Hearing Loss Panel

Test Gene List:
ABHD12, ACTB, ACTG1, ADCY1, AIFM1, ALMS1, ANKH, ATP6V1B1, BDP1, BSND, CABP2, CACNA1D, CCDC50, CD164, CDC14A, CDH23, CEACAM16, CHD7, CIB2, CLDN14, CLIC5, CLPP, CLRN1, COCH, COL2A1, COL11A1, COL11A2, COL4A3, COL4A4, COL4A5, COL4A6, CRYM, DCDC2, DFNA5, DIABLO, DIAPH1, DIAPH3, DNMT1, DSPP, EDN3, EDNRB, ELMOD3, EPS8, ESPN, ESRRB, EYA1, EYA4, FAM65B, FGF3, FGFR1, FGFR2, FGFR3, FOXI1, GATA3, GIPC3, GJA1, GJB2, GJB3, GJB6, GPR98, GPSM2, GRHL2, GRXCR1, HARS, HARS2, HGF, HOMER2, HSD17B4, ILDR1, KARS, KCNE1, KCNJ10, KCNQ1, KCNQ4, KITLG, LARS2, LHFPL5, LRTOMT, MARVELD2, MCM2, MIR96, MITF, MSRB3, MT-CO1, MT-RNR1, MT-TL1, MT-TS1, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, NDP, NLRP3, OPA1, OSBPL2, OTOA, OTOF, OTOG, OTOGL, P2RX2, PAX3, PCDH15, PDZD7, DFNB59, PMP22, PNPT1, POU3F4, POU4F3, POLR1D, PRPS1, PTPRQ, RDX, S1PR2, SALL1, SEMA3E, SERPINB6, SIX1, SIX5, SLC17A8, SLC26A4, SLC26A5, SLC33A1, SLITRK6, SMPX, SNAI2, SOX10, SOX2, STRC, SYNE4, TBC1D24, TBX1, TCOF1, TECTA, TIMM8A, TFAP2A, TJP2, TMC1, TMIE, TMPRSS3, TNC, TPRN, TRIOBP, TSPEAR, USH1C, USH1G, USH2A, WFS1, WHRN

Panel summary:
The GeneDx Hearing Loss Test comprises 146 nuclear genes and 6 variants in 4 mitochondrial genes accounting mainly for nonsyndromic forms of hearing loss and select genetic syndromes associated with hearing loss. Genes were carefully vetted and selected for their relevance to the condition and quality of the existing literature.

Clinical Features and Genetics:
Hearing loss is relatively common, affecting approximately 1 to 3 per 1000 infants.[1,2] Extremely heterogeneous in nature, hearing loss can be characterized by the affected structures of the ear, age of onset, and whether other organ systems are implicated[3]. The onset of hearing loss may be prelingual, with occurrence before normal speech development, or postlingual after normal speech development. There are three types of the hearing loss, conductive, sensorineural, and mixed. Of those three types of hearing loss, the most common is sensorineural[5]. Sensorineural hearing loss may be either syndromic or nonsyndromic. The majority of sensorineural hearing loss (~70%) is nonsyndromic.[5,6]

Genetic testing can be a very important and informative step in the diagnosis of hearing loss. Identification of one or more pathogenic variants in a specific gene or genes can provide the physician and family with important information regarding prognosis, treatment, and recurrence

risk in future offspring. It also provides other family members the option for variant-specific carrier testing and genetic counseling.

Inheritance Pattern:
Hearing loss can occur in a syndromic or non-syndromic context. Depending on the genetic cause, hearing loss can be inherited in an autosomal dominant, autosomal recessive, X-linked, or mitochondrial manner. Digenic inheritance has been reported.

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; copy number testing also includes common recurrent deletions involving the GJB2 and GJB6 genes, known to be associated with DFNB1. For the TBX1 gene, sequencing but not deletion/duplication analysis is performed. For the STRC gene, deletion/duplication analysis, but not sequencing, is performed. Only whole gene deletions/duplications will be reported for the ACTB, ESPN, and TPRN genes. Sequence analysis of the PTPRQ, DSPP, TRIOBP and OTOA genes has reduced sensitivity due to homology issues. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Concurrent targeted testing for 6 mitochondrial variants (MT-CO1: m.7445A>G; MT-RNR1: m.1555 A>G; m.1494 C>T; MT-TL1: m.3243 A>G; m.3291 T>C; MT-TS1: m.7511T>C) is also performed. Multiplex ligation-dependent probe amplification (MLPA) is used to detect common large deletions and duplications involving the STRC and OTOA genes. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Test Sensitivity:

Over 400 genes have been implicated in syndromic hearing loss, accounting for up to 30% of prelingual sensorineural hearing loss.[8] Additionally, over 90 genes have been implicated in nonsyndromic sensorineural hearing loss, with up to 80% of prelingual nonsyndromic hearing loss inherited in an autosomal recessive fashion, followed by dominant and X-linked inheritance in terms of relative frequency.[4,5,6,9] In individuals with autosomal recessive nonsyndromic hearing loss, approximately 50% have a variant associated with DFNB1, caused by pathogenic variants in the GJB2/GJB6 genes.[9] Clear statistics on postlingual nonsyndromic hearing loss are not yet available; however, autosomal dominant inheritance is commonly reported. The clinical sensitivity of this panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity of this test is highest for individuals with clearly defined hearing loss, family history of the disorder, and no history of environmental exposures. Specific information about the diagnostic yield for each gene in selected populations is summarized in the attached table.

References:

1. Morton et al. (2006) N. Engl. J. Med. 354 (20):2151-64 (PMID: 16707752)
2. Wroblewska-Seniuk et al. (2017) Pediatr. Res. : (PMID: 27861465)
3. Hilgert et al. (2009) Mutat. Res. 681 (2-3):189-96 (PMID: 18804553)
4. Sloan-Heggen et al. (2016) Hum. Genet. 135 (4):441-50 (PMID: 26969326)
5. Shearer et al. (2010) Proceedings Of The National Academy Of Sciences Of The United States Of America 107 (49):21104-9 (PMID: 21078986)
6. Sommen et al. (2016) Hum. Mutat. 37 (8):812-9 (PMID: 27068579)
7. Venkatesh et al. (2015) Med J Armed Forces India 71 (4):363-8 (PMID: 26663965)
8. Kochhar et al. (2007) Genet. Med. 9 (7):393-408 (PMID: 17666886)
9. Martínez et al. (2009) Antioxid. Redox Signal. 11 (2):309-22 (PMID: 18837651)

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
ABHD12	AR		Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)
ACTB	AD	79% of Baraitser-Winter syndrome (25052316)	Baraitser-Winter Syndrome
ACTG1	AD	21% of Baraitser-Winter syndrome (25052316)	Baraitser-Winter Syndrome / DFNA20 / DFNA26
ADCY1	AR		DFNB44
AIFM1	XLR	11/93 men with auditory neuropathy spectrum disorder (ANSD) (25986071)	Charcot-Marie-Tooth disease type 4 (CMTX4) / Auditory neuropathy spectrum disorder (ANSD)
ALMS1	AR	8/12 individuals with Alstrom syndrome harbored two pathogenic variants (16720663)	Alstrom syndrome
ANKH	AD	13/19 families and individuals with craniometaphyseal dysplasia (11326272, 11326338)	Craniometaphyseal dysplasia
ATP6V1B1	AR		Renal tubular acidosis with hearing loss
BDP1	AR		DFNB112
BSND	AR		Bartter Syndrome / SNHL with mild renal dysfunction

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
CABP2	AR		DFNB93
CACNA1D	AD/AR		Sinoatrial node dysfunction and deafness (SANDD) / Bradycardia and congenital hearing loss
CCDC50	AD		DFNA44
CD164	AD		DFNA66
CDC14A	AR		DFNB32 / AR deafness with or without immotile sperm
CDH23	AR	19%-35% of individuals with Usher syndrome type 1 (21234346)	Usher Syndrome Type 1 / DFNB12
CEACAM16	AD		DFNA4B
CHD7	AD	60-65% of CHARGE syndrome (15300250, 16155193, 16400610); 10% of Kallmann syndrome and 6% of IHH (19707180, 21209029)	CHARGE Syndrome / Kallmann Syndrome / Idiopathic Hypogonadotropic Hypogonadism (IHH)
CIB2	AR		Usher Syndrome Type 1J / DFNB48
CLDN14	AR	2.25% (18/800 families tested) (23235333)	DFNB29
CLIC5	AR		DFNB103
CLPP	AR	6/51 families with Perrault Syndrome (27650058)	Perrault Syndrome
CLRN1	AR	All individuals diagnosed with Usher syndrome type 3 had variants in the CLRN1 (USH3A) gene (21234346)	Usher Syndrome Type 3A / Retinitis Pigmentosa
COCH	AD	36.8% in Dutch and Belgian; In Japanese population 23 pts. w/ AD hearing loss and 20 pts. w/ Meniere's (28000701; 14512963)	DFNA9
COL11A1	AD/AR	10-20% of Stickler syndrome (20301479)	Stickler Syndrome / Marshall syndrome
COL11A2	AD/AR	1.4% (6/440) individuals (26969326)	Non-ocular stickler (STL3) / otospondylomegaepiphyseal dysplasia (OSMED) / DFNA13 / DFNB53
COL2A1	AD	80-90% of Stickler syndrome (20301479)	Stickler Syndrome
COL4A3	AD/AR	7.5% of Alport Syndrome (9195222, 25450602, 27627812, 24178893, 24052634)	Alport Syndrome
COL4A4	AD/AR	7.5% of Alport Syndrome (9195222, 25450602, 27627812, 24178893, 24052634)	Alport Syndrome
COL4A5	XL	65% of Alport syndrome (24033287, 24854265, 20301386)	Alport Syndrome
COL4A6	XLR		DFNX6
CRYM	AD		DFNA40
DCDC2	AR		DFNB66
DFNA5 (GSDME)	AD	c.991-15_991-13del observed in 2/65 Japanese individuals with AD nonsyndromic SNHL, additional case reports (24506266, 17868390)	DFNA5
DFNB59 (PJVK)	AR		DFNB59
DIABLO	AD	1/1119 individuals with SNHL (26969326)	DFNA64
DIAPH1	AD/AR	2/702 index cases with bleeding or platelet disorders, these 2 index cases also had hearing loss (26912466)	DFNA1
DIAPH3	AD/AR	1/19 Korean individuals with auditory neuropathy (PMID 23562982); 1 family with auditory neuropathy with supporting functional studies (15520414, 20624953).	Auditory Neuropathy, Autosomal Dominant, 1

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
DNMT1	AD	100% of HSAN1E patients (22338191)	Cerebellar ataxia, sensorineural deafness, and narcolepsy-cataplexy (ADCA-DN) / Hereditary sensory and autonomic neuropathy with dementia and hearing loss (HSAN1E)
DSPP	AD		Dentinogenesis imperfecta with deafness
EDN3	AD/AR	10% of individuals diagnosed with Waardenburg type 4 (26100139)	Waardenburg Syndrome type 4B
EDNRB	AD	19% of individuals diagnosed with Waardenburg type 4 (26100139)	Waardenburg Syndrome type 4A / Albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness (ABCD) syndrome
ELMOD3	AR		DFNB88
EPS8	AR		DFNB102
ESPN	AD/AR		DFNB36
ESRRB	AR		DFNB35
EYA1	AD	82% of individuals meeting diagnostic criteria (15146463, 19206155, 17637804)	Branchiootorenal (BOR) Syndrome
EYA4	AD	1/75 Japanese individuals with AD nonsyndromic SNHL was heterozygous for a likely pathogenic variant (27911912)	DFNA10
FAM65B	AR		DFNB104
FGF3	AR	100% of affected individuals (21480479)	Congenital deafness with labyrinthine aplasia, microtia, and microdontia (LAMM syndrome)
FGFR1	AD	10% of Kallmann syndrome and IGD (20301509); 5% of Pfeiffer syndrome type 1(20301628)	Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) / Kallmann Syndrome / Craniosynostosis Syndromes (Pfeiffer Syndrome)
FGFR2	AD	95% of Pfeiffer syndrome type 1, 100% of Crouzon syndrome and other craniosynostosis phenotypes (20301628)	Craniosynostosis Syndromes (Pfeiffer Syndrome, Crouzon Syndrome)
FGFR3	AD	100% of Crouzon syndrome with acanthosis nigricans (20301628); >99% of Muenke syndrome (8841188)	Craniosynostosis Syndromes (including Crouzon Syndrome with acanthosis nigricans (AN), Muenke syndrome)
FOXI1	AD/AR	Rare cause of Pendred syndrome, occasionally digenic with SLC26A4 (17503324)	Pendred syndrome / DFNB4
GATA3	AD		Hypoparathyroidism, sensorineural hearing loss, and renal disease (HDR)
GIPC3	AR	2/160 multiethnic families with AR nonsyndromic SNHL (26226137)	DFNB15
GJA1	AD/AR	2/260 (0.77%) Taiwanese individuals with nonsyndromic SNHL (17259707)	Oculodentodigital Dysplasia / AR SNHL
GJB2	AD/AR	98% of individuals with DFNB1 (AR nonsyndromic SNHL) are either homozygous or compound heterozygous for variants in GJB2 (20301449)	Bart-Pumphrey Syndrome / DFN3A / DFNB1A / Hystrix-like Ichthyosis with Hearing Loss
GJB3	AD/AR		Erythrokeratodermia variabilis et progressiva / DFNA2B / DFNB1A / Digenic hearing loss
GJB6	AD/AR	Heterozygous mutations in GJB6, in conjunction with a heterozygous mutation in GJB2, account for 1% of congenital SNHL in the U.S. population. 7-10% of North American individuals with a single GJB2 mutation also have large deletion involving GJB6 (digenic inheritance). (14571368, 15967879)	DFNA3B / DFNB1B / Digenic hearing loss
GPR98	AR	3%-7% of individuals with Usher syndrome type 2 (21234346)	Usher Syndrome type 2C
GPSM2	AR		Chudley-McCullough syndrome
GRHL2	AD/AR		DFNA28
GRXCR1	AR		DFNB25

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
HARS	AD/AR	(1) Founder pathogenic variant (Y454S) in Old Order Amish individuals, with carrier frequency of 1.7% (7/406) in this population. (22279524) (2) 1/58 individuals with retinal dystrophies (Usher syndrome) was compound heterozygous for missense variants by whole exome sequencing. (27353947) (3) 0/40 individuals with Usher syndrome sequenced for 14 genes including HARS (25404053)	Charcot-Marie-Tooth disease, axonal, type 2W / Usher syndrome type 3B
HARS2	AR	(1) 1/14 probands (7.1%) from the same family had a homozygous HARS2 variant. (27650058) (2) 0/8 probands with Perrault Syndrome who had whole exome sequencing. (26970254)	Perrault Syndrome
HGF	AR	3 homozygous variants identified in a cohort of 40 consanguineous Pakistani families with nonsyndromic SNHL (19576567)	DFNB39
HOMER2	AD		DFNA68
HSD17B4	AR	(1) 1/14 probands had a heterozygous variant in HSD17B4 (but no second variant was identified). (27650058) (2) 1/8 probands (12.5%) with Perrault Syndrome was compound heterozygous by whole exome sequencing (26970254) (3) 0/6 families with Perrault Syndrome (20673864)	Perrault Syndrome / D-bifunctional Protein Deficiency
ILDR1	AR	1/1119 (0.09%), (27260575); 3% (5/160 from multiethnic cohort, but only positive in those from Iran/Turkey) (26969326, 26226137)	DFNB42
KARS	AR		Charcot-Marie-Tooth disease, recessive intermediate, B / DFNB89
KCNE1	AD/AR	6/63 (9.5%) of individuals with Jervell and Lange-Nielson (16461811)	Jervell and Lange-Nielsen syndrome 2 (LNS) / Long QT syndrome 5
KCNJ10	AR		Seizures, sensorineural hearing loss, ataxia, mental retardation, and electrolyte imbalance (SeSAME) syndrome / Enlarged Vestibular Aqueduct (digenic) / Pendred syndrome
KCNQ1	AD/AR	57/63 (90.5%) of individuals with Jervell and Lange-Nielson (16461811)	Jervell and Lange-Nielsen syndrome / Long QT syndrome 1 / Long QT syndrome 2
KCNQ4	AD	15.4% of mostly Dutch individuals with hearing loss (28000701) KCNQ4 is the most prevalent gene responsible for autosomal dominant hearing loss in Japan, accounting for 6.6% (19/287) of cases. The most prevalent pathogenic variant was c.211delC and it accounted for 68.4% (13/19) of all KCNQ4 variants. (23717403)	DFNA2A
KITLG	AD		DFNA69
LARS2	AR		Perrault Syndrome
LHFPL5	AR		DFNB67
LRTOMT	AR		DFNB63
MARVELD2	AR	1.1% of Pakistani individuals with AR nonsyndromic SNHL (18084694)	DFNB49
MCM2	AD		DFNA70

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
MIR96	AD		DFNA50
MITF	AD	15% of individuals with Waardenburg syndrome type 2 (26512583, 20127975)	Waardenburg Syndrome, type 2A / Tietz Albinism-Deafness Syndrome / Coloboma, Osteopetrosis, Microphthalmia, Macrocephaly, Albinism, and Deafness (COMMAD)
MSRB3	AR	1/30 Pakistani families with AR SNHL (24949729)	DFNB74
MT-CO1	M	21/2434 (0.86%) subjects from a national hereditary deafness DNA repository had pathogenic mtDNA variant m.7445A>G (23525847)	Palmoplantar Keratoderma with Deafness / Nonsyndromic Sensorineural Mitochondrial Hearing Loss
MT-RNR1	M	Prevalence of pathogenic variants m.1555A>G and m.1494C>T varies by population, ranging from 0%-17% and 0.014%-1.3% respectively (20301595)	Nonsyndromic Sensorineural Mitochondrial Hearing Loss / Aminoglycoside-Induced Hearing Loss
MT-TL1	M	9/373 (2.7%) Japanese individuals with SNHL had pathogenic mtDNA variant m.3243A>G (20111055); several independent reports of m.3291T>C in association with MELAS and related disorders (23273904)	Maternally Inherited Diabetes and Deafness / Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)
MT-TS1	M	3/254 (1.2%) Japanese individuals with maternally inherited hearing loss (24401907) and 1/2651 (0.04%) Chinese individuals with hearing loss (25968158) had pathogenic variant m.7511T>C	Nonsyndromic Sensorineural Mitochondrial Hearing Loss
MYH14	AD	1.3% (4/300) individuals with hearing loss from Italy, Spain, Belgium, Germany; 1.3% (1/75) from Korean (27393652) and 0.5% (1/200) from The Netherlands (28000701)	Peripheral neuropathy, hoarseness, and hearing loss / DFNA4
MYH9	AD	4% (3/75) of Korean individuals with hearing loss (27393652); 0.5% (1/200) of Dutch individuals with hearing loss (28000701)	MYH9 related disease / Macrothrombocytopenia and progressive sensorineural hearing loss / DFNA17
MYO15A	AR	0.89% (10/1120) in a cohort of individuals with hearing loss (25792667)	DFNB3
MYO3A	AD/AR	1/131 Western Europeans individuals with prelingual, moderate to profound non-syndromic SNHL and no GJB2 mutation had bi-allelic variants (27068579); 2 “candidate” variants in 1/31 families with familial nonsyndromic SNHL (23990876)	DFNB30
MYO6	AD/AR	6/200 Dutch families (1/6544 with AR SNHL and 5/23 with AD SNHL) (28000701)	DFNA22 / DFNB37
MYO7A	AD/AR	29%-63% of individuals with Usher syndrome type 1 (21234346, 9382091, 21436283)	Usher Syndrome type 1B, rarely 3 / DFNA11/ DFNB2
NDP	XLR	95% of Norrie disease (20301506)	Norrie disease
NLRP3	AD	~75% of patients with MWS, and 51% of patients with CINCA/NOMID (17393462)	Muckle-Wells syndrome (MWS) / Neonatal Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurologic Cutaneous and Articular (CINCA) syndrome
OPA1	AD	~78% of optic atrophy type 1 (20301426)	Optic atrophy type 1
OSBPL2	AD		DFNA67
OTOA	AR	2/131 Western Europeans individuals with prelingual, moderate to profound non-syndromic SNHL and no GJB2 mutation had bi-allelic variants (including one copy number variant) (27068579)	DFNB22

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
OTOF	AR	1/131 Western Europeans individuals with prelingual, moderate to profound non-syndromic SNHL and no GJB2 pathogenic variant had bi-allelic variants (27068579)	Auditory neuropathy, autosomal recessive, 1 / DFNB9
OTOG	AR	1/ 60 unrelated Spanish families with AR SNHL had biallelic variants (23122587)	DFNB18B
OTOGL	AR		DFNB84B
P2RX2	AD		DFNA41
PAX3	AD	3% (18241065)	Waardenburg Syndrome types 1 and 3
PCDH15	AR	11%-19% of individuals with Usher syndrome type 1 (21234346)	Usher Syndrome Type 1D and 1F / DFNA23
PDZD7	AR		Usher Syndrome / Nonsyndromic hearing loss
PMP22	AD		Charcot-Marie-Tooth disease type 1A and 1E / Dejerine-Sottas disease / Inflammatory Demyelinating Neuropathy / Recurrent Neuropathy with Pressure Palsies / Roussy-Levy Syndrome
PNPT1	AR		DFNB70
POLR1D	AR	6% of individuals with Treacher Collins syndrome (20301704)	Treacher Collins Syndrome 2
POU3F4	XLR	22/1119 hearing loss individuals referred to a clinical diagnostic laboratory (26969326)	DFNX2
POU4F3	AD	1/42 Korean individuals with AD nonsyndromic SNHL (20434433); 1/30 Dutch individuals with various types of hearing loss (1822859); 3/16 Han Chinese families with AD nonsyndromic SNHL (28053790)	DFNA15
PRPS1	XLR	2/13 Spanish and 2/16 Italian families with X-linked hearing loss; variants segregated with hearing loss and mild peripheral neuropathy (25785835, 25182139)	DFNX1 / Charcot-Marie-Tooth disease-5 / Arts syndrome
PTPRQ	AR	3/220 Japanese individuals with SNHL (25788564)	DFNB84A
RDX	AR		DFNB24
S1PR2	AR		DFNB68
SALL1	AD	64-83% of Townes-Brocks syndrome (9973281, 10533063)	Townes-Brocks Syndrome
SEMA3E	AD		CHARGE Syndrome / Kallmann Syndrome
SERPINB6	AR		DFNB91
SIX1	AD	2-4% of individuals who meet the clinical criteria for a diagnosis of BOS/BOR syndrome (18330911, 21700001)	Branchiootic syndrome 3 / DFNA23
SIX5	AD	5/95 individuals with BOR syndrome (17357085)	Branchiootorenal syndrome 2
SLC17A8	AD	4/216 (1.8%) Japanese individuals with SNHL (23967202)	DFNA25
SLC26A4	AR	50% of individuals with Pendred syndrome (11317356)	Pendred syndrome / DFNB4
SLC26A5	AR		DFNB61
SLC33A1	AR		Congenital cataracts, hearing loss, and neurodegeneration (CCHLND)
SLITRK6	AR	3 homozygous nonsense variants reported in individuals with myopia and hearing loss, many from Amish population (23543054, 23946138).	Deafness and Myopia
SMPX	XLR	0.4% (1/226) of individuals with SNHL (22911656)	DFNX4

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
SNAI2	AD/AR	<5% of individuals with Waardenburg syndrome type 2 (20127975)	Waardenburg Syndrome type 2D
SOX10	AD	1% (2/400) of individuals with Waardenburg syndrome (28000701)	Waardenburg type 4C and 2E / Peripheral Demyelinating Neuropathy, Central Dysmyelination, Waardenburg Syndrome, and Hirschsprung Disease (PCWH)
SOX2	AD	11-20% of individuals with anophthalmia/microphthalmia had heterozygous missense or protein truncating variants (12612584, 19921648); 10% (5/52) of individuals with severe microphthalmia/anophthalmia had a SOX2 whole gene deletion. (17522144)	Syndromic Microphthalmia Type 3
STRC	AR	2% (4/200) of nonsyndromic SNHL (28000701); part of a contiguous gene deletion (with CATSPER2) in 100% of individuals with DIS (20301780)	Deafness-Infertility Syndrome (DIS) / DFNB16
SYNE4	AR		DFNB76
TBC1D24	AR	2% (3/136) of nonsyndromic SNHL in Morocco (26371875)	Epilepsy / Deafness, Onychodystrophy, Osteodystrophy, Mental Retardation, and Seizures (DOOR) Syndrome / DFNB86 / DFNA65
TBX1	AD		DiGeorge Syndrome (Velocardiofacial Syndrome)
TCOF1	AD	63-93% of individuals with Treacher Collins syndrome (20301704)	Treacher Collins Syndrome 1
TECTA	AD/AR	0.2% to 10% of nonsyndromic SNHL depending on ethnicity: 0.2% - 5.8% of Japanese individuals; 1% of Americans; 4.5% of Spanish individuals; 3.2% of Koreans; 8.3% of Italian and Qatari individuals; 10% of Palestinian families (25788563, 23967202, 21520338, 20947814, 23990876, 24657061, 19888295)	DFNA8 / DFNA12 / DFNB21
TFAP2A	AD	>95% of branchiooculofacial syndrome (21634087)	Branchiooculofacial Syndrome
TIMM8A	XLR		Mohr-Tranebjaerg syndrome
TJP2	AD/AR		Progressive Familial Intrahepatic Cholestasis 4 / Familial Hypercholanemia / DFNA51
TMC1	AD/AR	Up to 8% (0.09% in Japan; 3.3% in Pakistan; 5% of consanguineous families in Turkey and Iran; 8% of consanguineous families in Turkey) (25788563, 24949729, 23226338, 21117948)	DFNA36 / DFNB7
TMIE	AR	Up to 8% (4% in Jordan and Pakistan in families without GJB2 mutations; 8% in consanguineous families from Turkey; 3.4% in individuals from Turkey with AR nonsyndromic SNHL; 0.1% - 0.8% in India) (16389551, 26561413, 21117948, 25788563, 24416283)	DFNB6
TMPRSS3	AR	<1% of AR nonsyndromic SNHL in Caucasians (11907649, 26036852)	DFNB8 / DFNB10
TNC	AD		Nonsyndromic deafness
TPRN	AR		DFNB79
TRIOBP	AR	0.5-6.5% (23967202, 23226338, 22903915, 28000701)	DFNB28
TSPEAR	AR		DFNB98
USH1C	AR	4.5%-7% of individuals with Usher syndrome type 1 (21234346, 21436283)	Usher Syndrome Type 1C / DFNA18
USH1G	AR	7% of individuals with Usher syndrome type 1 (21234346)	Usher Syndrome Type 1G

Gene	Inheritance	Sensitivity (PubMed ID)	Disorder
USH2A	AR	74%-90% of individuals with Usher syndrome type 2A (8880575; 10729113)	Usher Syndrome Type 2A
WFS1	AD/AR	90-95% of individuals with Wolfram syndrome (11317350, 12754709) and 1.4-4.5% of individuals with AD nonsyndromic SNHL (17492394, 28000701, 17073007)	Wolfram Syndrome and WFS like disorder / DFNA6 / DFNA14 / DFNA38
WHRN	AR	0%-9.5% of individuals with Usher syndrome type 2 (21234346, 22147658)	Usher Syndrome Type 2D / DFNB31

Abbreviations: AR- Autosomal Recessive; AD- Autosomal Dominant; XLR: X-linked recessive; XLD: X-linked dominant; M: Mitochondrial; SNHL: Sensorineural hearing loss; DFNA: Autosomal dominant deafness; DFNB: Autosomal recessive deafness