Hearing Loss

Hearing loss can be syndromic or nonsyndromic (NSHL) and may be a result of genetic, physiological, or disease factors. Depending on the cause, hearing loss may have a variable age of onset from birth to early childhood, and range in severity from mild to profound. A genetic cause is found in 50% of individuals born with hearing loss.

Disease Overview

Symptoms

- Hearing loss may be:
  - Prelingual or postlingual onset
  - Syndromic (associated with other findings) or nonsyndromic
  - Sensorineural, conductive, or mixed etiology
  - Variable in presentation based on genetic and environmental cause(s) of the hearing loss

Prevalence and/or Incidence

- 1/500 born with hearing loss
  - 50% of individuals with hearing loss have a genetic cause.
- 1/2,600 – NSHL
  - 50% are homozygous for *GJB2* variants.
  - 2-4% are compound heterozygous for *GJB2* variant and *GJB6* deletion.
  - Homozygous *GJB6* deletions are rare.
  - 1-2% have causative mitochondrial variants.

Genotype-Phenotype Correlation

- Hearing loss associated with *GJB2* (connexin 26) or *GJB6* (connexin 30) variants – bilateral and stable with prelingual onset
- Hearing loss and other manifestations associated with mitochondrial (mtDNA) variants vary in severity and age of onset
  - m.1555A>G – stable, severe to profound hearing loss with variable age of onset, predisposition to aminoglycoside ototoxicity
  - m.7445A>G – palmoplantar keratoderma and progressive, mild to severe hearing loss of childhood onset

Test Description

See Genes Tested table for genes included in the panel.

Tests to Consider

Expanded Hearing Loss Panel, Sequencing and Deletion/Duplication 2008803

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

- Most comprehensive genetic test for NSHL and syndromic hearing loss
- Recommended test for NSHL if *GJB2*, *GJB6*, and mitochondrial variant testing is negative
- Recommended test for syndromic hearing loss if symptoms are consistent with disorders included on the panel

Hearing Loss, Nonsyndromic Panel (GJB2) Sequencing, (GJB6) 2 Deletions and Mitochondrial DNA 2 Mutations 2001992

Method: Polymerase Chain Reaction/Capillary Electrophoresis/Sequencing

First-tier genetic test for individuals with NSHL

Connexin 26 (GJB2), Sequencing 0051374

Method: Polymerase Chain Reaction/Sequencing

- Diagnostic test or carrier screening for *GJB2*-related NSHL
- May be used as first-tier genetic test for individuals with NSHL

Hearing Loss, Nonsyndromic, Connexin 30 (GJB6) 2 Deletions 2001956

Method: Polymerase Chain Reaction/Capillary Electrophoresis

- Diagnostic test for individuals with NSHL and 1 identified *GJB2* variant

Clinical Sensitivity

- Hearing Loss, Nonsyndromic Panel (*GJB2*) Sequencing, (*GJB6*) 2 Deletions and Mitochondrial DNA 2 Mutations[1,2]
  - 50-55% for Caucasians with NSHL; unknown in other ethnicities
- Connexin 26 (*GJB2*) Sequencing[1]
  - 95% of *GJB2* pathogenic variants are detected[1]

Limitations

- A negative result does not exclude a heritable form of hearing loss.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *ESPN, GIPC3, ILDR1, LOXHD1, LRTOMT, MT-RNR1, OTOA, PDZD7, SIX1*
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *COCH* (NM_001347720) 2
    - *DNMT1* (NM_001130823) 5
    - *OTOA* (NM_144672) 20, 21, 22, 23, 24, 25, 26, 27, 28
    - *MT-RNR1*: targeted sequencing is performed for m.1555A>G only. Other variants in this gene will not be detected.
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Variants in *MT-RNR1* other than the targeted m.1555A>G variant
  - Heteroplasmy present at less than 25% for the *MT-RNR1* m.1555A>G variant
  - Single exon deletions/duplications in the following exons:

Gene	Exon(s)
CCDC50	(NM_178335) 1, 12
CDH23	(NM_022124) 28, 63
CLRN1	(NM_001195794) 3
CLRN1	(NM_001256819) 2
CLRN1	(NM_052995) 1, 4
COL11A2	(NM_080680) 62
DIAPH1	(NM_001314007) 29

- Carrier screening if family history of *GJB6* deletion or for reproductive partner of individual with *GJB6* or *GJB2* variants

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known.

Gene	Exon(s)
DIAPH1	(NM_005219) 18, 28
DNMT1	(NM_001130823) 1, 5, 41
HARS2	(NM_012208) 1
HSD17B4	(NM_000414) 24
HSD17B4	(NM_001199291) 1
KCNQ4	(NM_004700) 9
MASP1	(NM_139125) 1
MYH14	(NM_024729) 3, 13, 17, 24, 25, 30, 34
MYH9	(NM_002473) 13, 23, 29, 30, 39
MYO15A	(NM_016239) 25, 26, 33, 49, 62
MYO7A	(NM_000260) 17, 26, 29
OTOF	(NM_194248) 26
PCDH15	(NM_001142769) 13
RDX	(NM_001260495) 3
RDX	(NM_001260496) 5
RDX	(NM_002906) 6, 10
SLC26A4	(NM_000441) 21
SLC26A5	(NM_001321787) 19
SLC26A5	(NM_206884) 15
TMC1	(NM_138691) 6, 24
TMIE	(NM_147196) 1
TMPRSS3	(NM_024022) 4
TRIOBP	(NM_001039141) 14, 21
TRIOBP	(NM_138632) 8
USH1C	(NM_005709) 1
USH1C	(NM_153676) 26

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ACTG1	102560	Progressive sensorineural NSHL	AD
ADGRV1	602851	Usher syndrome type 1	AR
CCDC50	611051	Progressive sensorineural NSHL	AD
CDH23	605516	Stable NSHL Usher syndrome type 1	AR
CEACAM16	614591	Progressive sensorineural NSHL	AD
CLDN14	605608	Stable sensorineural NSHL	AR
CLRN1	606397	Retinitis pigmentosa Usher syndrome type 3	AR
COCH	603196	Postlingual, progressive sensorineural NSHL, with or without vestibular involvement	AD
COL11A2	120290	Sensorineural NSHL Otospondylomegaepiphyseal dysplasia (OSMED syndrome)	AR
		Sensorineural NSHL	AD
CRYM	123740	Sensorineural NSHL	AD
DIAPH1	602121	Progressive sensorineural NSHL	AD

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

Gene	MIM Number	Disorder	Inheritance
DNMT1	126375	Cerebellar ataxia, deafness, and Narcolepsy, autosomal dominant Neuropathy, hereditary sensory, type IE	AD
DSPP	125485	Progressive sensorineural hearing loss with dentinogenesis	AD
ESPN	606351	Sensorineural NSHL with or without vestibular involvement	AR or AD
ESRRB	602167	Sensorineural NSHL	AR
EYA4	603550	Progressive sensorineural NSHL	AD
GIPC3	608792	Stable NSHL	AR
GJB2 (connexin 26)	121011	Stable sensorineural NSHL	AR
		Progressive sensorineural NSHL Keratitis-ichthyosis-deafness (KID) syndrome Hystrix-like ichthyosis-deafness (HID) syndrome Vohwinkel syndrome Bart-Pumphrey syndrome	AD
GJB3	603324	Disorder Progressive sensorineural NSHL Erythrokeratodermia variabilis	AD
GJB6 (connexin 30)	604418	Stable sensorineural NSHL	AR
		Progressive sensorineural NSHL Hidrotic ectodermal dysplasia type 2/Clouston syndrome KID syndrome	AD
GPSM2	609245	Chudley-McCullough syndrome	AR
GRHL2	608576	Progressive, postlingual sensorineural hearing loss	AD
GSDME	608798	Progressive sensorineural NSHL	AD
HARS2	600783	Perrault syndrome 2	AR
HSD17B4	601860	Perrault syndrome 1 D-bifunctional protein deficiency	AR
ILDR1	609739	Stable sensorineural NSHL	AR

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Gene	MIM Number	Disorder	Inheritance
KCNQ4	603537	Progressive sensorineural NSHL	AD
LHFPL5	609427	Stable NSHL	AR
LOXHD1	613072	Progressive sensorineural NSHL	AR
LRTOMT	612414	Sensorineural NSHL	AR
MARVELD2	610572	Stable NSHL	AR
MASP1	600521	3MC syndrome 1	AR
MYH14	608568	Progressive sensorineural NSHL Peripheral neuropathy, myopathy, hoarseness, and hearing loss	AD
MYH9	160775	Progressive sensorineural NSHL Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss	AD
MYO15A	602666	Sensorineural NSHL	AR
MYO3A	606808	Progressive NSHL	AR
MYO6	600970	Progressive sensorineural NSHL	AD
		NSHL	AR
MYO7A	276903	Progressive sensorineural NSHL	AD
		Sensorineural NSHL Usher syndrome type 1	AR
OTOA	607038	Stable sensorineural NSHL	AR
OTOF	603681	Stable sensorineural NSHL Nonsyndromic auditory neuropathy (NSAN)	AR
PCDH15	605514	Stable sensorineural NSHLS Usher syndrome type 1	AR
PDZD7	612971	Usher syndrome, type 2 Sensorinerual NSHL	AR

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Gene	MIM Number	Disorder	Inheritance
PJVK	610219	Sensorineural NSHL	AR
POU3F4	300039	NSHL	XL
POU4F3	602460	Progressive sensorineural NSHL	AD
RDX	179410	Stable sensorineural NSHL	AR
SIX1	601205	NSHL Branchiootic syndrome 3	AD
SLC26A4	605646	Stable or progressive NSHL with enlarged vestibular aqueduct Pendred syndrome	AR
SLC26A5	604943	Stable sensorineural NSHL	AR
SMPX	300226	Progressive sensorineural hearing loss	XL
TECTA	602574	Sensorineural NSHL	AR or AD
TMC1	606706	Progressive sensorinerual NSHL	AD
		Stable sensorineural NSHL	AR
TMIE	607237	Stable sensorineural NSHL	AR
TMPRSS3	605511	Sensorineural NSHL	AR
TPRN	613354	Progressive sensorineural NSHL	AR
TRIOBP	609761	Stable sensorineural NSHL	AR
USH1C	605242	Stable sensorineural NSHL; Usher syndrome type 1	AR
USH1G	607696	Usher syndrome type 1	AR
USH2A	608400	Usher syndrome type 2; Retinitis pigmentosa	AR
WFS1	606201	Progressive sensorineural NSHL, Wolfram-like syndrome	AD
		Wolfram syndrome	AR
WHRN	607928	Sensorineural NSHL Usher syndrome type 2	AR

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

References

1. Smith RJH, Jones MKN. Nonsyndromic Hearing Loss and Deafness, DFNB1. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Aug 2016; Accessed: Feb 2020]

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3. Shearer AE, Hildebrand MS, Smith RJH. Hereditary Hearing Loss and Deafness Overview. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Jul 2017; Accessed: Feb 2020]

Related Information

Hereditary Nonsyndromic Hearing Loss - Connexin 26 or 30

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