

## 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.

#### Clinical Sensitivity

- Hearing Loss, Nonsyndromic Panel (*GJB2*) Sequencing, (*GJB6*) 2 Deletions and Mitochondrial DNA 2 Mutations (Smith, 2016; Usami, 2018)
  - 50-55% for Caucasians with NSHL; unknown in other ethnicities
- Connexin 26 (*GJB2*) Sequencing (Smith, 2016)
  - 95% of *GJB2* pathogenic variants are detected (Smith, 2016)

#### Limitations

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

#### [Hearing Loss, Nonsyndromic, Mitochondrial DNA 2 Mutations](#)

- 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)
<i>CCDC50</i>	(NM_178335) 1, 12
<i>CDH23</i>	(NM_022124) 28, 63
<i>CLRN1</i>	(NM_001195794) 3
<i>CLRN1</i>	(NM_001256819) 2
<i>CLRN1</i>	(NM_052995) 1, 4
<i>COL11A2</i>	(NM_080680) 62
<i>DIAPH1</i>	(NM_001314007) 29
<i>DIAPH1</i>	(NM_005219) 18, 28
<i>DNMT1</i>	(NM_001130823) 1, 5, 41
<i>HARS2</i>	(NM_012208) 1
<i>HSD17B4</i>	(NM_000414) 24
<i>HSD17B4</i>	(NM_001199291) 1
<i>KCNQ4</i>	(NM_004700) 9
<i>MASP1</i>	(NM_139125) 1
<i>MYH14</i>	(NM_024729) 3, 13, 17, 24, 25, 30, 34
<i>MYH9</i>	(NM_002473) 13, 23, 29, 30, 39
<i>MYO15A</i>	(NM_016239) 25, 26, 33, 49, 62
<i>MYO7A</i>	(NM_000260) 17, 26, 29
<i>OTOF</i>	(NM_194248) 26
<i>PCDH15</i>	(NM_001142769) 13
<i>RDX</i>	(NM_001260495) 3
<i>RDX</i>	(NM_001260496) 5
<i>RDX</i>	(NM_002906) 6, 10
<i>SLC26A4</i>	(NM_000441) 21
<i>SLC26A5</i>	(NM_001321787) 19
<i>SLC26A5</i>	(NM_206884) 15
<i>TMC1</i>	(NM_138691) 6, 24
<i>TMIE</i>	(NM_147196) 1
<i>TMPRSS3</i>	(NM_024022) 4

#### 2002044

Method: Polymerase Chain Reaction/Sequencing

- Diagnostic test for individuals with NSHL and no identified variants in *GJB2* or *GJB6*
- Carrier screening if family history of m.1555A>G or m.7445A>G

#### Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

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

Gene	Exon(s)
<i>TRIOBP</i>	(NM_001039141) 14, 21
<i>TRIOBP</i>	(NM_138632) 8
<i>USH1C</i>	(NM_005709) 1
<i>USH1C</i>	(NM_153676) 26

### Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%)	Analytical Sensitivity (PPA) 95% Credibility Region <sup>a</sup> (%)
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

<sup>a</sup>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
<i>ACTG1</i>	102560	Progressive sensorineural NSHL	AD
<i>ADGRV1</i>	602851	Usher syndrome type 1	AR
<i>CCDC50</i>	611051	Progressive sensorineural NSHL	AD
<i>CDH23</i>	605516	Stable NSHL Usher syndrome type 1	AR
<i>CEACAM16</i>	614591	Progressive sensorineural NSHL	AD
<i>CLDN14</i>	605608	Stable sensorineural NSHL	AR
<i>CLRN1</i>	606397	Retinitis pigmentosa Usher syndrome type 3	AR
<i>COCH</i>	603196	Postlingual, progressive sensorineural NSHL, with or without vestibular involvement	AD
<i>COL11A2</i>	120290	Sensorineural NSHL	AR
		Otospondylomegaepiphyseal dysplasia (OSMED syndrome) Sensorineural NSHL	AD
<i>CRYM</i>	123740	Sensorineural NSHL	AD
<i>DIAPH1</i>	602121	Progressive sensorineural NSHL	AD
<i>DNMT1</i>	126375	Cerebellar ataxia, deafness, and Narcolepsy, autosomal dominant Neuropathy, hereditary sensory, type IE	AD
<i>DSPP</i>	125485	Progressive sensorineural hearing loss with dentinogenesis	AD
<i>ESPN</i>	606351	Sensorineural NSHL with or without vestibular involvement	AR or AD
<i>ESRRB</i>	602167	Sensorineural NSHL	AR
<i>EYA4</i>	603550	Progressive sensorineural NSHL	AD
<i>GIPC3</i>	608792	Stable NSHL	AR
<i>GJB2 (connexin 26)</i>	121011	Stable sensorineural NSHL	AR

Gene	MIM Number	Disorder	Inheritance
		Progressive sensorineural NSHL Keratitis-ichthyosis-deafness (KID) syndrome Hystrix-like ichthyosis-deafness (HID) syndrome Vohwinkel syndrome Bart-Pumphrey syndrome	AD
<b>GJB3</b>	603324	Progressive sensorineural NSHL Erythrokeratoderma variabilis	AD
<b>GJB6 (connexin 30)</b>	604418	Stable sensorineural NSHL	AR
		Progressive sensorineural NSHL Hidrotic ectodermal dysplasia type 2/Clouston syndrome KID syndrome	AD
<b>GPSM2</b>	609245	Chudley-McCullough syndrome	AR
<b>GRHL2</b>	608576	Progressive, postlingual sensorineural hearing loss	AD
<b>GSDME</b>	608798	Progressive sensorineural NSHL	AD
<b>HARS2</b>	600783	Perrault syndrome 2	AR
<b>HSD17B4</b>	601860	Perrault syndrome 1	AR
		D-bifunctional protein deficiency	
<b>ILDR1</b>	609739	Stable sensorineural NSHL	AR
<b>KCNQ4</b>	603537	Progressive sensorineural NSHL	AD
<b>LHFPL5</b>	609427	Stable NSHL	AR
<b>LOXHD1</b>	613072	Progressive sensorineural NSHL	AR
<b>LRTOMT</b>	612414	Sensorineural NSHL	AR
<b>MARVELD2</b>	610572	Stable NSHL	AR
<b>MASP1</b>	600521	3MC syndrome 1	AR
<b>MYH14</b>	608568	Progressive sensorineural NSHL	AD
		Peripheral neuropathy, myopathy, hoarseness, and hearing loss	
<b>MYH9</b>	160775	Progressive sensorineural NSHL	AD
		Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss	
<b>MYO15A</b>	602666	Sensorineural NSHL	AR
<b>MYO3A</b>	606808	Progressive NSHL	AR
<b>MYO6</b>	600970	Progressive sensorineural NSHL	AD
		NSHL	AR
<b>MYO7A</b>	276903	Progressive sensorineural NSHL	AD
		Sensorineural NSHL	AR
		Usher syndrome type 1	
<b>OTOA</b>	607038	Stable sensorineural NSHL	AR
<b>OTOF</b>	603681	Stable sensorineural NSHL	AR
		Nonsyndromic auditory neuropathy (NSAN)	
<b>PCDH15</b>	605514	Stable sensorineural NSHLS	AR
		Usher syndrome type 1	

Gene	MIM Number	Disorder	Inheritance
<b>PDZD7</b>	612971	Usher syndrome, type 2 Sensorineural NSHL	AR
<b>PJVK</b>	610219	Sensorineural NSHL	AR
<b>POU3F4</b>	300039	NSHL	XL
<b>POU4F3</b>	602460	Progressive sensorineural NSHL	AD
<b>RDX</b>	179410	Stable sensorineural NSHL	AR
<b>SIX1</b>	601205	NSHL Branchiotoxic syndrome 3	AD
<b>SLC26A4</b>	605646	Stable or progressive NSHL with enlarged vestibular aqueduct Pendred syndrome	AR
<b>SLC26A5</b>	604943	Stable sensorineural NSHL	AR
<b>SMPX</b>	300226	Progressive sensorineural hearing loss	XL
<b>TECTA</b>	602574	Sensorineural NSHL	AR or AD
<b>TMC1</b>	606706	Progressive sensorineural NSHL	AD
		Stable sensorineural NSHL	AR
<b>TMIE</b>	607237	Stable sensorineural NSHL	AR
<b>TMPRSS3</b>	605511	Sensorineural NSHL	AR
<b>TPRN</b>	613354	Progressive sensorineural NSHL	AR
<b>TRIOBP</b>	609761	Stable sensorineural NSHL	AR
<b>USH1C</b>	605242	Stable sensorineural NSHL; Usher syndrome type 1	AR
<b>USH1G</b>	607696	Usher syndrome type 1	AR
<b>USH2A</b>	608400	Usher syndrome type 2; Retinitis pigmentosa	AR
<b>WFS1</b>	606201	Progressive sensorineural NSHL, Wolfram-like syndrome	AD
		Wolfram syndrome	AR
<b>WHRN</b>	607928	Sensorineural NSHL Usher syndrome type 2	AR

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

## REFERENCES

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## RELATED INFORMATION

[Hereditary Nonsyndromic Hearing Loss - Connexin 26 or 30](#)

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