Genetics of Hearing Loss—Nonsyndromic

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KEYWORDS

• Nonsyndromic hearing loss • DFNA • DFNB • GJB2 • Next-generation sequencing • Massively parallel sequencing

KEY POINTS

- Autosomal-recessive (AR) nonsyndromic hearing loss is usually prelingual and frequently results in severe hearing loss, although milder and progressive hearing loss forms also exist. GJB2 and SLC26A4 are the 2 most common AR genes.
- Autosomal-dominant (AD) nonsyndromic hearing loss is often postlingual and progressive. No single gene accounts for any significant proportion of AD hearing loss.
- High-throughput sequencing techniques, also called next-generation sequencing (NGS) or massively parallel sequencing (MPS), now allow comprehensive testing of all known deafness-associated genes in a child presenting with congenital hearing loss.

Hearing loss is the most common congenital sensory impairment, affecting 1 in 500 newborns and 1 in 300 children by the age of 4.[1] Approximately 1 in 1000 newborns has genetically inherited hearing loss. Nonsyndromic etiologies account for 70% of genetic hearing loss, with only 30% being syndromic and demonstrating other clinical findings.[2]

Autosomal-recessive (AR) inheritance accounts for 80% of nonsyndromic genetic hearing loss and is usually prelingual. Autosomal-dominant (AD) inheritance accounts for most of the other 20% and is more often postlingual. AR nonsyndromic hearing loss (designated "DFNB#") most frequently results in severe hearing loss, which presents early, whereas AD nonsyndromic hearing loss (designated "DFNA#") typically results in progressive sensorineural hearing loss (SNHL) with variable severity, which begins at 10 to 40 years.[3] Patients with mitochondrial inheritance tend to develop progressive SNHL, which begins at 5 to 50 years, and the degree of hearing loss is variable.[4] X-linked (designated "DFNX#") and mitochondrial inheritance account for only 1% to 2% of nonsyndromic hearing loss.

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Nonsyndromic SNHL may be caused by mutations in any one of an increasing number of identified genes. Currently, over 100 genes for SNHL have been mapped, some listed on **Table 1** (a more comprehensive updated list can be found on the Hereditary Hearing Loss Homepage, http://hereditaryhearingloss.org).[5] For AR SNHL, the most frequent causative genes in order of frequency are GJB2, SLC26A4, MYO15A, OTOF, CDH23, and TMC1. Common mutations of AD inheritance include WFS1, TECTA, COCH, and KNCQ4. Several of these genes are also implicated in syndromic hearing loss.

AUTOSOMAL-RECESSIVE GENES

In AR inheritance, there is often no family history of hearing loss. Although AR SNHL is more common in families in which parents are related (consanguinity), they are not exclusive to such families, and most affected individuals have a negative history of consanguinity within the family tree. According to the hereditary hearing loss homepage, 60 genetic mutations have been identified causing nonsyndromic AR hearing loss.[5]

GJB2 (DFNB1A)

GJB2 encodes the gap junction protein Connexin 26, a critical component of the intracellular pathway for potassium cycling between the endolymph and perilymph of the cochlea. Mutations in GJB2 account for up to 50% of patients with nonsyndromic AR SNHL. Hearing loss from GJB2 was first described in 1997,[6] and since then, routine DNA sequencing of the coding region of GJB2 reported across the world has demonstrated interesting patterns of genotypes across populations. Particularly prevalent mutant alleles include 35delG, found in Europe and the Middle East (particularly regions surrounding the Mediterranean); 235delC, found in East Asia, V37I, common in Southeast Asia; and W24X, common in India.[7]

Inactivating truncating mutations in GJB2 (stop codons or frameshift mutations, such as small insertions/deletions) are generally associated with severe-to-profound SNHL. In contrast, noninactivating nontruncating mutations in GJB2 (base changes that result in single amino acid substitutions) are associated with moderate or even mild SNHL.[8] The large, noncoding deletions involving the adjacent GJB6 gene, which encodes for the protein Connexin 30, are thought to cause hearing loss through their effects on GJB2 expression, and not through the effects on GJB6.[9]

Table 2 lists some of the more common truncating and nontruncating GJB2 mutations. The number of discovered mutations continues to increase over time, and a more comprehensive updated list can be found at the Connexin-deafness homepage (http://www.crg.es/deafness).[10] Patients with 2 truncating mutations tend to have severe-to-profound hearing loss, while those with a truncating and nontruncating mutation have more moderate hearing loss, and those with 2 nontruncating mutations tend to have mild hearing loss.[11] However, those with 2 nontruncating mutations, especially those homozygous for V37I, had up to a 39% to 50% rate of progression of hearing loss.[12,13] GJB2 sequencing, along with computed tomography (CT)/MRI of the temporal bone remain 2 of the highest yield diagnostic evaluations for children presenting with SNHL.[14–16]

Although GBJ2 hearing loss is thought to be AR, thus requiring 2 mutations to result in the hearing loss phenotype, meta-analysis of carrier rates between normal hearing and hearing loss populations demonstrates significantly increased rates of truncating mutations in the hearing loss populations, suggesting an unidentified genetic factor contributing to hearing loss in some heterozygote carriers, or alternatively, that there