Test Definition: AHLP

AudioloGene Hearing Loss Panel, Varies

Overview

Useful For

Establishing a diagnosis of a syndromic or nonsyndromic hereditary hearing loss disorder

Identifying variants within genes known to be associated with hereditary hearing loss, allowing for predictive testing of at-risk family members

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Genetics Test Information

Hereditary hearing loss is a genetically heterogeneous condition that can be either syndromic or nonsyndromic in origin.

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 200 genes associated with hereditary hearing loss: *ABHD12*, *ACTG1*, *ADCY1*, *ADGRV1* (GPR98), *AIFM1*, *ALMS1*, *ARSG*, *ATP2B2*, *ATP6V1B1*, *ATP6V1B2*, *BCS1L*, *BSND*, *BTD*, *CABP2*, *CACNA1D*, *CATSPER2*, *CCDC50*, *CD164*, *CDC14A*, *CDH23*, *CEACAM16*, *CEP250*, *CEP78*, *CHD7*, *CIB2*, *CISD2*, *CLDN14*, *CLIC5*, *CLPP*, *CLRN1*, *COCH*, *COL11A1*, *COL11A2*, *COL2A1*, *COL4A3*, *COL4A4*, COL4A5, *COL4A6*, *COL9A1*, *COL9A2*, *COL9A3*, *CRYL1*, *CRYM*, *DCDC2*, *DFNA5*, *DIABLO*, *DIAPH1*, *DIAPH3*, *DMXL2*, *DNMT*, *DSPP*, *EDN3*, *EDNRB*, *ELMOD3*, *EPS8*, *EPS8L2*, *ESPN*, *ESRRB*, *EYA1*, *EYA4*, *FDXR*, *FGF3*, *FGFR2*, *FGFR3*, *FITM2*, *FLNA*, *FOXC1*, *FOXI1*, *GATA3*, *GIPC3*, *GJB2* (DFNB1), *GJB6*, *GPSM2*, *GREB1L*, *GRHL2*, *GRXCR1*, *GRXCR2*, *HARS2*, *HGF*, *HOMER2*, *HOXA2*, *HSD17B4*, *ILDR1*, *KARS* (KARS1), *KCNE1*, *KCNJ10*, *KCNQ1*, *KCNQ4*, *KITLG*, *LARS2*, *LHFPL5*, *LMX1A*, *LOXHD1*, *LRP2*, *LRTOMT*, *MAN2B1*, *MANBA*, *MARVELD2*, *MCM2*, *MET*, *MIR96*, *MITF*, *MPZL2*, *MSRB3*, *MT-RNR1*, *MT-TS1*, *MYH14*, *MYH9*, *MYO15A*, *MYO3A*, *MYO6*, *MYO7A*, *NARS2*, *NDRG1*, *NF2*, *NLRP3*, *OPA1*, *OSBPL2*, *OTOA*, *OTOF*, *OTOG*, *OTOGL*, *P2RX2*, *PAX3*, *PCDH15*, *PDZD7*, *PEX1*, *PEX10*, *PEX11B*, *PEX12*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, *PEX2*, *PEX26*, *PEX3*, *PEX5*, *PEX6*, *PEX7*, *PHYH*, *PJVK* (DFNB59), *PLS1*, *PNPT1*, *POLR1B*, *POLR1C*, *POLR1D*, *POU3F4*, *POU4F3*, *PRPS1*, *PTPN11*, *PTPRQ*, *RAI1*, *RDX*, *RIPOR2* (FAM65B), *RMND1*, *S1PR2*, *SALL1*, *SERAC1*, *SERPINB6*, *SIX1*, *SLC12A2*, *SLC17A8*, *SLC19A2*, *SLC22A4*, *SLC26A4*, *SLC26A5*, *SLC29A3*, *SLC4A11*, *SLC52A2*, *SLC52A3*, *SLITRK6*, *SMPX*, *SNAI2*, *SOX10*, *SPATA5*, *STRC*, *SUCLA2*, *SYNE4*, *TBC1D24*, *TCOF1*, *TECTA*, *TFAP2A*, *TIMM8A*, *TJP2*, *TMC1*, *TMEM132E*, *TMIE*, *TMPRSS3*, *TNC*, *TPRN*, *TRIOBP*, *TUBB4B*, *TWNK*, *USH1C*, *USH1G*, *USH2A*, *WBP2*, *WFS1*, *WHRN*. See Targeted Genes and Methodology Details for AudioloGene Hearing Loss Panel and Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for hereditary hearing loss.

Testing Algorithm

For skin biopsy or cultured fibroblast specimens, fibroblast culture will be performed at an additional charge. If viable cells are not obtained, the client will be notified.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Molecular Genetics: Hereditary Hearing Loss Patient Information
- Targeted Genes and Methodology Details for AudioloGene Hearing Loss Panel

Method Name
Sequence Capture and Amplicon-Based Targeted Next-Generation Sequencing, Polymerase Chain Reaction (PCR), Digital Droplet PCR (ddPCR), Sanger Sequencing, and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the genes on this panel. For more information see FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Necessary Information
Molecular Genetics: Hereditary Hearing Loss Patient Information or a recent clinical note should be submitted along with the sample.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant
Specimen Volume: 3 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Skin biopsy
Supplies: Fibroblast Biopsy Transport Media (T115)
Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin.
Specimen Volume: 4-mm punch
Specimen Stability Information: Refrigerated (preferred)/Ambient
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Specimen Type: Cultured fibroblasts
Container/Tube: T-25 Flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured fibroblast cells from a skin biopsy from another laboratory. Cultured cells from a prenatal specimen will **not** be accepted.
Specimen Stability Information: Ambient (preferred)/Refrigerated (<24 hours)
Additional Information: A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing (Spanish) (T826)
2. Molecular Genetics Hereditary Hearing Loss Patient Information
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Reject Due To
All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information
Hereditary hearing loss encompasses a heterogeneous group of syndromic and nonsyndromic conditions. A comprehensive diagnostic genetic test is useful to help determine a molecular etiology for hearing loss and, therefore,

identify other organ systems that may be involved, establish long-term prognosis, and ascertain the inheritance pattern and recurrence risk within a family.

Individuals with syndromic hearing loss typically have other organ or organ system involvement and may have malformations of the external ear. Individuals with nonsyndromic hearing loss may have abnormalities of the middle ear or inner ear but typically do not have visible abnormalities of the external ear. Additionally, they often do not have additional organ system involvement or other related medical problems.

In developed countries, approximately 50% to 60% of individuals with congenital hearing loss have a genetic etiology. Of those, approximately 70% of individuals have a nonsyndromic condition, and the remaining 30% have one of over 400 syndromes involving hearing loss. Of the individuals with nonsyndromic hearing loss, at least three-quarters have an autosomal recessive condition, approximately 25% of whom have variants in the *GJB2* or *GJB6* genes.(1)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(2,3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions

(delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Refer to the Targeted Genes and Methodology Details for AudioloGene Hearing Loss Panel for the most up to date list of genes included in this test. For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(2,3) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Sloan-Heggen CM, Bierer AO, Shearer AE, et al: Comprehensive genetic testing in the clinical evaluation of 1119 patients with hearing loss. Hum Genet. 2016 Apr;135(4):441-450
2. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424
3. Oza AM, DiStefano MT, Hemphill SE, et al: Expert specification of the ACMG/AMP variant interpretation guidelines for genetic hearing loss. Hum Mutat. 2018 Nov;39(11):1593-1613
4. Alford RL, Arnos KS, Fox M, et al: American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med. 2014 Apr;16(4):347-355
5. DiStefano MT, Hemphill SE, Oza AM, et al: ClinGen expert clinical validity curation of 164 hearing loss gene-disease pairs. Genet Med. 2019 Oct;21(10):2239-2247
6. Morton CC, Nance WE: Newborn hearing screening-a silent revolution. N Engl J Med. 2006 May 18;354(20):2151-2164
7. Shearer AE, Hildebrand MS, Smith RJH: Hereditary hearing loss and deafness overview. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated July 27, 2017. Accessed October 25, 2022. Available at www.ncbi.nlm.nih.gov/books/NBK1434/

Performance

Method Description

Capture-based or amplicon-based next-generation sequencing (NGS) is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or multiplex ligation-dependent probe amplification is performed to test for the presence of deletions and duplications in the genes analyzed. Digital droplet polymerase chain reaction is performed to test for 3 mitochondrial variants.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

See Targeted Genes and Methodology Details for AudioloGene Hearing Loss Panel the for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.

Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ABHD12, ACTG1, ADCY1, ADGRV1 (GPR98), AIFM1, ALMS1, ARSG, ATP2B2, ATP6V1B1, ATP6V1B2, BCS1L, BSND, BTD, CABP2, CACNA1D, CATSPER2, CCDC50, CD164, CDC14A, CDH23, CEACAM16, CEP250, CEP78, CHD7, CIB2, CISD2, CLDN14, CLIC5, CLPP, CLRN1, COCH, COL11A1, COL11A2, COL2A1, COL4A3, COL4A4, COL4A5, COL4A6, COL9A1, COL9A2, COL9A3, CRYL1, CRYM, DCDC2, DIABLO, DIAPH1, DIAPH3, DMXL2, DNMT1, DSPP, EDN3, EDNRB, ELMOD3, EPS8, EPS8L2, ESPN, ESRRB, EYA1, EYA4, FDXR, FGF3, FGFR2, FGFR3, FITM2, FLNA, FOXC1, FOXI1, GATA3, GIPC3, GJB2 (DFNB1), GJB6, GPSM2, GREB1L, GRHL2, GRXCR1, GRXCR2, GSDME, HARS2, HGF, HOMER2, HOXA2, HSD17B4, ILDR1, KARS1, KCNE1, KCNJ10, KCNQ1, KCNQ4, KITLG, LARS2, LHFPL5, LMX1A, LOXHD1, LRP2, LRTOMT, MAN2B1, MANBA, MARVELD2, MCM2, MET, MIR96, MITF, MPZL2, MSRB3, MT-RNR1, MT-TS1, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, NARS2, NDRG1, NF2, NLRP3, OPA1, OSBPL2, OTOA, OTOF, OTOG, OTOGL, P2RX2, PAX3, PCDH15, PDZD7, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PHYH, PJVK, PLS1, PNPT1, POLR1B, POLR1C, POLR1D, POU3F4, POU4F3, PRPS1, PTPN11, PTPRQ, RAI1, RDX, RIPOR2, RMND1, S1PR2, SALL1, SERAC1, SERPINB6, SIX1, SLC12A2, SLC17A8, SLC19A2, SLC22A4, SLC26A4, SLC26A5, SLC29A3, SLC4A11, SLC52A2, SLC52A3, SLITRK6, SMPX, SNAI2, SOX10, SPATA5, STRC, SUCLA2, SYNE4, TBC1D24, TCOF1, TECTA, TFAP2A, TIMM8A, TJP2, TMC1, TMEM132E, TMIE, TMPRSS3, TNC, TPRN, TRIOBP, TUBB4B, TWNK, USH1C, USH1G, USH2A, WBP2, WFS1,* and *WHRN*

PDF Report
Supplemental

Day(s) Performed
Varies

Report Available
28 to 42 days

Specimen Retention Time
Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Cultured fibroblasts and skin biopsy: 1 month

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81430

81431
88233-Tissue culture, skin, solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
AHLP	AudioloGene Hearing Loss Panel	99972-2

Result ID	Test Result Name	Result LOINC® Value
619373	Test Description	62364-5
619374	Specimen	31208-2
619375	Source	31208-2
619376	Result Summary	50397-9
619377	Result	82939-0
619378	Interpretation	69047-9
619379	Additional Results	82939-0
619380	Resources	99622-3
619381	Additional Information	48767-8
619382	Method	85069-3
619383	Genes Analyzed	48018-6
619384	Disclaimer	62364-5
619385	Released By	18771-6