Hearing Loss Panel: Sequencing and CNV Analysis

Test Code: MM190
Turnaround time: 6 weeks
CPT Codes: 81430 x1

Condition Description

This panel includes the following components:

- Sequencing of hearing loss genes, including GJB2 and GJB6.
- Testing for the GJB6 common deletion.
- Testing for the common mitochondrial hearing loss mutations.

Hearing loss can be categorized by type, onset, or severity. Sensorineural hearing loss is the result of impairment of the inner ear structures. Conductive hearing loss is the result of abnormalities of the external ear and/or the middle ear. Mixed hearing loss is a combination of sensorineural and conductive hearing loss. Central auditory dysfunction is the result of damage or dysfunction of the eighth cranial nerve, auditory brain stem, or cerebral cortex. Age of onset is characterized as prelingual (before speech develops) or postlingual (after speech develops). Severity ranges from mild to profound.

The prevalence of bilateral sensorineural hearing loss is 1 in 500 newborns and 3.5 per 1000 adolescents. While the causes of hearing loss are diverse, at least 50% (and possibly up to two-thirds) of prelingual hearing loss is genetic in origin. The remaining cases of hearing loss are thought to be due to environmental factors or unidentified genetic factors. Hearing loss can be associated with a particular genetic syndrome, such as Usher syndrome or Pendred syndrome; however, most cases of prelingual sensorineural hearing loss are the result of an autosomal recessive, nonsyndromic condition. Genetic hearing loss can be inherited in many ways. Autosomal recessive causes account for approximately 80% of hearing loss cases and are typically prelingual in onset. Autosomal dominant causes account for approximately 20% of hearing loss cases and are typically postlingual in onset. Less than 1% of hearing loss cases are inherited through the mitochondria or the X chromosome. Approximately 50% of autosomal recessive nonsyndromic hearing loss cases are caused by mutations in the GJB2 and GJB6 genes.

In the presence of specific mitochondrial DNA (mtDNA) mutations, moderate to severe hearing loss can result from exposure to aminoglycoside antibiotics such as gentamicin, tobramycin, amikacin, kanamycin, or streptomycin [6]. Pathogenic variants in the mitochondrial MTM1, MTN1, and MTS1 genes 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 MTM1 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 MTS1) 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 nonsyndromic 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 sequencing of genes in which pathogenic variants are known to cause hearing loss or have hearing loss as part of the clinical spectrum of disease.

This test is indicated for:

- GeneReviews
- OMIM
- Hilgert et al. (2009), Mutation Research, 681:189-196.

References:

- ABHD12, ABHD5, ACTG1, ADCY1, ADGRV1, AIFM1, ALMS1, ATP6V1B1, BSN1, BTD, C16orf15, CACNA1D, CCDC50, CDH23, CEACAM16, CHD7, CIB2, CISO2, CLDN14, CLIC5, CLPP, CLRN1, COCH, COL11A2, COL2A1, COL4A3, COL4A4, COL4A5, COL4A6, COL9A1, CRYP, DCDC2, DIA1LQ, DIAP1, DNM1, DSSP, EDN3, EDNRB, ELMOD3, EPSP, ESR8, EYA1, EYA4, FGFR3, FOXC1, FOX11, GIPC3, GJB2, GJB3, GJB6, GNAS2, GRHL2, GRXCR1, GSDME, HARS2, HGF, HOMER2, HSD17B4, ILDR1, IARS1, KCNE1, KCNJ10, KCNQ1, KCNQ4, LARS2, LHFPFL5, LOXHD1, LRTOMT, MARVELD2, MAS1P1, MITE, MSRB3, MT-RNR1, MYH14, MYO1A, MYO3A, MYO5D, MYO7A, OPA1, OSLBP2, OTA2, OTOF, OTOML, P2RX2, PAX2, PCDH15, PITX2, POLR1C, POLR1D, POLR3D, PRPS1, RDX, RIPOR2, RPS6KA3, SALL1, SALL4, SERPINC6, SI1X, SI5X, SLC17A8, SLC26A4, SLC26A5, SLC29A3, SLITRK6, SMPX, SOX10, SYNE1, TBC1D24, TCOF1, TECTA, TIMM8A, TJP2, TMC1, TMEM132E, TMIE, TMPRS53, TPRN, TRIOBP, TSPEAR, USH1C, USH1G, USH2A, WFS1, WHRN

Genes

| ABHD12 | ABHD5 | ACTG1 | ADCY1 | ADGRV1 | AIFM1 | ALMS1 | ATP6V1B1 | BSN1 | BTD | CABPB2 | CACNA1D | CCDC50 | CDH23 | CEACAM16 | CHD7 | CIB2 | CISO2 | CLDN14 | CLIC5 | CLPP | CLRN1 | COCH | COL11A2 | COL2A1 | COL4A3 | COL4A4 | COL4A5 | COL4A6 | COL9A1 | CRYP | DCDC2 | DIA1LQ | DIAP1 | DNM1 | DSSP | EDN3 | EDNRB | ELMOD3 | EPSP | ESR8 | EYA1 | EYA4 | FGFR3 | FOXC1 | FOX11 | GIPC3 | GJB2 | GJB3 | GJB6 | GNAS2 | GRHL2 | GRXCR1 | GSDME | HARS2 | HGF | HOMER2 | HSD17B4 | ILDR1 | IARS1 | KCNE1 | KCNJ10 | KCNQ1 | KCNQ4 | LARS2 | LHFPFL5 | LOXHD1 | LRTOMT | MARVELD2 | MAS1P1 | MITE | MSRB3 | MT-RNR1 | MYH14 | MYO1A | MYO3A | MYO5D | MYO7A | OPA1 | OSLBP2 | OTA2 | OTOF | OTOML | P2RX2 | PAX2 | PCDH15 | PITX2 | POLR1C | POLR1D | POLR3D | PRPS1 | RDX | RIPOR2 | RPS6KA3 | SALL1 | SALL4 | SERPINC6 | SI1X | SI5X | SLC17A8 | SLC26A4 | SLC26A5 | SLC29A3 | SLITRK6 | SMPX | SOX10 | SYNE1 | TBC1D24 | TCOF1 | TECTA | TIMM8A | TJP2 | TMC1 | TMEM132E | TMIE | TMPRS53 | TPRN | TRIOBP | TSPEAR | USH1C | USH1G | USH2A | WFS1 | WHRN |

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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 GJB6 gene 342kb deletion is detected by allele-specific amplification.

Copy Number Analysis: Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

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. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype. The GJB6 deletion component of this test will detect nearly all 342kb common deletion alleles in Connexin 30.

Analytical sensitivity for sequence variant detection is ~99%.

Copy Number Analysis: The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

Specimen Requirements

Submit only 1 of the following specimen types

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old): 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: DNA, Isolated

Specimen Requirements:
Microtainer
15µg
Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

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

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Related Tests

- Hearing Loss Panel: GJB2 and GJB6 Sequencing, GJB6 Common Deletion, and Targeted Mitochondrial Analysis
- Hearing Loss: GJB2 & GJB6 Gene Sequencing Panel
- Hearing Loss: GJB2 Gene Sequencing

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• Hearing Loss: GJB6 Gene Sequencing
• Hearing Loss: Deletion/Duplication Panel