DFNB1 Autosomal Recessive Hearing Loss (GJB2 Sequencing and Common *GJB6* Deletions)

DISORDER ALSO KNOWN AS
Autosomal recessive deafness DFNB1, Autosomal dominant deafness DFNA3A, Connexin 26-related hearing loss

CLINICAL FEATURES
Autosomal recessive nonsyndromic 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]. Affected individuals have sensorineural hearing loss, which has been described as prelingual, symmetric, non-progressive, and with varied severity ranging from mild to profound hearing loss[3-5].

Autosomal dominant nonsyndromic hearing loss DFNA3A is due to heterozygous pathogenic variants in GJB2, and is characterized as sensorineural, progressive and moderate to severe, with prelingual or postlingual onset[9].

OTHER RELATED DISORDERS
Missense variants in the *GJB2* gene are also associated with several different forms of syndromic hearing loss with palmoplantar keratoderma (PPK; thickening of the skin of palms and soles), such as Vohwinkel syndrome, Bart-Pumphrey syndrome, and Keratitis-Ichthyosis-Deafness (KID) syndrome[12].

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 (∆GJB6-D13S1830) and a smaller 232 kb deletion (∆GJB6-D13S1854)[1,6,8].

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
Genomic DNA is extracted from the submitted specimen. The DNA is PCR amplified and capillary sequencing is performed for the complete coding region, splice junctions, and a regulatory region of the *GJB2* gene. Bi-

directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. 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. Primer sequences are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. If present, apparently homozygous variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the genes/exons involved. 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.

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