Hearing Loss

Indications for Ordering

Confirm diagnosis or determine etiology of nonsyndromic (NSHL) or syndromic hearing loss

Test Description

Expanded Hearing Loss Panel, Sequencing and Deletion/Duplication

- Targeted capture of all coding exons and exon-intron junctions followed by massively parallel sequencing of all genes listed in table below
  - Sanger sequencing is used to provide data for bases with insufficient coverage
  - All clinically significant variants are confirmed by independent Sanger sequencing
- Tiled custom comparative genomic hybridization array detects large deletions or duplications within all genes listed in table below except *ESPN*, *OTOA*, and *STRC*

GJB2 (connexin 26) sequencing

- Bidirectional sequencing of entire coding region, exon/intron boundaries, and 5'-UTR

GJB6 (connexin 30) – two deletions

- Multiplex polymerase chain reaction (PCR) with deletion-specific primers followed by capillary gel electrophoresis
- Targets two variants
  - 309kb deletion (previously known as 342kb)
  - 232kb deletion

Mitochondrial DNA (mtDNA) – two variants

- Targeted bidirectional sequencing for two mitochondrial DNA variants
  - mt-RNR1, m.1555A>G
  - mt-TS1, m.7445A>G

Tests to Consider

Primary tests

Expanded Hearing Loss Panel, Sequencing and Deletion/Duplication 2008803

- 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

- First-tier genetic test for individuals with NSHL

Connexin 26 (*GJB2*), Sequencing 0051374

- 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

- Diagnostic test for individuals with NSHL and one 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 2002044

- 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

Related tests

Familial Mutation, Targeted Sequencing 2001961

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

Disease Overview

Prevalence and/or incidence

- 1/500 born with hearing loss
  - Due to genetic cause – 50%
- 1/2,600 – NSHL
  - Homozygous for *GJB2* variants – 50%
  - Compound heterozygous for *GJB2* variant and *GJB6* deletion – 2-4%
  - Homozygous for *GJB6* deletions – rare
  - Mitochondrial variants – 1-2%

Symptoms – see table for related disorders and phenotypes

- Hearing loss may be
  - Prelingual or postlingual onset
  - Syndromic (associated with other findings) or nonsyndromic
  - Sensorineural, conductive, or mixed etiology
  - Autosomal recessive, autosomal dominant, X-linked, or multifactorial/environmental
  - Variable presentation based on genetic and environmental cause(s) of the hearing loss
- 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

Genetics

Genes – see table for gene-specific information

Variants

- *GJB2* c.35delG – most common *GJB2* pathogenic variant in persons of Northern European ancestry
- *GJB6* – hearing loss results from either two *GJB6* deletions (rare) or one *GJB6* deletion and one *GJB2* variant on the opposite chromosome

Test Interpretation

Clinical sensitivity – depends on disorder

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

Results

- Positive
  - One pathogenic variant detected in an autosomal dominant (AD) gene
    - Causative for hearing loss
  - One pathogenic variant detected in an autosomal recessive (AR) gene
    - Individual is a carrier of AR hearing loss
  - One pathogenic variant detected in an X-linked gene
    - Causative for hearing loss in males
    - Females are carriers
  - Two pathogenic variants detected in AR gene
    - Causative for hearing loss
  - mtDNA variant present – may cause NSHL
- Negative
  - No causative variants identified
    - Cause of hearing loss unknown, refer to limitations
- Inconclusive
  - Variant(s) of uncertain clinical significance
    - Unable to determine if detected variants are benign or pathogenic
    - Definitive cause of hearing loss unknown

Limitations

- A negative result does not exclude a diagnosis of hereditary hearing loss
- Not determined or evaluated
  - Regulatory region variants
  - Deep intronic variants
  - Variants in genes not targeted
- Diagnostic errors can occur due to rare sequence variations
- Large deletions or duplications are not detected in *ESPN*, *OTOA*, and *STRC* genes, or in exon 5 of *DNMT1* gene or exon 18 of *DIAPH1* gene
- Small deletions or insertions may not be detected by massively parallel sequencing
- Due to the high homology with pseudogenes some of the functional gene variants in the following genes may be missed
  - *ADGRV1*
  - *DSPP*
  - *ESPN*
  - *KCNQ4*
  - *MYO15A*
  - *STRC*
  - *TRIOBP*
  - *WSF1*
- In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions

Gene Symbol	Gene Name	Locus	NM #	OMIM #	Inh.	Associated Phenotype or Syndrome
ACTG1	Actin, gamma 1	DFNA20/DFNA26	001614	102560	AD	Progressive sensorineural NSHL
ADGRV1	Adhesion G protein-coupled receptor V1	USH2C	032119	602851	AR	Usher syndrome type 2; familial febrile seizures
CCDC50	Coiled-coil domain containing 50	DFNA44	178335	611051	AD	Progressive sensorineural NSHL

Gene Symbol	Gene Name	Locus	NM #	OMIM #	Inh.	Associated Phenotype or Syndrome
CDH23	Cadherin related 23	DFNB12/USH1D	022124	605516	AR	Stable NSHL; Usher syndrome type 1
CEACAM16	Carcinoembryonic antigen-related cell adhesion molecule 16	DFNA4B	001039213	614591	AD	Progressive sensorineural NSHL
CLDN14	Claudin 14	DFNB29	012130	605608	AR	Stable sensorineural NSHL
CLRN1	Clarin 1; Usher syndrome type-3 protein	USH3A	174878	606397	AR	Retinitis pigmentosa, Usher syndrome type 3
COCH	Coagulation factor C homolog, cochlin	DFNA9	004086	603196	AD	Postlingual, progressive sensorineural NSHL with or without vestibular involvement
COL11A2	Collagen, type XI, alpha 2	DFNA13	080680	120290	AD	Sensorineural NSHL; Stickler syndrome type 3, Weissenbacher-Zweymuller syndrome
		DFNB53			AR	Sensorineural NSHL; otospondylomegaepiphyseal dysplasia (OSMED syndrome)
CRYM	Crystallin, mu	DFNA40	001888	123740	AD	Sensorineural NSHL
DFNA5	Deafness, autosomal dominant 5	DFNA5	004403	608798	AD	Progressive sensorineural NSHL
DFNB59	Deafness, autosomal recessive 59	DFNB59	001042702	610219	AR	Sensorineural NSHL
DIAPH1	Diaphanous related formin 1	DFNA1	005219	602121	AD	Progressive sensorineural NSHL, with or without thrombocytopenia
DNMT1	DNA (cytosine-5-)-methyltransferase 1		001130823	126375	AD	Hereditary sensory neuropathy type IE (HSNIE)/*DNMT1*-related dementia, deafness, and sensory neuropathy
DSPP	Dentin sialophosphoprotein	DFNA39	014208	125485	AD	Progressive NSHL,dentinogenesis imperfecta
ESPN	Espin	DFNB36	031475	606351	AR	Sensorineural NSHL with or without vestibular involvement
					AD	Sensorineural NSHL without vestibular involvement
ESRRB	Estrogen-related receptor beta	DFNB35	004452	602167	AR	Sensorineural NSHL
EYA4	Eyes absent homolog 4 (Drosophila)	DFNA10	004100	603550	AD	Progressive sensorineural NSHL; dilated cardiomyopathy type 1J
GJB2 (connexin 26)	Gap junction protein, beta 2, 26kDa	DFNA3	004004	121011	AD	Progressive sensorineural NSHL; keratitis-ichthyosis-deafness (KID) syndrome; Hystrix-like ichthyosis-deafness (HID) syndrome; Vohwinkel syndrome; Bart-Pumphrey syndrome
		DFNB1			AR	Stable sensorineural NSHL
GJB3	Gap junction protein, beta 3, 31kDa	DFNA2B	024009	603324	AD	Progressive sensorineural NSHL; erythrokeratodermia variabilis
GJB6 (connexin 30)	Gap junction protein, beta 6, 30kDa	DFNA3	006783	604418	AD	Progressive sensorineural NSHL; Hidrotic ectodermal dysplasia type 2/Clouston syndrome; KID syndrome
		DFNB1			AR	Stable sensorineural NSHL
GPSM2	G-protein signaling modulator 2	DFNB32/DFNB82	013296	609245	AR	Chudley-McCullough syndrome
GRHL2	Grainyhead-like 2 (Drosophila)	DFNA28	024915	608576	AD	Progressive, postlingual sensorineural hearing loss
HARS2	Histidyl-tRNA synthetase 2, mitochondrial		012208	600783	AR	Perrault syndrome type 2
HSD17B4	Hydroxysteroid (17-beta) dehydrogenase 4		001199291	601860	AR	Perrault syndrome type 1, D-bifunctional protein deficiency
KCNQ4	Potassium voltage-gated channel, KQT-like subfamily, member 4	DFNA2	004700	603537	AD	Progressive sensorineural NSHL
LHFPL5	Lipoma HMGIC fusion partner-like 5	DFNB67	182548	609427	AR	Stable NSHL

Gene Symbol	Gene Name	Locus	NM #	OMIM #	Inh.	Associated Phenotype or Syndrome
MARVELD2	MARVEL domain containing 2	DFNB49	001038603	610572	AR	Stable NSHL
MASP1	Mannan-binding lectin serine peptidase 1		001879	600521	AR	3MC syndrome 1
MYH14	Myosin heavy chain 14	DFNA4A	024729	608568	AD	Progressive sensorineural NSHL; peripheral neuropathy, myopathy, hoarseness, and hearing loss
MYH9	Myosin, heavy chain 9, nonmuscle	DFNA17	002473	160775	AD	Progressive sensorineural NSHL; *MYH9*-related syndromes (Epstein syndrome, Fechtner syndrome, May-Hegglin anomaly, and Sebastian syndrome)
MYO15A	Myosin XVA	DFNB3	016239	602666	AR	Sensorineural NSHL
MYO1A	Myosin IA	DFNA48	005379	601478	AD	Progressive NSHL
MYO3A	Myosin IIIA	DFNB30	017433	606808	AR	Progressive NSHL
MYO6	Myosin VI	DFNA22	004999	600970	AD	Progressive sensorineural NSHL
		DFNB37			AR	NSHL
MYO7A	Myosin VIIA	DFNA11	000260	276903	AD	Progressive sensorineural NSHL
		DFNB2/USH1B			AR	Sensorineural NSHL; Usher syndrome type 1
OTOA	Otoancorin	DFNB22	144672	607038	AR	Stable sensorineural NSHL
OTOF	Otoferlin	DFNB9	194248	603681	AR	Stable sensorineural NSHL; nonsyndromic auditory neuropathy (NSAN)
PCDH15	Protocadherin related 15	DFNB23/USH1F	033056	605514	AR	Stable sensorineural NSHL; Usher syndrome type 1
POU4F3	POU class 4 homeobox 3	DFNA15	002700	602460	AD	Progressive sensorineural NSHL
RDX	Radixin	DFNB24	002906	179410	AR	Stable sensorineural NSHL
SLC26A4	Solute carrier family 26, member 4	DFNB4	000441	605646	AR	Stable or progressive NSHL with enlarged vestibular aqueduct; Pendred syndrome
SLC26A5	Solute carrier family 26, member 5	DFNB61	198999	604943	AR	Stable sensorineural NSHL
SMPX	Small muscle protein, X-linked	DFNX4 (DFN6)	014332	300226	XL	Progressive sensorineural hearing loss
STRC	Stereocilin	DFNB16	153700	606440	AR	Stable sensorinerual NSHL
TECTA	Tectorin alpha	DFNA8/DFNA12	005422	602574	AD	Sensorineural NSHL
		DFNB21			AR	Sensorineural NSHL
TMC1	Transmembrane channel-like 1	DFNA36	138691	606706	AD	Progressive NSHL
		DFNB7/DFNB11			AR	Stable sensorineural NSHL
TMIE	Transmembrane inner ear	DFNB6	147196	607237	AR	Stable sensorineural NSHL
TMPRSS3	Transmembrane protease, serine 3	DFNB8/DFNB10	024022	605511	AR	Sensorineural NSHL
TPRN	Taperin	DFNB79	001128228	613354	AR	Progressive sensorineural NSHL
TRIOBP	TRIO and F-actin binding protein	DFNB28	001039141	609761	AR	Stable sensorineural NSHL
USH1C	Usher syndrome 1C	DFNB18	153676	605242	AR	Stable sensorineural NSHL; Usher syndrome type 1
USH1G	Usher syndrome 1G		173477	607696	AR	Usher syndrome type 1
USH2A	Usher syndrome 2A		206933	608440	AR	Usher syndrome type 2; retinitis pigmentosa
WFS1	Wolfram syndrome 1 (wolframin)	DFNA6/DFNA14/ DFNA38	006005	606201	AD	Progressive sensorineural NSHL, Wolfram-like syndrome
					AR	Wolfram syndrome
WHRN	Whirlin	DFNB31/USH2D	015404	607928	AR	Sensorineural NSHL; Usher syndrome type 2

AD, autosomal dominant; AR, autosomal recessive; Inh., inheritance; XL, X-linked