Testing for the common mitochondrial hearing loss mutations (MTCO1 and MTT5S) have been associated with aminoglycoside ototoxicity in an estimated 2% of deaf individuals in the US [7-8]. The prevalence is higher, 15-30%, among deaf persons with a history of aminoglycoside exposure [9]. One of the most common mitochondrial pathogenic variants is the m.1555A>G substitution in the MTFRN17 gene which can be found in 0.6-2.5% of Caucasian, 3-5% of Asian and as high as 17% of the Spanish population with non-syndromic hearing loss [10].

The mitochondrial variants m.7,445A>G/m.7,443A>G/m.7,444G>A in the tRNA serine gene (MTCO1 and MTT5S) have been found in patients with maternally inherited sensorineural hearing loss, but they are less likely to cause aminoglycoside hypersensitivity. Of individuals with mitochondrial nonsyndromic hearing loss, 14% have pathogenic variants m.7443A>G, m.7444G>A, or m.7445A>G. Most mitochondrial DNA mutations causing non-syndromic hearing loss are maternally inherited. However, heteroplasmic states (uneven distribution of mitochondrial DNA during cell division) and variable penetrance may be related to the level of mutant mitochondria present, and is not quantitated by this assay. The Hearing Loss Panel includes genes.

In the presence of specific mitochondrial DNA (mtDNA) mutations, moderate to severe hearing loss can result from exposure to aminoglycoside antibiotics such as gentamycin, tobramycin, amikacin, kanamycin, or streptomycin [6]. Pathogenic variants in the mitochondrial MTTS1 gene have been associated with aminoglycoside ototoxicity with an estimated 2% of deaf individuals in the US [7-8]. The prevalence is higher, 15-30%, among deaf persons with a history of aminoglycoside exposure [9]. One of the most common mitochondrial pathogenic variants is the m.1555A>G substitution in the MTFRN17 gene which can be found in 0.6-2.5% of Caucasian, 3-5% of Asian and as high as 17% of the Spanish population with non-syndromic hearing loss [10].

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• Confirmation of a clinical diagnosis of hearing loss.
• Carrier testing in adults with a family history of hearing loss.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members. The \textit{GJB6} gene 342kb deletion is detected by allele-specific amplification.

Detection

Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype. The \textit{GJB6} deletion component of this test will detect nearly all 342kb common deletion alleles in Connexin 30.

Analytical Sensitivity: ~99%.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
Infants (Children (>2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

Type: Isolated DNA

Specimen Requirements:

In microtainer: 60 ug

Isolation using the Qiagen\textsuperscript{TM} Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

Related Tests

• Hearing Loss Panel: \textit{GJB2} and \textit{GJB6} Sequencing, \textit{GJB6} Common Deletion, and Targeted Mitochondrial Analysis
• Hearing Loss: \textit{GJB2} & \textit{GJB6} Gene Sequencing Panel
• Hearing Loss: \textit{GJB2} & \textit{GJB6} Gene Deletion/Duplication Panel
• Hearing Loss: \textit{GJB2} Gene Sequencing
• Hearing Loss: \textit{GJB6} Gene Sequencing
• Hearing Loss: Deletion/Duplication Panel