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Mining Immune Epitopes in the Inner Ear

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Abstract

Etiologies for many inner ear disorders, including autoimmune inner ear disease, sudden sensorineural hearing loss, and Meniere's disease, remain unknown. Indirect evidence suggests an immune-mediated process involving an allergic or autoimmune mechanism. We examined whether known immunogenic proteins share sequence similarity with inner ear proteins, which may lead to cross-reactivity and detrimental immune activation. Comprehensive bioinformatic analyses of primary sequences of intact and mutated proteins associated with human hearing loss and all proteins known to be expressed in the human inner ear were compared with all immune epitopes in the Immune Epitope Database. The exact match and basic local alignment search tool computational algorithms identified 3036 and 106 unique epitope matches, respectively, the majority of which were infectious epitopes. If validated in future clinical trials, these candidate immune epitopes in the inner ear would be potential novel targets for diagnosis and treatment of some inner ear disorders and the resulting hearing loss.

Keywords

hearing loss, epitopes, inner ear disease, Meniere's disease, autoimmune inner ear disease, computational, bioinformatics, cross-reactivity

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Abnormal immune activation can occur with an auto-
 logous epitope in autoimmune disorders, a hetero-
 logous epitope in allergic diseases, or by cross-
 reactivity when similar proteins trigger a response. Meniere's
 disease, sudden sensorineural hearing loss (SNHL), and auto-
 immune inner ear disease (AIED) are poorly understood ear
 disorders for which immune activation through allergic and
 autoimmune mechanisms has been suggested.^{1,2} Sudden sen-
 sorineural hearing loss in AIED was associated with a 68- to

72-kDa inner ear antigen, with candidate epitopes of the heat
 shock protein 70 and choline transporter-like protein 2.²
 There is indirect evidence that Meniere's disease is an
 immune-mediated disorder,¹ since people with Meniere's dis-
 ease have a 3-fold increased incidence of allergic disease, a
 2-fold higher incidence of IgE sensitivity to wheat, elevated
 levels of immune complexes and lymphocytes in the inner
 ear, and higher levels of anti-herpes IgG in perilymph.

Inherent difficulties in studying the inner ear have lim-
 ited identification of causes for many types of SNHL. The
 purpose of this study was to identify candidate epitopes that
 may be responsible for immunologic pathogenesis of some
 inner ear disorders.

Methods

Comprehensive bioinformatic analyses were performed to
 determine protein similarity between known immune epitopes
 and all ear-related proteins. Intact and mutated proteins associ-
 ated with human syndromic and nonsyndromic hearing loss
 and all proteins previously found to be expressed in the human
 inner ear were amassed via a PubMed literature search,
 Washington University Inner Ear Protein Database, Hereditary
 Hearing Loss Homepage, and data from the inner ear pro-
 teome.³ The primary protein sequences were collected in
 FASTA format from the National Center for Biotechnology
 Information library and modified appropriately for mutated
 sequences.

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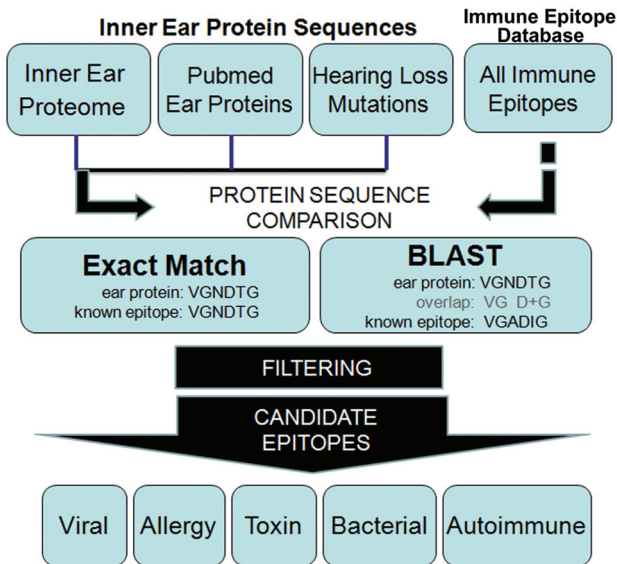


Figure 1. Methods used for computational analysis and comparison of all known ear protein sequences and all known immune epitopes. Letters represent different amino acids. (+) denotes amino acids with similar properties. BLAST, basic local alignment search tool.

Immune epitopes were obtained from the Immune Epitope Database (IEDB; www.immuneepitope.org), a comprehensive online repository of all known epitopes that have been reported in the literature and have passed stringent criteria of inclusion. Two separate computational algorithms were used for comparison of protein sequences: exact match and basic local alignment search tool (BLAST), which includes scoring based on amino acid (AA) similarity

(BLOSUM62). Python software was used to perform sequence comparisons (**Figure 1**). Results of the exact match analyses were filtered to limit findings to epitopes of at least 6 AA in length in accordance with the Food and Health Organization/World Health Organization allergenicity guidelines and to exclude epitopes implicating an identical protein (eg, collagen epitope in collagen protein). The BLAST results were limited to an Expect value (E) <1. When E is smaller, the alignment is stronger. Institutional review board approval was not required for this study.

Results

The IEDB contained 151,086 epitopes identified in autoimmune, allergic, and infectious diseases. The inner ear proteins used for analyses included 128 known inner ear proteins, 127 proteins from genes identified in syndromic and nonsyndromic hearing loss, and 1533 protein sequences with known mutations that contribute to SNHL (**Table 1** and Appendix 1, available at otojournal.org).

The exact match algorithm revealed 3036 matches, of which 24 fulfilled inclusion criteria for viral (17), bacterial (4), and allergy-related (3) epitopes (**Table 2**). The BLAST algorithm discovered 23 matches, which included toxin-derived (17), infectious (3), and allergy-related (3) epitopes (**Table 2**).

Discussion

We used a novel approach to identify candidate inner ear epitopes that may cause SNHL via cross-reactivity. Clinical validation through patient-specific study of lymphocytes or serum antibodies is needed to validate these computational findings. We found infectious disease epitopes to be the

Table 1. Comprehensive list of inner ear proteins used for computational analyses for sequence similarity to all known epitopes.^a

Sequence Source (Key ^a)	No. of Proteins	No. of Hits	
		BLAST	Exact
HL proteins			
Syndromic HL proteins (1)	64	17	776
Mutations in syndromic HL proteins (2)	809	10	0
Nonsyndromic HL proteins (3)	63	30	222
Mutations in nonsyndromic HL proteins (4)	724	5	1
Syndromic and nonsyndromic proteins (5)	(127)	(47)	(998)
Mutations in syndromic and nonsyndromic proteins (6)	(1533)	(15)	(1)
Syndromic and nonsyndromic proteins + mutations (7)	(1660)	(63)	(999)
Inner ear proteome			
Human perilymph proteins (8)	50	23	367
Human inner ear proteins not in perilymph (9)	56	16	1225
Human proteins in the inner ear and perilymph (10)	22	4	445
Inner ear proteome (perilymph + inner ear)	(128)	(43)	(2037)
All			
All proteins with mutations	(1788)	(106)	(3036)
All proteins without mutations	(255)	(90)	(3035)

Abbreviations: BLAST, basic local alignment search tool; HL, hearing loss.

^aNumbers in parentheses denote summation from above numbers.

^bKey denotes where protein sequence in **Table 2** and Appendix 1 originated.

Table 2. Results of protein sequence comparison, by the exact match and BLAST algorithms, between all inner ear proteins^a and the immune epitope database.^b

Ear-Associated Protein (Source ^c)	Epitope (Source)	Sequence (letters) ^d /E (numbers) ^e
TRIO and F-actin binding protein (3)	Large delta antigen (p27, hepatitis delta virus)	EELERD
Glutathione peroxidase 3 (8)	Large delta antigen (p27, hepatitis delta virus)	GGGFVP
Paired box protein Pax-3 (1)	Large delta antigen (p27, hepatitis delta virus)	LEELER
Espin (3,9)	Large delta antigen (p27, hepatitis delta virus)	RKKLEE
Usher1 (1,9)	Large delta antigen (p27, hepatitis delta virus)	QGVPEs
Myosin VI (3)	Large delta antigen (p27, hepatitis delta virus)	EEDEKR
Nidogen-1 (9)	Large delta antigen (p27, hepatitis delta virus)	RRKALE
Treacle protein (1)	Capsid protein VPI (chicken anemia virus)	VLAQKA
Solute carrier family 12 member 1 (9)	Capsid protein VPI (chicken anemia virus)	VSALDN
Merlin (1)	Capsid protein VPI (chicken anemia virus)	LAQKAA
Keratin, type II cytoskeletal I (8)	Capsid protein VPI (chicken anemia virus)	GSGGGGGGG
X-linked retinitis pigmentosa GTPase regulator (1)	Genome polyprotein (hepatitis C virus)	VGNDTG
Zinc-alpha-2-glycoprotein (10)	Genome polyprotein (hepatitis C virus)	PATLRK
Gelsolin (8)	Envelope glycoprotein (hemorrhagic septicemia virus)	GDSYII
Tenascin (9)	Structural protein I (human herpesvirus 3)	DLPQLG
Zinc-alpha-2-glycoprotein (10)	Envelope glycoprotein (hemorrhagic septicemia virus)	ATLRKY
Heparan sulfate proteoglycan core protein (8)	Polyprotein (foot-and-mouth disease virus)	SGDLGS
G-protein-coupled receptor 98 (1)	CFA/I fimbrial subunit B precursor (<i>Escherichia coli</i>)	GQVLST
Whirlin (1,3)	CFA/I fimbrial subunit B precursor (<i>E coli</i>)	AGTAPT
Inter-alpha-trypsin inhibitor heavy chain HI (8)	Cholera toxin B protein (<i>Vibrio cholerae</i>)	TPQNIT
Taperin (3)	Stage VI sporulation protein D (<i>Bacillus subtilis</i>)	EEEEEEEE
Complement C3 (8)	Major latex allergen Hev b 5 (rubber tree)	APETEK
Myelin protein P0 (1)	Histone H5 (chicken)	LVLSPA
X-linked retinitis pigmentosa GTPase regulator (1)	Testis cDNA clone: QtsA-15219 (cynomolgus monkey)	FAAPHRGVA
Prothrombin (8)	Flavoxobin (<i>Protophthrops flavoviridis</i>)	0.00003
Prothrombin (8)	Thrombin-like enzyme elegaxobin-1 (elegant pitviper)	0.0001
Plasminogen (8)	Flavoxobin (<i>P flavoviridis</i>)	0.000002
Plasminogen (8)	Thrombin-like enzyme elegaxobin-1 (elegant pitviper)	0.0004
Complement factor (8)	Thrombin-like enzyme elegaxobin-1 (elegant pitviper)	0.61
Fibrinogen gamma chain (8)	Botulinum neurotoxin B precursor (<i>Clostridium botulinum</i>)	0.95
Apolipoprotein B-100 (8)	BoNT/F (<i>C botulinum</i>)	0.41
Complement factor I (8)	Flavoxobin (<i>P flavoviridis</i>)	0.0004
Apolipoprotein A-IV (9)	Botulinum neurotoxin type A (<i>C botulinum</i>)	0.074
Hepatocyte growth factor (3)	Flavoxobin (<i>P flavoviridis</i>)	0.077
Hepatocyte growth factor (3)	Elegaxobin-2 (<i>Protophthrops elegans</i>)	0.004
Transmembrane protease serine 3 (3)	Flavoxobin (<i>P flavoviridis</i>)	0.00007
Transmembrane protease serine 3 (3)	Elegaxobin-1 (<i>P elegans</i>)	0.0009
Plasma membrane calcium-transporting (3)	Botulinum neurotoxin type C1 (<i>C botulinum</i>)	0.88
Otoconin-90 (9)	Crotoxin acid chain (South American rattlesnake)	0.012
DNA excision repair protein ERCC-6 (1)	Tetanus toxin precursor (<i>Clostridium tetani</i>)	0.64
POU domain, class 4, transcription factor (3)	Botulinum neurotoxin A precursor (<i>C botulinum</i>)	0.1
Protein diaphanous homolog (3)	P30 adhesin (<i>Mycoplasma pneumoniae</i>)	0.16
Complement C3 (8)	p67 protein (<i>Theileria parva</i>)	0.28
Inter-alpha (globulin) inhibitor H4 (8)	Polyprotein (dengue virus)	0.28
Apolipoprotein D (10)	Bla g 4 (German cockroach)	0.004
Protein AMBP (8)	Equ c I (horse)	0.72
Protein S100-B (9)	Polcalcin Phl p 7 (timothy grass)	0.092

^aInner ear proteins obtained by proteomics,³ known genes to cause hearing loss, sequence mutations for hearing loss genes, and Washington University Inner Ear Protein Database.

^bFood and Agriculture Organization/World Health Organization.

^cSee Table 1 (key) for ear protein source.

^dExact match amino acid sequence.

^eE value for basic local alignment search tool (BLAST).

most common epitope type that shares sequence similarity with inner ear proteins. This bioinformatic finding provides a mechanistic insight into the clinical observations that sudden SNHL often occurs in the setting of a respiratory infection.

The exact match algorithm identified several viruses, including human herpes virus 3 (HHV3, varicella zoster) and hepatitis D virus. HHV3 is well known to cause SNHL in herpes zoster oticus via an unknown mechanism. Our study suggests that cross-reactivity between HHV3 and tenascin in the inner ear may be a mechanism by which postinfectious SNHL occurs. Tenascin is expressed in the adult human basilar membrane, osseous spiral lamina, and osteocytes.⁴ Interestingly, we found another extracellular protein, nidogen 1, to have sequence homology with a hepatitis D epitope. Nidogen 1 is a basement membrane protein known to co-localize with cochlin, which is the most abundant protein in the inner ear. An immune reaction targeting cochlin has been suggested in human SNHL because of higher frequencies of circulating T cells producing interferon- γ or interleukin-5 in response to recombinant human cochlin⁵ and increased frequency of T cells specific for cochlin in sudden SNHL. Our findings suggest that cross-reactivity between infectious epitopes and extracellular matrix proteins may trigger local inflammation to cause SNHL.

A limitation of this study is the use of linear sequences to predict epitope binding that occurs with tertiary structures. The BLAST algorithm partly addresses that issue by allowing for and scoring gaps in linear sequence to represent protein folding. More accurate predictions will be possible as additional information on inner ear conformational structure becomes available. Analyses of serum antibodies via enzyme-linked immunosorbent assays or electrochemiluminescence assays in patients with inner ear disorders will allow for clinical validation of immune reactivity to candidate epitopes identified here. Identification of a cross-reactive epitope would be beneficial for diagnosis of inner ear disease and for treatment through allergen avoidance, immunotherapy, or immunomodulatory pharmaceuticals.

Conclusion

Abnormal immune activation is suspected in some inner ear disorders. We present a novel, high-throughput methodology that identified candidate epitopes that may contribute to the pathogenesis of SNHL. Future validation of these candidates will allow translation of our bioinformatic findings to novel diagnostic and therapeutic tools for SNHL.

Author Contributions

Michael Platt, conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published; **Sonam Dilwali**, acquisition of data, analysis of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published; **Alphi Elackattu**, acquisition of data, analysis of data, drafting the article, final approval of the version to be published; **Jignesh R. Parikh**, acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published; **Konstantina M. Stankovic**, conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published.

Disclosures

Competing interests: None.

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Supplemental Material

Additional supporting information may be found at <http://oto.sagepub.com/content/by/supplemental-data>

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Appendix 1 (online only). A list of gene used for computational analyses of protein sequences based on their involvement with human syndromic and non-syndromic hearing loss, or expression in the inner ear.

Proteins described in the human inner ear	
Protein	Coding Gene
Afamin	<i>AFM</i>
Albumin	<i>ALB</i>
Alpha 1 acid glycoprotein 1	<i>ORM1</i>
Alpha 1 microglobin	<i>AMBP</i>
Alpha-1-antichymotrypsin	<i>SERPINA3</i>
Alpha-1-antitrypsin	<i>SERPINA1</i>
Alpha-1-B glycoprotein	<i>A1BG</i>
Alpha-2 antiplasmin	<i>SERPINF1</i>
Alpha-2-glycoprotein 1, zinc-binding	<i>AZGP1</i>
Alpha-2-HS-Glycoprotein	<i>ASHG</i>
Alpha-2-macroglobulin	<i>A2M</i>
Angiotensinogen	<i>SERPINE1</i>
Antithrombin-III	<i>SERPINC1</i>
Apolipoprotein A-I	<i>APOA1</i>
Apolipoprotein A-II	<i>APOA2</i>
Apolipoprotein A-IV	<i>APOA4</i>
Apolipoprotein B-100	<i>APOB</i>
Apolipoprotein D	<i>APOD</i>
Apolipoprotein E	<i>APOE</i>
Aquaporin-1	<i>AQP1</i>
Aquaporin-3	<i>AQP3</i>
Aquaporin-4	<i>AQP4</i>
Aquaporin-6	<i>AQP6</i>
Atrial natriuretic peptide receptor 2	<i>NPR2</i>
Beta-2-glycoprotein 1	<i>B2GP1</i>
Cadherin 23	<i>CHD23</i>
Calbindin 3	<i>CALB3</i>
Carbonic anhydrase 1	<i>CA1</i>
Carbonic anhydrase 2	<i>CA2</i>

Ceruloplasmin	<i>CP</i>
Clusterin	<i>CLU</i>
Cochlin	<i>COCH</i>
Collagen alpha-1(II) chain	<i>COL2A1</i>
Collagen alpha-1(IV) chain	<i>COL4A1</i>
Collagen alpha-2(IV) chain	<i>COL4A2</i>
Collagen alpha-3(IV) chain	<i>COL4A3</i>
Collagen alpha-4(IV) chain	<i>COL4A4</i>
Collagen alpha-5(IV) chain	<i>COL4A5</i>
Complement C3	<i>C3</i>
Complement component 4B	<i>C4B</i>
Complement component C7	<i>C7</i>
Complement factor B	<i>CFB</i>
Complement factor H	<i>CFH</i>
Complement factor I	<i>CFI</i>
Connexin-32	<i>GJB1</i>
Cystatin C	<i>CST3</i>
Dystroglycan 1	<i>DAG1</i>
Espin	<i>ESPN</i>
Fc fragment of IgG binding protein	<i>FCGR</i>
Fibrinogen alpha chain	<i>FGA</i>
Fibrinogen beta chain	<i>FGB</i>
Fibrinogen gamma chain	<i>FGG</i>
Flavin reductase	<i>BLVRB</i>
Gelsolin	<i>GSN</i>
Glutathione peroxidase 3	<i>GPX3</i>
Glutathione-independent prostaglandin D synthase	<i>PTGDS</i>
Haptoglobin	<i>HP</i>
Hemoglobin beta chain	<i>HBB</i>
Hemoglobin, alpha 2	<i>HBA2</i>
Hemoglobin, delta	<i>HBD</i>
Hemopexin	<i>HPX</i>
Heparan sulfate proteoglycan 2	<i>HSPG2</i>
Histidine-rich glycoprotein	<i>HRG</i>
Ig kappa chain C region	<i>IGKC</i>
Immunoglobulin lambda constant 2 (Kern-Oz-marker)	<i>IGLC2</i>
Immunoglobulin heavy chain gamma	<i>IGHG1</i>
Immunoglobulin light chain (lambda)	<i>IGLC1</i>

Immunoglobulin heavy constant alpha 1	<i>IGHA1</i>
Immunoglobulin heavy constant gamma 4	<i>IGHG4</i>
Immunoglobulin heavy constant mu	<i>IGHM</i>
Immunoglobulin kappa variable 1-5	<i>IGKV</i>
Immunoglobulin kappa variable 4-1	<i>IGKJ</i>
Inter-alpha (globulin) inhibitor H1	<i>ITIH1</i>
Inter-alpha (globulin) inhibitor H2	<i>ITIH2</i>
Inter-alpha (globulin) inhibitor H4	<i>ITIH4</i>
Interleukin-1 alpha	<i>IL1A</i>
Interleukin-1 beta	<i>IL1B</i>
Keratin 1	<i>KRT1</i>
Keratin 10	<i>KRT10</i>
Keratin 5	<i>KRT5</i>
Keratin 9	<i>KRT9</i>
Kininogen 1	<i>KNG1</i>
Laminin, beta 2	<i>LAMB2</i>
Myosin 1C	<i>MYO1C</i>
NF-kappa-B inhibitor alpha	<i>IKBA</i>
Nidogen-1	<i>NID1, NID</i>
Oncomodulin-1	<i>OCM</i>
Orosomucoid 2	<i>ORM2</i>
Otoconin-90	<i>OC90</i>
Otogelin	<i>OTOG</i>
Otolin-1	<i>OTOL1</i>
Otopetrin	<i>OTOP1, OTOP2</i>
Pendrin	<i>SLC26A4</i>
Peroxiredoxin 2	<i>PRDX2</i>
Plasma protease C1 inhibitor	<i>SERPING1</i>
Plasminogen	<i>PLG</i>
Prestin	<i>SLC26A5</i>
Prothrombin	<i>F2</i>
Protocadherin 15	<i>PCDH15</i>
Retinol-binding protein 4	<i>RBP4</i>
S-100 protein beta chain	<i>S100B</i>
Secreted phosphoprotein 1	<i>OPN, SPP1</i>
Single-chain Fv fragment	<i>SCFV</i>
Sodium/potassium-transporting ATPase subunit alpha-1	<i>ATP1A1</i>
Sodium/potassium-transporting ATPase subunit alpha-2	<i>ATP1A2</i>

Sodium/potassium-transporting ATPase subunit Beta-1	<i>ATP1B1</i>
Sodium/potassium-transporting ATPase subunit Beta-2	<i>ATP1B2</i>
Solute carrier family 12 member 1	<i>SLC12A1</i>
Solute carrier family 12 member 2	<i>SLC12A2</i>
S-phase kinase-associated protein 1	<i>SKP1A</i>
Tectorin alpha	<i>TECTA</i>
Tectorin beta	<i>TECTB</i>
Tenascin C	<i>TNC</i>
Transcription factor p65	<i>RELA</i>
Transferrin	<i>TF</i>
Transthyretin	<i>TTR</i>
Tumor Necrosis Factor	<i>TNF</i>
Usherin 1C	<i>USH1C</i>
Usherin/ usherin 2A	<i>USH2A</i>
Vitamin D binding protein	<i>GC</i>
von Willebrand factor A domain-related protein	<i>VWA1</i>
Proteins encoded by genes associated with non-syndromic hearing loss	
Protein Name	Coding Gene
Actin, cytoplasmic 2	<i>ACTG1</i>
Alpha-tectorin	<i>TECTA</i>
ATP-sensitive inward rectifier potassium channel 10	<i>KCNJ10</i>
Cadherin-23	<i>CDH23</i>
Choline transporter-like protein 2	<i>SLC44A2</i>
Claudin-14	<i>CLDN14</i>
Cochlin	<i>COCH</i>
Coiled-coil domain-containing protein 50	<i>CCDC50</i>
Collagen alpha-2(XI) chain	<i>COL11A2</i>
DFNA5 protein	<i>DFNA5</i>
Diablo homolog, mitochondrial	<i>DIABLO</i>
Espin	<i>ESPN</i>
Eyes absent homolog 4	<i>EYA4</i>
Gap junction alpha-1 protein	<i>GJA1</i>
Gap junction beta-6 protein	<i>GJB6</i>
Glutaredoxin domain-containing cysteine-rich protein 1	<i>GRXCR1</i>
Grainyhead-like protein 2 homolog	<i>GRHL2</i>
Harmonin	<i>USH1C</i>
Hepatocyte growth factor	<i>HGF</i>
Immunoglobulin-like domain-containing receptor 1	<i>ILDR1</i>

Lipoxygenase homology domain-containing protein 1	<i>LOXHD1</i>
MARVEL domain-containing protein 2	<i>MARVELD2</i>
Methionine-R-sulfoxide reductase B3	<i>MSRB3</i>
Mu-crystallin homolog	<i>CRYM</i>
MYH14 protein	<i>MYH14</i>
Myosin-9	<i>MYH9</i>
Myosin-Ia	<i>MYO1A</i>
Myosin-IIIa	<i>MYO3A</i>
Myosin-VI	<i>MYO6</i>
Myosin-VIIa	<i>MYO7A</i>
Myosin-XV	<i>MYO15A</i>
not found	<i>MIRN96</i>
Otoancorin	<i>OTOA</i>
Otoferlin	<i>OTOF</i>
PDZ domain-containing protein GIPC3	<i>GIPC3</i>
Pejvakin	<i>PJVK</i>
Pendrin	<i>SLC26A4</i>
Phosphatidylinositol phosphatase	<i>PTPRQ</i>
Plasma membrane calcium-transporting ATPase 2	<i>ATP2B2</i>
Potassium voltage-gated channel subfamily KQT member 4	<i>KCNQ4</i>
POU domain, class 3, transcription factor 4	<i>POU3F4</i>
POU domain, class 4, transcription factor 3	<i>POU4F3</i>
Prestin	<i>SLC26A5</i>
Protein diaphanous homolog 1	<i>DIAPH1</i>
Protein diaphanous homolog 3	<i>DIAPH3</i>
Protein KIAA1199	<i>KIAA1199</i>
Protocadherin-15	<i>PCDH15</i>
Radixin	<i>RDX</i>
Ribose-phosphate pyrophosphokinase 1	<i>PRPS1</i>
Serpin Peptidase Inhibitor, Clade Beta, Member 6	<i>SERPINB6</i>
Small muscular protein	<i>SMPX</i>
Stereocilin	<i>STRC</i>
Steroid hormone receptor ERR2	<i>ESRRB</i>
Taperin	<i>TPRN</i>
Tetraspan membrane protein of hair cell stereocilia	<i>LHFPL5</i>
Thiomorpholine-carboxylate dehydrogenase	<i>CRYM</i>
Tight junction protein ZO-2	<i>TJP2</i>
Transmembrane channel-like protein 1	<i>TMC1</i>

Transmembrane inner ear expressed protein	<i>TMIE</i>
Transmembrane O-methyltransferase, Leucine-rich repeat-containing protein 51	<i>LRTOMT</i>
Transmembrane protease serine 3	<i>TMPRSS3</i>
TRIO and F-actin-binding protein	<i>TRIOBP</i>
Whirlin	<i>WHRN</i>
Wolframin	<i>WFS1</i>
Proteins encoded by genes associated with syndromic hearing loss	
Protein	Coding Gene
Aquaporin-1	<i>AQP1</i>
ATP-binding cassette sub-family C member 8	<i>ABCC8</i>
ATP-sensitive inward rectifier potassium channel 11	<i>KCNJ11</i>
Cadherin-23	<i>CDH23</i>
CD151 antigen	<i>CD151</i>
Chromodomain-helicase-DNA-binding protein 7	<i>CHD7</i>
Clarin-1	<i>CLRN</i>
Cochlin	<i>COCH</i>
Collagen alpha-1(II) chain	<i>COL2A1</i>
Collagen alpha-1(IX) chain	<i>COL9A1</i>
Collagen alpha-1(XI) chain	<i>COL11A1</i>
Collagen alpha-2(XI) chain	<i>COL11A2</i>
Collagen alpha-3(IV) chain	<i>COL4A3</i>
Collagen alpha-4(IV) chain	<i>COL4A4</i>
Collagen alpha-5(IV) chain	<i>COL4A5</i>
Collagen alpha-6(IV) chain	<i>COL4A6</i>
Dentin sialophosphoprotein	<i>DSPP</i>
DNA excision repair protein ERCC-6	<i>ERCC6</i>
DNA excision repair protein ERCC-8	<i>ERCC8</i>
Dynamin-like 120 kDa protein, mitochondrial	<i>OPA1</i>
Endothelin B receptor	<i>EDNRB</i>
Endothelin-3	<i>EDN3</i>
Eyes absent homolog 1- transcription factor	<i>EYA1</i>
Fibroblast growth factor 3	<i>FGF3</i>
Forkhead box protein I1	<i>FOXI1</i>
Gap junction beta-2 protein	<i>GJB2</i>
Gap junction beta-2 protein (Connexin 26)	<i>GJB2</i>
Gap junction beta-3 protein	<i>GJB3</i>
G-protein coupled receptor 98	<i>GPR98</i>

G-protein-signaling modulator 2	<i>GPSM2</i>
Harmonin	<i>USH1C</i>
Homeobox protein Hox-A2	<i>HOXA2</i>
Homeobox protein SIX1	<i>SIX1</i>
Homeobox protein SIX5	<i>SIX5</i>
Interleukin-1 receptor type 2	<i>IL1R2</i>
Merlin	<i>NF2</i>
Microphthalmia-associated transcription factor	<i>MITF</i>
Myelin Protein Zero	<i>MPZ</i>
Myosin-VIIa	<i>MYO7A</i>
NACHT, LRR and PYD domains-containing protein 3	<i>NLRP3</i>
N-chimaerin	<i>CHN1</i>
Norrin	<i>NDP</i>
Otoferlin	<i>OTOF</i>
Paired box protein Pax-3	<i>PAX3</i>
Pendrin	<i>SLC26A4</i>
Potassium voltage-gated channel subfamily E member 1	<i>KCNE1</i>
Potassium voltage-gated channel subfamily KQT member 1	<i>KCNQ1</i>
Probable ATP-dependent DNA helicase HFM1	<i>HFM1</i>
Protocadherin-15	<i>PCDH15</i>
RAF proto-oncogene serine_threonine-protein kinase	<i>RAF1</i>
Sal-like protein 1	<i>SALL1</i>
Sal-like protein 4	<i>SALL4</i>
Serine_threonine-protein kinase B-raf	<i>BRAF</i>
Solute carrier family 52, riboflavin transporter, member 3	<i>SLC52A3</i>
Transcription factor SOX-10	<i>SOX10</i>
Transmembrane anterior posterior transformation protein 1 homolog	<i>TAPT1</i>
Treacle protein	<i>TCOF1</i>
Tyrosine-protein phosphatase non-receptor type 11	<i>PTPN11</i>
Urocortin	<i>UCN</i>
Usher syndrome type-1G protein	<i>USH1G</i>
Usherin	<i>USH2A</i>
Whirlin	<i>WHRN</i>
Wolframin	<i>WFS1</i>
X-linked retinitis pigmentosa GTPase regulator	<i>RPGR</i>
Zinc finger protein SNAI2	<i>SNAI2</i>