GJB2 (Connexin 26)/GJB6 (Connexin 30) gene analysis for autosomal dominant or recessive nonsyndromic hearing loss

Disorder also known as: Autosomal recessive deafness DFNB1, Autosomal dominant deafness DFNA3A

Clinical Features:
Autosomal recessive non-syndromic hearing loss or deafness DFNB1 is due to homozygous or compound heterozygous pathogenic variants in the GJB2 gene, and accounts for up to 50% of cases in certain ethnic groups\(^1,2\). The hearing loss in affected individuals has been described as prelingual, symmetric, non-progressive, and with varied severity ranging from mild to profound hearing loss\(^3-5\).

Autosomal dominant sensorineural hearing loss DFNA3A is due to heterozygous pathogenic variants in GJB2, and is characterized as progressive and moderate to severe, with prelingual or postlingual onset\(^6\).

Other related disorders:
Missense variants in \(GJB2\) may also cause several different forms of palmoplantar keratoderma (PPK; thickening of the skin of palms and soles) associated with hearing loss, such as Vohwinkel syndrome, Bart-Pumphrey syndrome, and Keratitis-Ichthyosis-Deafness (KID) syndrome\(^7\). See information material for test #130.

Genetics:
The GJB2 gene encodes connexin 26 (Cx26), a beta 2-type gap junction protein that forms hemichannels and intercellular gap junction channels in various epithelia, including the inner ear. Sequence variants in GJB2 can lead to autosomal dominant (DFNA3A) or autosomal recessive (DFNB1) hearing loss. Variants associated with DFNA3A often exert a dominant-negative effect on connexins forming gap junctions\(^10\), while variants associated with DFNB1 often result in loss of function or interfere with protein translation\(^11\). In the vast majority of individuals, autosomal recessive hearing loss DFNB1 is caused by homozygous or compound heterozygous variants in the GJB2 gene\(^13\). Rarely (<1%), a heterozygous GJB2 sequence variant in trans with one of three known deletions involving sequences upstream of \(GJB2\) and a part of \(GJB6\), or such a deletion in the homozygous state have been reported\(^1,6,7\). Most common are a 309 kb deletion (\(\Delta GJB6-D13S1830\)) and a smaller 232 kb deletion (\(\Delta GJB6-D13S1854\))\(^1,6,8\).
Test Information Sheet

Test Sensitivity:
Variants in GJB2 alone or in combination with deletions involving GJB6 account for up to 50% of autosomal recessive nonsyndromic congenital hearing loss in the United States, France, Britain, New Zealand, and Australia. Prevalence varies in other studied populations. The analysis offered at GeneDx is expected to identify 99% of existing variants in the coding sequence of GJB2, as well as the deletions previously reported as ∆GJB6-D13S1830 and ∆GJB6-D13S1854, if present. This assay will not detect intragenic GJB6 sequence variants, but GJB6 testing is available as a separate test.

As hearing loss is highly heterogeneous and may have many genetic and non-genetic causes, additional genetic tests, including a multi-gene Next-generation sequencing panel for hearing loss, may be considered.

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of GJB2 are PCR amplified and capillary sequencing was performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Two common GJB6 deletions, ~309 kb del (∆GJB6-D13S1830) and ~232 kb del (∆GJB6-D13S1854), are assessed by multiplex junction specific PCR with primers designed to flank the breakpoints of these deletions. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence variants are reported according to the Human Genome Variation Society (HGVS). Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References: