Mutation Spectrum of Common Pathogenic Genes in Hereditary Hearing Loss: A Literature Review

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Abstract. Hereditary hearing loss constitutes one of the most prevalent sensory disorders globally, affecting approximately 466 million individuals, with genetic factors accounting for 50-60% of congenital and early-onset cases across more than 120 identified causative genes that present substantial challenges for accurate molecular diagnosis and personalized clinical management. This review systematically synthesizes current evidence regarding the mutation spectrum characteristics of common pathogenic genes implicated in both non-syndromic and syndromic hereditary hearing loss, with particular emphasis on population-specific distribution patterns and genotype-phenotype correlations derived from recent high-quality studies published between 2020 and 2024. The comprehensive analysis demonstrates that GJB2 and SLC26A4 represent the most frequently implicated genes in non-syndromic hearing loss, while MYO7A and USH2A predominate in Usher syndrome cases, with hotspot mutations exhibiting remarkable ethnic heterogeneity attributable to founder effects and historical population migrations, as exemplified by the predominance of GJB2 c.35delG in European populations versus GJB2 c.235delC in East Asian populations. Next-generation sequencing technologies have achieved diagnostic yields ranging from 18% to 48.6%, depending on patient selection criteria, enabling implementation of population-specific tiered genetic testing strategies that optimize diagnostic efficiency while facilitating informed clinical decisions regarding intervention timing, cochlear implantation candidacy, and reproductive counseling. Interpretation of mutation spectrum data remains constrained by heterogeneity in study designs, variable sequencing methodologies, and underrepresentation of certain ethnic populations in existing cohorts, warranting cautious extrapolation across diverse clinical settings.

1 Introduction

1.1 Epidemiology and genetic heterogeneity of hereditary hearing loss

Hearing loss represents the most prevalent sensory deficit affecting human populations worldwide; approximately 466 million individuals experience disabling hearing impairment according to global epidemiological estimates. Genetic factors contribute substantially to this burden, accounting for 50-60% of congenital and early-onset cases in developed countries. The genetic architecture of hereditary hearing loss exhibits remarkable heterogeneity, with more than 120 distinct genes currently implicated in various forms of auditory dysfunction, thereby presenting significant challenges for accurate molecular diagnosis and appropriate clinical intervention [1]. Hereditary hearing loss is traditionally classified into syndromic forms, which constitute approximately 30% of cases and present with additional systemic manifestations affecting organs beyond the auditory system, and non-syndromic forms, which account for the remaining 70% and manifest exclusively as auditory impairment without associated phenotypic features. The inheritance patterns of non-syndromic hearing loss demonstrate considerable diversity, with autosomal recessive transmission (designated DFNB loci) representing the predominant mode at 75-80% of cases, autosomal dominant inheritance (DFNA loci) accounting for 20-25%, and X-linked and mitochondrial inheritance contributing less than 2% collectively.

1.2 Clinical significance and objectives of this review

The elucidation of pathogenic gene mutation spectra carries profound implications for clinical practice, as precise molecular diagnosis enables accurate prognostic assessment, informed genetic counseling for affected families, and evidence-based selection of rehabilitation strategies including hearing aids and cochlear implantation. The advent of next-generation sequencing (NGS) technologies has revolutionized the diagnostic landscape by enabling simultaneous analysis of multiple deafness-associated genes, achieving diagnostic yields ranging from 18.0% in late-onset cases to 48.6% in congenital presentations, with rates varying substantially across different age groups and populations [2]. This review systematically summarizes the mutation spectra of

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common pathogenic genes in hereditary hearing loss, encompassing both non-syndromic and syndromic forms, with particular emphasis on population-specific variant distributions and genotype-phenotype correlations that inform clinical genetic diagnosis and counseling.

2 Mutation spectrum of common pathogenic genes in non-syndromic hearing loss

2.1 GJB2 gene mutation spectrum

The GJB2 gene, located on chromosome 13q12.11, encodes the gap junction protein connexin 26 (CX26), which plays a critical role in potassium ion recycling within the cochlea and maintains the endocochlear potential essential for auditory signal transduction.

Mutations in GJB2 represent the most common genetic cause of autosomal recessive non-syndromic hearing loss worldwide, accounting for up to 50% of cases in certain populations, with carrier frequencies ranging from 2% to 4% depending on ethnic background.

The mutation spectrum of GJB2 demonstrates remarkable population specificity, with distinct founder mutations predominating in different geographic regions owing to historical migrations and genetic drift effects. In European and Mediterranean populations, the c.35delG mutation constitutes the most prevalent pathogenic variant, accounting for 70-85% of all mutant alleles, whereas the c.235delC mutation predominates in East Asian populations including Japanese, Korean, and Chinese individuals, representing approximately 70-80% of pathogenic alleles in these groups. The c.167delT mutation demonstrates particularly elevated frequency in the Ashkenazi Jewish population, with carrier rates approaching 4-7%, reflecting a distinct founder effect in this community.

Haplotype analysis has revealed that these recurrent mutations arose from common ancestors rather than representing mutational hotspots, with the c.235delC mutation estimated to have originated approximately 6,500-11,500 years ago based on genetic clock calculations, supporting the founder mutation hypothesis for the ethnic-specific distribution patterns [3].

Genotype-phenotype correlation studies have demonstrated that truncating mutations generally result in more severe hearing impairment compared to missense variants, with biallelic truncating genotypes typically associated with profound congenital deafness, while certain missense mutations such as p.V37I may cause milder phenotypes with progressive characteristics. The mutation spectrum characteristics of major non-syndromic hearing loss genes are summarized in Table 1.

Table 1. Mutation spectrum characteristics of common pathogenic genes in non-syndromic hearing loss.

Gene	Chromosomal Location	Inheritance	Encoded Protein	Major Hotspot Mutations	High-frequency Population	Hearing Phenotype
GJB2	13q12.11	AR	Connexin 26	c.35delG, c.235delC, c.167delT	European, East Asian, Jewish	Congenital severe-profound, stable
SLC26A4	7q22.3	AR	Pendrin	c.919-2A>G, p.H723R, p. T416P	East Asian	Progressive, fluctuating, with EVA
MYO7A	11q13.5	AR/AD	Myosin VIIa	Highly heterogeneous	Global distribution	Congenital severe-profound
MT-RNR1	mtDNA	Maternal	12S rRNA	m.1555A>G, m.1494C>T	East Asian, European	Aminoglycoside-induced, progressive
MYO15A	17p11.2	AR	Myosin XVa	Highly heterogeneous	Middle East, South Asia	Congenital profound
OTOF	2p23.3	AR	Otoferlin	p.Q829X, c.5816G>A	Spanish, Japanese	ANSD, temperature-sensitive

Note: AR = autosomal recessive; AD = autosomal dominant; EVA = enlarged vestibular aqueduct; ANSD = auditory neuropathy spectrum disorder

2.2 SLC26A4 gene mutation spectrum

The SLC26A4 gene encodes pendrin, a transmembrane anion exchanger expressed in the inner ear, thyroid gland, and kidney, in which tissues it mediates chloride, iodide, and bicarbonate transport essential for endolymphatic fluid homeostasis and thyroid hormone synthesis.

Mutations in SLC26A4 are associated with a phenotypic continuum ranging from Pendred syndrome, characterized by sensorineural hearing loss with goiter and abnormal iodide organification, to non-syndromic hearing loss associated with enlarged vestibular aqueduct (DFNB4) without thyroid involvement.

The mutation spectrum of SLC26A4 exhibits substantial ethnic variation, with the splice site mutation c.919-2A>G representing the most prevalent pathogenic variant in East Asian populations, particularly in Japanese, Korean, and Chinese patients, among whom it accounts for 50-80% of all mutant alleles. Other common mutations include p.H723R, which exhibits high frequency in Japanese and Korean populations, and p.T416P, which is frequently observed in Northern European patients.

The phenotypic expression of SLC26A4 mutations demonstrates considerable variability even among individuals carrying identical genotypes, with hearing loss typically presenting as congenital or early-onset, and characterized by progressive, fluctuating courses, often exacerbated by minor head trauma or sudden pressure changes [4]. Radiological evaluation reveals the enlarged vestibular aqueduct and/or the Mondini dysplasia in the majority of affected individuals, thus providing valuable diagnostic clues that prompt targeted genetic testing.

The genotype-phenotype correlations in SLC26A4-related hearing loss remain incompletely understood,

suggesting that modifier genes, epigenetic factors, or environmental influences may modulate disease expression independently of the primary pathogenic variants.

2.3 Other common autosomal recessive genes

Beyond GJB2 and SLC26A4, several key additional genes contribute significantly to autosomal recessive non-syndromic hearing loss, each with distinctive mutation spectra and clinical characteristics, as outlined in Table 1.

The MYO7A gene, encoding the unconventional myosin VIIA protein essential for stereocilia organization and mechanotransduction in cochlear hair cells, causes both syndromic (Usher syndrome type 1B) and non-syndromic hearing loss (DFNB2 and DFNA11) depending on the nature and location of mutations. Large-cohort studies encompassing over 10,000 Japanese hearing loss patients have identified MYO7A mutations in approximately 1.36% of cases, with 70 distinct disease-causing variants documented including 36 novel mutations, and the majority of autosomal dominant cases harboring missense mutations or in-frame deletions while autosomal recessive cases invariably carry at least one missense variant [5]. The clinical presentation of MYO7A-related non-syndromic hearing loss typically manifests as congenital severe-to-profound sensorineural impairment, with affected individuals demonstrating favorable outcomes following cochlear implantation.

The OTOF gene, encoding otoferlin that is critical for synaptic vesicle exocytosis at the inner hair cell ribbon synapse, represents the primary genetic cause of auditory neuropathy spectrum disorder, characterized by absent or severely abnormal auditory brainstem responses despite preserved otoacoustic emissions.

Additional key genes including MYO15A, TMC1, and STRC contribute to the genetic heterogeneity of autosomal recessive hearing loss, with MYO15A mutations particularly prevalent in consanguineous populations of the Middle East and South Asia where founder effects and endogamy increase the frequency of rare recessive alleles.

2.4 Autosomal dominant and mitochondrial DNA mutations

Autosomal dominant non-syndromic hearing loss, though less common than autosomal recessive non-syndromic forms, typically presents with postlingual onset and progressive deterioration predominantly affecting high-frequency ranges. Genes such as WFS1 and KCNQ4 cause characteristic patterns of progressive hearing loss, with WFS1 mutations uniquely affecting low frequencies, in contrast to KCNQ4 mutations result in high-frequency impairment resembling age-related presbycusis.

Mitochondrial DNA mutations constitute a distinct category of hereditary hearing loss with maternal inheritance patterns and its variable penetrance influenced by heteroplasmy levels and nuclear modifier genes. The m.1555A>G mutation in the MT-RNR1 gene encoding mitochondrial 12S ribosomal RNA represents the most clinically significant mitochondrial variant, conferring heightened susceptibility to the aminoglycoside-induced ototoxicity through structural alterations that enhance binding affinity between the mutant ribosome and aminoglycoside antibiotics, thereby disrupting mitochondrial protein synthesis in cochlear cells [6]. Clinical investigations have demonstrated that individuals harboring this mutation may develop irreversible profound hearing loss following even single therapeutic doses of aminoglycosides, particularly streptomycin, while carriers without antibiotic exposure often exhibit mild progressive high-frequency hearing loss with variable age of onset ranging from childhood to late adulthood. The m.1494C>T mutation affects the same functional domain within the ribosomal decoding site and confers similar aminoglycoside susceptibility, thus underscoring the clinical importance of genetic screening prior to aminoglycoside administration in populations with elevated carrier frequencies to prevent iatrogenic hearing loss.

3 Mutation spectrum of common pathogenic genes in syndromic hearing loss

3.1 Usher syndrome-related genes

Usher syndrome represents the most prevalent cause of combined deaf-blindness worldwide, with an estimated prevalence of 4-17 per 100,000 individuals, and is characterized by congenital sensorineural hearing loss accompanied by progressive retinitis pigmentosa leading to visual impairment that typically manifests during adolescence or early adulthood.

The established clinical classification delineates Usher syndrome divides the disorder into three major subtypes based on the severity and progression of hearing loss, the presence or absence of vestibular dysfunction, and the age at onset of retinal degeneration, with each subtype demonstrating distinct genetic etiologies involving mutations in specific sets of genes. Nine genes have been definitively established as causative for Usher syndrome, comprising five genes for type 1 (MYO7A, USH1C, CDH23, PCDH15, and USH1G), three genes for type 2 (USH2A, ADGRV1, and WHRN), and one gene for type 3 (CLRN1), with their encoded proteins forming intricate molecular networks essential for the structural and functional integrity of both cochlear hair cell stereocilia and photoreceptor connecting cilia [7].

The MYO7A gene, responsible for Usher syndrome type 1B (USH1B), accounts for more than 50% of all type 1 cases and encodes an unconventional myosin motor protein critical for stereocilia development and maintenance, with pathogenic mutations typically resulting in congenital profound hearing loss, vestibular areflexia, and an early prepubertal onset of retinitis pigmentosa. The USH2A gene represents the most frequently mutated gene in Usher syndrome overall, accounts for approximately 80% of type 2 cases, and is associated with moderate-to-severe congenital hearing

loss without vestibular involvement, accompanied by a delayed later-onset retinal degeneration that generally becomes symptomatic during the second or third decade of life.

The overlapping expression of Usher proteins in both the inner ear and retina explains the dual sensory phenotype, as these proteins interact to form multiprotein complexes at critical subcellular locations including the stereocilia tip-links and photoreceptor transition zones.

3.2 Other common syndromic hearing loss genes

Beyond Usher syndrome, numerous other hereditary syndromic forms of hearing loss have been characterized at the molecular level, each with distinctive mutation spectra and clinical presentations that facilitate differential diagnosis via comprehensive genetic testing approaches.

Waardenburg syndrome, characterized by sensorineural hearing loss in combination with pigmentary abnormalities affecting the hair, skin, and iris, results from mutations in genes encoding transcription factors and signaling molecules essential for neural crest cell development, including PAX3 (types 1 and 3), MITF (type 2), and SOX10 (type 4), with the specific gene involved determining the associated extra-auditory manifestations and inheritance patterns.

Comprehensive genetic analysis of syndromic hearing loss patients using next-generation sequencing panels targeting 36 genes associated with 14 distinct syndromes has yielded an overall diagnostic rate of approximately 56%, among these, branchio-oto-renal syndrome (caused by EYA1 and SIX1 mutations), Pendred syndrome (SLC26A4), and Waardenburg syndrome exhibit the highest molecular confirmation rates among the evaluated conditions [8].

The clinical utility of such genetic testing extends beyond diagnostic confirmation to prognostic assessment and surveillance recommendations, as the identification of specific gene mutations may uncover previously unrecognized syndromic features requiring multidisciplinary management, including renal anomalies in branchio-oto-renal syndrome, thyroid dysfunction in Pendred syndrome, and cardiac arrhythmias in Jervell and Lange-Nielsen syndrome caused by KCNQ1 and KCNE1 mutations.

4 Population differences and clinical applications

4.1 Ethnic variations in mutation spectrum

The distribution of pathogenic mutations in hearing loss genes demonstrates striking ethnic and geographic heterogeneity, reflecting the combined influences of founder effects, genetic drift, and historical population migrations that have shaped the genetic landscape of hereditary deafness across different continental populations. In European populations, the GJB2 c.35delG mutation predominates as the single most common cause of autosomal recessive non-syndromic monogenic hearing loss, accounting for 50-80% of all pathogenic alleles in Mediterranean and Northern European countries, with carrier frequencies reaching 2-4% in certain regions [9]. East Asian populations exhibit a distinctly different mutation spectrum characterized by high frequencies of GJB2 c.235delC and SLC26A4 c.919-2A>G, in contrast, Middle Eastern and South Asian populations demonstrate elevated rates of mutations in genes such as MYO15A and TMC1. As illustrated in Fig 1, the carrier frequencies of major hotspot mutations vary substantially across ethnic groups, necessitating population-specific approaches to genetic screening and diagnostic algorithms.

These ethnic variations must be interpreted with recognition of methodological limitations in cross-population comparisons. Published prevalence estimates derive predominantly from East Asian and European cohorts with advanced genetic testing infrastructure, while African, Latin American, and indigenous populations remain underrepresented, potentially introducing ascertainment bias that limits generalizability. Variable diagnostic criteria across studies further complicate direct prevalence comparisons, and the underrepresentation of non-coding variants in conventional sequencing may result in underestimation of specific gene contributions to hereditary hearing loss burden.

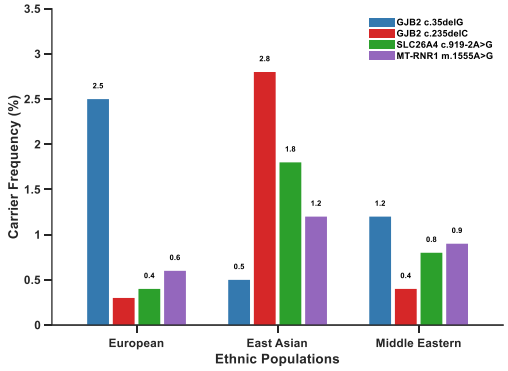

Fig. 1. Carrier frequency of major hotspot mutations across ethnic populations.

4.2 Genetic diagnosis strategies and clinical translation

The recognition of population-specific mutation spectra has profound implications for the design of efficient and cost-effective hereditary hearing loss-focused genetic testing strategies, enabling tiered approaches that prioritize high-yield targets based on the patient's ethnic background and clinical presentation [10]. Contemporary clinical practice guidelines recommend initiating genetic evaluation with targeted analysis of the most prevalent mutations in the relevant population, followed by comprehensive gene panel testing or exome sequencing for cases remaining undiagnosed after first-tier screening. The integration of genetic diagnosis into routine clinical care facilitates accurate prognostic counseling regarding hearing loss progression, informs decisions regarding cochlear implantation candidacy and expected outcomes,

and enables carrier testing and prenatal diagnosis for at-risk family members seeking reproductive guidance. The establishment of standardized variant interpretation frameworks specific to hearing loss, incorporating gene-level and variant-level evidence according to established criteria, has in turn substantially improved the clinical actionability of genetic testing results and reduced the proportion of variants of uncertain significance (VUS) reported in clinical testing.

5 Conclusion

5.1 Summary of main findings

This review synthesizes current knowledge regarding the mutation spectrum of common key pathogenic genes associated with hereditary hearing loss, revealing that GJB2, SLC26A4, MYO7A, and MT-RNR1 represent the most frequently implicated genes across diverse populations, while the specific distribution of hotspot mutations demonstrates remarkable ethnic heterogeneity attributable to founder effects and population demographic history. The recognition of population-specific mutation patterns, exemplified by the predominance of c.35delG in European populations versus c.235delC in East Asian populations, provides the scientific foundation for implementing tiered genetic testing strategies that maximize diagnostic efficiency while minimizing healthcare expenditure.

5.2 Limitations and future directions

Despite substantial advances, approximately 30-50% of cases remain genetically unresolved, suggesting that novel pathogenic genes, non-coding regulatory variants, and oligogenic inheritance patterns await discovery through long-read sequencing and functional genomics approaches. Current literature exhibits notable limitations including predominant reliance on retrospective designs susceptible to selection bias, inconsistent variant pathogenicity classification, and limited functional validation data for variants of uncertain significance. The preponderance of studies from tertiary referral centers may additionally inflate mutation detection rates relative to general practice outcomes. Gene therapy and gene editing strategies demonstrate promising preliminary results in preclinical models and early-phase trials, though challenges regarding delivery efficiency, immunogenicity, and long-term safety necessitate continued investigation.

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