PJVK, which are essential for neural function.
Conclusions: ANSD is a multifactorial condition resulting from genetic mutations in key genes, which disrupt auditory pathways and impair sound signal transmission. Further research is needed to identify additional genes and understand molecular mechanisms contributing to ANSD. This knowledge will improve diagnosis, prognosis, and therapeutic strategies, and could lead to innovative treatment approaches in the future.
Keywords: Auditory Neuropathy, Genetic mutation, hearing loss

Introduction

Individuals with auditory neuropathy spectrum disorder often exhibit a notable discrepancy between their hearing thresholds, which may appear normal, and their difficulties with speech comprehension, particularly in noisy environments (1). Terms like auditory neuropathy (AN) primarily describe this discrepancy, emphasizing the difficulty in understanding speech despite the ability to hear sounds (1). Auditory desynchrony is another term for the primary issue: timing problems in neural transmission make it challenging to process sound information accurately. Auditory synaptopathy has recently emerged, focusing on potential dysfunctions at connections between inner hair cells and auditory nerve fibers, which can significantly impair auditory processing (2,3).

Audiological findings in ANSD often reveal a unique pattern. Hearing loss, typically bilateral and sensorineural, can range from mild to severe, with a particular emphasis on lower frequencies. Audiograms may exhibit varied configurations, including peaked or saucer-shaped patterns (4). Otoacoustic emissions (OAEs) are often preserved despite hearing loss, indicating that outer hair cell function is intact. On the other hand, Auditory Brainstem Responses (ABRs) are usually absent or distorted, suggesting a disruption in neural transmission. The acoustic stapedial reflex isn't present in most people with ANSD, which is more evidence that the brain isn't working right. Cochlear microphonics, also often present, provide further evidence of optimal outer hair cell performance (5,6).

While reported prevalence estimates range from less than 1% to 10% of individuals with hearing impairment (2), ANSD prevalence varies greatly, clearly depending on the specific population under study. Research indicates a greater prevalence among children with sensorineural hearing loss, especially those with severe to profound hearing impairment. The wide range in reported prevalence suggests that ANSD may be underdiagnosed in some populations (7–9).

ANSD can arise from various etiologies, including environmental and acquired factors. Some common non-genetic causes are early birth, high bilirubin levels, lack of oxygen, congenital brain defects, and exposure to drugs that damage the ears. If you have an acquired form of ANSD, you may start losing your hearing earlier than if you have a genetic form (10). Genetic causes significantly influence the development of ANSD, with about 40% of cases having a genetic basis. There are different ways that these genetic factors can be passed down, such as through autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance (11). Understanding the genetic basis of ANSD is essential for accurate diagnosis, effective treatment, and the development

of management strategies, such as gene therapy, as well as for predicting disease progression. Genetic mutations can act as diagnostic markers, and comprehending genotype-phenotype correlations facilitates personalized medicine, ultimately enhancing patient outcomes. This study aims to investigate the role of genetics in the development of both syndromic and non-syndromic ANSD and to analyze their related clinical and audiological manifestations.

Method

A comprehensive search was conducted across PubMed, Scopus, and Web of Science from January 2010 to December 2023, using relevant keywords such as 'Auditory Neuropathy Spectrum Disorder' and 'genetics,' along with suitable variations, to identify studies related to the genetic aspects of ANSD. Boolean operators (AND, OR) refined the search strategy. This review included peer-reviewed articles that specifically addressed the genetic causes of ANSD, described the audiological characteristics associated with genetic conditions, and provided clinical profiles of individuals diagnosed with ANSD. Studies were excluded if they did not primarily focus on the genetic aspects of ANSD, discussed treatment options without including genetic information, lacked audiological data, or failed to provide full-text access.

Results

We identified 52 articles, encompassing a diverse range of case reports, case series, clinical reviews, genetic investigations, observational studies, and experimental research. These studies explore neurological and auditory disorders, examining genetic mutations, disease progression, clinical characteristics, and therapeutic interventions, providing valuable insights into both hereditary and acquired conditions affecting hearing and neural function. We will give the review results in greater detail by classifying the data into two main groups: syndromic and nonsyndromic variants. Each category will be examined thoroughly, highlighting the unique genetic pathways, crucial linked genes, and the clinical manifestations reported in both syndromic and nonsyndromic auditory neuropathy.

Syndromic

Brown-Vialetto-Van Laere Syndrome (BVVL) is a rare neurodegenerative disorder that affects the sensorimotor nerves, the optic nerve, the bulbar nerve, and the lungs. Symptoms can include pontobulbar palsy, muscle weakness, and respiratory compromise. Patients may experience difficulties with feeding, hypotonia, and impairments to cranial nerves. Magnetic resonance imaging findings can show abnormalities like T2 hyperintensity in the spinal cord. BVVL is primarily inherited through autosomal recessive genes. Changes in the riboflavin transporter genes Solute Carrier Family 52 Member 2 (SLC52A2) and SLC52A3 cause it. These genes encode riboflavin transporters Riboflavin Transporter 2 (RFVT2) and RFVT3, respectively. There is evidence of genetic heterogeneity, with some cases suggesting a possible autosomal dominant pattern. Inheritance or involvement of a mutant gene on the X chromosome (12–14). Audiological investigations in BVVLS patients typically reveal ANSD, exhibiting standard otoacoustic emissions but lacking ABR, and the hearing loss in BVVLS is likely of post-synaptic origin (15). Charcot-Marie-Tooth (CMT) disease is the most common genetic neuromuscular condition, impacting approximately 1 in 2,500 individuals (16). It is characterized by peripheral nerve degeneration, leading to distal muscular weakness, atrophy, foot deformities, and sensory loss. CMT is genetically heterogeneous, with over 60 genes implicated in its pathogenesis. These genes are crucial for preserving neuronal integrity, facilitating axon transport, and enabling nerve signal

transmission (17). Key genes include Peripheral Myelin Protein 22, Myelin Protein Zero, Gap Junction Protein Beta 1, and SH3 Domain Containing Transcription Factor 2 (18). Research on hearing loss in CMT disease reveals a complex audiologic profile characterized by cochlear and neural deficits. Studies have found varying degrees of hearing loss, ranging from mild to severe, with difficulties in speech perception, especially in noisy environments. Audiological abnormalities include elevated or absent acoustic reflexes, abnormal ABR, and distorted otoacoustic emissions (19). Hearing deficiency in CMT patients is significant, with one study reporting 28% of cases affected (20). Auditory neuropathy appears to be present in all CMT4C patients, often detectable unilaterally in infancy and progressing with age. The hearing loss in CMT is generally bilateral and may be more severe in male patients (21).

Friedreich ataxia (FRDA) is an autosomal recessive neurodegenerative condition that mainly impacts the nervous system and heart. It is defined by decreased coordination and neurologic and cardiac complications (22). The disease is induced by mutations in the FRDA gene, with 98% of cases resulting from Guanine-Adenine-Adenine (GAA) trinucleotide repeat expansions in intron 1, resulting in decreased levels of the protein frataxin (23). Frataxin deficiency affects the muscular, nervous, and cardiovascular systems, leading to progressively worsening symptoms over time (24). The pathogenesis involves mitochondrial iron accumulation, leading to increased free radical production and cellular damage (23). FRDA is associated with auditory dysfunction, characterized by impaired temporal and spectral processing. Patients often exhibit sensorineural hearing loss and abnormal ABRs (25). The degree of auditory dysfunction correlates with the GAA trinucleotide repeat expansion, particularly when GAA1 exceeds 500 repeats. Auditory spatial processing deficits are also observed and may be linked to mild cognitive impairment in FRDA patients (26).

X-linked recessive ANSD is a hearing impairment primarily attributed to genetic mutations inherited in an X-linked recessive pattern. These mutations occur in the apoptosis-inducing factor gene (AIFM1), located on the X chromosome. AIFM1 plays crucial roles in cellular processes, including programmed cell death and mitochondrial function. At the same time, while AIFM1 mutations are associated with various disorders, including mitochondrial diseases with neurological and muscular manifestations, such as Cowchock Syndrome, their involvement in X-linked recessive ANSD results explicitly in hearing impairment due to abnormalities within the auditory neural pathways. These mutations, often missense mutations that alter the protein's function, disrupt the normal functioning of AIFM1, leading to the characteristic hearing loss associated with this disorder. X-linked recessive ANSD is defined by variable hearing loss, ranging from mild to severe, with some individuals initially exhibiting normal hearing. Despite potentially normal outer hair cell function, as evidenced by standard otoacoustic emissions, abnormal auditory brainstem responses suggest that the primary issue lies in the neural conduction of the auditory signal to the brain. This late-onset condition, typically manifesting during adolescence, often spares female carriers of the AIFM1 gene mutation, who usually have normal hearing, thus emphasizing this disorder's X-linked recessive inheritance pattern (27–29).

Kallmann syndrome (KS) is a genetic disorder described by hypogonadotropic hypogonadism and anosmia. KS results from impaired hypothalamic gonadotropin-releasing hormone secretion, leading to reduced sex hormone levels and delayed puberty. Recent research has identified five genes associated with KS: KAL-1, FGFR1, PROKR2, PROK2, and NELF. These genes have essential functions in the migration and maturation of olfactory and GnRH neurons. KS exhibits genetic heterogeneity, with autosomal dominant, autosomal recessive, and X-linked recessive inheritance patterns reported (30). Studies have reported cases of KS patients with sensorineural

hearing loss; the auditory deficits in KS may be part of a broader spectrum of auditory neuropathy disorders. Genetic investigations have revealed mutations in genes such as KAL1 as potential causes of KS with hearing loss. Additionally, radiological examinations have shown abnormal temporal bone anatomy and labyrinthine morphology in KS patients, which may contribute to both auditory and vestibular dysfunction (31–33).

CHARGE syndrome is a complex genetic disorder identified by a specific pattern of congenital anomalies, including coloboma, heart defects, choanal atresia, growth retardation, genital hypoplasia, and ear abnormalities. The syndrome is primarily due to mutations in the Chromodomain Helicase DNA Binding Protein 7 (CHD7) gene on chromosome 8q12.1. Individuals with CHD7 mutations are more frequently associated with ocular colobomas, temporal bone abnormalities, and facial nerve paralysis than those without (34–36). CHARGE syndrome is related to various auditory abnormalities, including sensorineural hearing loss and auditory neuropathy. Patients often have hypoplastic or absent auditory nerves, which can affect cochlear implant outcomes. Temporal bone abnormalities, such as ossicular deformities and cochlear malformations, are common (37).

Sotos syndrome is a rare genetic disorder defined by abnormal growth, distinctive facial features, macrocephaly, and varying degrees of learning difficulties. The condition is primarily due to mutations or deletions in the Nuclear Receptor Binding SET Domain Protein 1, located on chromosome 5q35, which encodes a histone methyltransferase involved in transcriptional regulation. Associated features may include hypotonia, feeding difficulties, seizures, and an increased risk of tumors (38,39). It is related to various otolaryngologic manifestations. At the same time, conductive hearing loss and chronic otitis media are commonly reported. ANSD has been observed in conjunction with Sotos syndrome (40,41).

CAPOS syndrome is an uncommon inherited neurological condition resulting from mutations in the ATP1A3 gene, specifically the c.2452G>A (p.Glu818Lys) variant. The syndrome is defined by cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss, typically triggered by febrile episodes in childhood. Patients may experience recurrent acute ataxic encephalopathy, with symptoms improving within days but showing slow progression afterward (42,43). CAPOS syndrome is associated with auditory neuropathy spectrum disorder. This rare condition presents with intact outer hair cell activity with impaired neural synchronization along the auditory pathway. Audiological evaluations typically show preserved otoacoustic emissions and cochlear microphonics but abnormal auditory brainstem responses. Patients often experience poor speech perception, especially in noisy environments (44,45).

Non-syndromic

Some changes in the OTOF gene are linked to a condition called non-syndromic recessive auditory neuropathy, which affects the auditory pathway but doesn't affect the outer hair cells. This results in different levels of hearing impairment highlighted by the presence of OAEs in some patients, indicating intact OHC function, distinguishing them from other forms of hearing loss. The OTOF gene is important for auditory neuropathy because it creates a protein that is needed for the inner hair cells in the cochlea to work. This protein affects the release of neurotransmitters and the transmission of auditory signals (46). New OTOF mutations and their varying frequencies in AN have been found in studies involving a wide range of populations. In Taiwan, a new p.E1700Q mutation was found in 23% of AN family, which points to a possible founder effect (47). Six new pathogenic variants were found in research from Brazil. OTOF mutations were found in 7.7% of cases of autosomal recessive hearing loss and were more common in AN case (48). Italian studies

identified five new OTOF mutations in children with AN, further solidifying the gene's role in this condition (49). A new homozygous frameshift mutation (c.1981dupG) in the OTOF gene was also found to be the reason why one Iranian family had trouble hearing (50).

Changes in the PJVK gene, which codes for pejvakin, cause DFNB59, an autosomal recessive non-syndromic hearing loss with different symptoms. A Pakistani family with p.C343S (51) and a Chinese family with c.930_931del AC both have new mutations (52). Other mutations found in Spanish cases are p.Leu224Arg, p.His294Ilefs*43, p.His294Asp, and p.Phe317Serfs*20. PJVK mutations can result in both cochlear dysfunction and ANSD. Patients with PJVK mutations typically demonstrated severe to profound hearing impairment (53).

Changes in the TMC1 gene are associated with two types of hearing loss that don't exhibit any other symptoms: autosomal recessive (DFNB7/11) and autosomal dominant (DFNA36). DFNB7/11 typically results in congenital or prelingual severe to profound hearing loss, while DFNA36 causes post-lingual, progressive hearing loss. TMC1 mutations disrupt mechanical-to-electrical conversion in inner ear hair cells. Studies have identified novel mutations in different populations, including four in Turkish families and five in other families. Interestingly, some TMC1 mutations can cause moderate to severe hearing loss rather than profound deafness, which suggests that the protein still functions (54–56).

The DIAPH3 gene has been recognized as the cause of autosomal dominant nonsyndromic auditory neuropathy. A change in DIAPH3's 5' UTR leads to the overexpression of the protein, resulting in hearing loss in humans and Drosophila (57). A new frameshift variant, c.3551_3552del (p.Glu1184AlafsTer11), was identified in the DIAPH1 gene in a separate study. This change, located in exon 26 within a linkage region with a high LOD score, is associated with AN in the studied family, strongly suggesting that it contributes to the observed hearing impairment phenotype (58).

Mutations in the OPA1 gene, primarily associated with dominant optic atrophy, can also cause auditory neuropathy and vestibular dysfunction. Studies have identified specific mutations, such as R445H, that lead to deafness by affecting the function of auditory nerve terminals. The Opa1delTTAG mouse model exhibited adult-onset progressive auditory neuropathy, characterized by the breakdown of spiral ganglion neuron fibers and loss of inner hair cells. A review of 327 patients with OPA1 mutations revealed that 6.4% experienced sensorineural hearing loss, with varying onset ranging from childhood to adulthood. Audiological tests often support the diagnosis of auditory neuropathy in these cases (59–61).

A new type of autosomal-dominant auditory synaptopathy/neuropathy called AUNA2 has been found in a German family. It was first linked to chromosomes 12q24 and 13q34. AUNA2 is characterized by slowly progressive post-lingual hearing loss, accompanied by no additional symptoms (62).

GJB2 gene mutations mainly cause non-syndromic sensorineural hearing loss (NSHL) in various populations. Studies in Chinese patients have identified several mutations, with 235delC being the most prevalent. The mutation spectrum differs between ethnic groups, with 235delC being more common in East Asian populations than the 35delG mutation prevalent in Caucasians (63). GJB2 mutations can cause both autosomal recessive and dominant forms of NSHL. Some GJB2 mutations also lead to persistent skin and hearing problems, which typically follow a dominant inheritance pattern (64). A study found no significant correlation between ANSD and GJB2 mutations, with only 7.5% of ANSD patients harboring GJB2 mutations (65). Recently, though, 16 of the 117 people with ANSD who were studied had GJB2 mutations. This suggests that GJB2 variants may be associated with ANSD in a deleterious manner (66).

Treatment options for ANSD

This section provides a brief overview of current treatment strategies, and a more comprehensive discussion of treatment options for ANSD is beyond the scope of this review. The treatment of ANSD currently focuses on maximizing auditory function through a multidisciplinary approach. Hearing aids are the primary treatment for mild to moderate hearing loss. Also, people with severe to profound hearing loss are thought to be getting cochlear implants. This is especially true if the inner hair cells don't function correctly or if hearing aids don't provide significant relief. Careful patient counseling, considering individual needs and expectations, is essential in selecting the most appropriate amplification strategy. FM-listening systems can significantly improve signal-to-noise ratios in challenging listening environments, enhancing speech understanding. Gene therapy holds tremendous promise for the future of ANSD treatment. New methods, such as CRISPR-Cas9, SMaRT, and AAV-mediated gene therapy, are being used to correct underlying genetic changes, stimulate the growth of new auditory synapses, and restore the nerves that control hearing. Early preclinical and clinical trials have yielded promising results, but further research is necessary to address challenges such as developing accurate animal models, refining diagnostic tools, and assessing the long-term safety and efficacy of the drug. Gene therapy products, such as DB-OTO and OTOF-GT, which have been approved by the FDA, represent a significant step forward in the search for effective and targeted treatments for genetic forms of ANSD (67,68).

Conclusion

ANSD is a complex, multifactorial condition that arises from various genetic causes, occurring in both syndromic and nonsyndromic forms. Recent genetic studies have highlighted mutations in several key genes, including OTOF, PJVK, TMC1, DIAPH3, and OPA1, which significantly contribute to the development of this disorder. These genetic changes can disrupt the normal functioning of auditory pathways, resulting in impaired transmission of sound signals from the inner ear to the brain, even when the outer hair cells remain intact.

Given the diversity and complexity of these genetic disorders, further research is necessary to identify additional genes and gain a deeper understanding of the molecular mechanisms that contribute to auditory neuropathy. This understanding will lay the groundwork for improvements in diagnosis, prognosis, and the development of individualized therapeutic strategies. Additionally, exploring the interactions among various genes and their impact on the structure and function of the auditory system could provide valuable insights and contribute to the development of innovative treatment approaches in the future.

Authors' contribution:

M.K.: conceptualization and drafting of the manuscript, M.A.: critical revisions and supervised the overall development of the review, M.Aj: literature selection and ensured the accuracy of clinical interpretations, N.S.: refining the scientific content, S.M.: organization and synthesis of key findings, G.M.: reviewing and improving the final manuscript before submission. All authors read and approved the final version of the manuscript.

Conflict of interest:

The authors declare that they have no conflicts of interest related to this study.

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