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Gene Expression Profiles of the Cochlea and Vestibular Endorgans: Localization and Function of Genes Causing Deafness

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Abstract

Objectives: We sought to elucidate the gene expression profiles of the causative genes as well as the localization of the encoded proteins involved in hereditary hearing loss.

Methods: Relevant articles (as of September 2014) were searched in PubMed databases, and the gene symbols of the genes reported to be associated with deafness were located on the Hereditary Hearing Loss Homepage using *localization, expression*, and *distribution* as keywords.

Results: Our review of the literature allowed us to systematize the gene expression profiles for genetic deafness in the inner ear, clarifying the unique functions and specific expression patterns of these genes in the cochlea and vestibular endorgans.

Conclusions: The coordinated actions of various encoded molecules are essential for the normal development and maintenance of auditory and vestibular function.

Keywords

deafness, gene expression, immunocytochemistry, in situ hybridization, localization

Introduction

Hearing loss is one of the most common and frequently diagnosed sensory disorders worldwide, with 50% to 70% of cases attributable to genetic causes.[1] Hereditary hearing loss demonstrates great heterogeneity. To date, over 80 genes have been identified as causing nonsyndromic hearing loss, and approximately 100 genes are presumed to be involved in hearing loss.[2]

The coordinated actions of various encoded molecules are essential for the normal development and maintenance of auditory processing in the cochlea. The identification of deafness-associated genes has been the most influential factor in the recent extensive advances in our knowledge of the biology of hearing.

In terms of clinical applications, the most remarkable aspect of these advances is that ENT clinicians can now make highly accurate molecular diagnoses through the use of genetic testing, enabling a clearer understanding of the mechanisms involved, more appropriate and precise treatment selection, and greatly improved genetic counseling.

Recent advances in genetic analysis technology using massively parallel DNA sequencing have not only accelerated the exploration of novel genes involved in genetic hearing loss but have also allowed the identification of mutations in rare causative genes.

However, such rapid progress in gene/mutation identification has, at times, disrupted our understanding of their precise function. It is now necessary to systematize the huge amounts of data available on the expression and localization profiles of causative genes.

The present review highlights the gene expression profiles of the causative genes as well as the localization of the encoded proteins involved in hereditary hearing loss. We conducted a literature search for studies describing in situ hybridization, reporter expression, and immunocytochemistry. In addition, we also reported functional predictions using

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gene ontology analysis and summarized the cochlea and vestibular distribution of functional genes.

Subjects and Methods

Literature Search

PubMed database was searched as of September 2014. The gene symbols of the genes reported to be associated with deafness were located on the Hereditary Hearing Loss Homepage,[2] with *localization, expression*, and *distribution* used as keywords. After the database search, papers reporting on immunocytochemistry, reporter expression, or in situ hybridization were selected. For each gene linked to deafness, cell-specific localization as well as the methods utilized in the study were annotated and summarized (Tables 1 and 2).

Computer Analysis and Database Survey

The gene ontology was analyzed using the PANTHER website[3,4] with the symbols for the genes expressed in each type of cochlea cell as well as in the vestibular endorgans (Table 3). We also used the GeneCard website.[5] Gene expression profiles for each human body part were surveyed using the RefEX website.[6] The results of the RefEX search produced by DBCLS are licensed under a Creative Commons Attribution 2.1 Japan License as (CC) BY. The domain structure information was cited from the UniProt website.[7]

Results and Discussions

A review of the gene expression profiles for hearing loss–associated genes in the inner ear revealed their unique functions and specific expression patterns of the genes in the cochlear and vestibular endorgans (Figures 1, 2, and 3). Each cell-specific gene expression profile is discussed in the following.

Inner Hair Cells Are Crucial for Sound Transduction

Inner hair cells (IHCs), the actual sensory receptors, play a crucial role in the conversion of mechanical movements to electric signals.[8-14] Hearing ability relies on the rapid gating of the mechanoelectrical transduction (MET) channels believed to be located in the tip of the hair cell stereocilia (Figure 2A).[15,16] The genes encoding the MET channel have not yet been identified. Transmembrane channel 1 and 2 genes (*TMC1* and *2*) are 2 candidates encoding the MET channels in the stereocilia.[17,18] Furthermore, the MET channels are believed to bind directly to the tip link between the adjacent cilia consisting of the cadherin 23 (*CDH23*) and protocadherin 15 (*PCDH15*). Movement of the stereocilia mechanically pulls the MET channels and potassium ion (K^+) included in the endolymph flow into the IHCs (Figure 3).[9,11,16] This potassium ion incorporation results in depolarization of the IHCs, and the subsequent opening of the voltage-dependent calcium channels.[9,19] Calcium ions (Ca^{2+}) act as triggers for the exocytosis of vesicles, which contain the neurotransmitter glutamate.[11,16,19]

The majority (95%) of the fibers of the auditory nerve, which conveys electric stimulation to the brain, arise from IHCs. At the bottom of the IHCs is another unique component known as the ribbon synapse. The ribbon synapse is a type of neuronal synapse consisting of thousands of vesicles. This multivesicular component acts as a large reservoir of the glutamate neurotransmitter. The broad dynamic range of IHC sound sensing is ensured by the rapid, multiple vesicular exocytosis of the ribbon synapse at a level corresponding to the loudness of the sound.[19,20] Otoferlin (encoded by *OTOF*) is known to play an important role in this calcium-dependent exocytosis process, with *otof* knockout mice displaying deafness due to the absence of exocytosis in IHCs.[21]

With regard to gene expression, various genes linked to deafness are expressed in IHCs and in outer hair cells (OHCs; Figure 1). This reflects the unique and important characteristics of IHCs in the sound transduction mechanisms. To examine the gene expression linked to deafness in IHCs, we analyzed the gene ontology and searched a number of databases. As a result, gene expression in the IHCs and OHCs was characterized into 4 groups of genes.

The first group of genes is associated with vesicle transport, neuronal transmission, and calcium-binding functions. This group includes *CABP2* (calcium-binding protein 2), membrane traffic protein *OTOF* (otoferlin), *SLC17A8* (vesicular glutamate transporter 3), and *TBC1D24* (TBC domain-containing RAB-specific GTPase-activating protein 24). Mutations in these genes are known to cause DFNB93, DFNB48, DFNB9, DFNA25, and DFNA65/DFNB86.[22-26] The limited expression of these genes in the sensor cells and neurons reflects the importance of calcium ion (Ca^{2+}) and vesicle transport for effective neuronal transmission. *TMPRSS3* (transmembrane protease serine 3) is a serine protease required for epithelial sodium channel (ENaC) maturation, and *TMPRSS3* expression is also limited in IHCs, OHCs, and spiral ganglions.[27]

The second group of genes consists of components of the stereocilia and includes *ACTG1* (actin gamma 1), *CDH23* (cadherin 23), *CIB2* (calcium- and integrin-binding family member 2), *ESPN* (espin), *MYO3A* (myosin IIIa), *MYO7A* (unconventional myosin VIIa), *MYO15A* (unconventional myosin XV), *PCDH15* (Protocadherin 15), *PDZD7* (PDZ domain-containing 7), *RDX* (radixin), *STRC* (stereocilin), *TMC1* (transmembrane channel-like protein 1), *TPRN* (taperin) *TRIOBP* (TRIO and F-actin-binding protein), *USH1C* (harmonin), *USH2A* (usherin), and *WHRN* (whirlin) (Figures 2A, 2B). Mutations in these genes also cause hearing

Table 1. Summary of Gene Expression Profiles of the Causative Genes and Localization of the Encoded Proteins Involved in Hereditary Hearing Loss in the Cochlea.

Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
ACTG1	Actin gamma 1	DFNA20/26	+	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–		Mouse, guinea pig	IF, EM	28, 100	Cytoskeletal non-muscle actin protein gamma. Localized in F-actin gap region of stereocilia. *ESPN* also observed in this region.
ADCY1	Adenylate cyclase type 1	DFNB44	+	+	–	–	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	+	Stereocilia	Rat	IHC	101, 102	cAMP synthetase required for functional AMPA receptor and synaptic plasticity regulation. *ESPN-ADCY1* complex is involved in microvillar elongation.
BDP1	B double prime 1, subunit of RNA polymerase III transcription initiation factor IIIB	DFNB49	–	–	–	–	–	–	–	–	–	+	+	+	–	–	–	–	Basilar membrane	Mouse	IHC	103	Component of U6 RNA transcriptional initiation complex. *BDP1* binds to U6 RNA polymerase III promotor.
CABP2	Calcium binding protein 2	DFNB93	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Brain, retina	Mouse	IF	104	Calcium-binding protein required for the regulation of Ca(v) 1.3 Ca^{2+} channels.
CCDC50	Coiled-coil domain-containing 50	DFNA44	–	+	NA	+	+	–	–	–	–	+	+	–	–	–	+	–		Mouse	IF	105	Effector of *EGF*-mediated cell signaling and required for microtubule-based cytoskeleton organization in pillar cells and the stria vascularis.
CDH23	Cadherin-related 23	DFNB12/USH1D	+	+	NA	–	–	–	–	NA	NA	NA	NA	+	NA	NA	NA	NA	Tip link, presynaptic region	Mouse, guinea pig	ISH, IF, EM	106, 107	Component of tip link and transient lateral links of stereocilia. Component of pre-synaptic region of IHCs and OHCs.
CEACAM16	Carcinoembryonic antigen-related cell adhesion molecule 16	AD-NSHL	+	+	–	+	+	–	–	–	–	–	–	–	+	+	–	–	Stereocillia tips	Mouse	IHC, IF, ISH, X-gal	108, 109	Glycoprotein that interacts with *TECTA*. *CEACAM16* may have a role in connecting stereocilia with the tectorial membrane.
CHD7	Chromodomain helicase DNA-binding protein 7	CHARGE syndrome	+	+	+	+	–	–	–	–	+	+	+	+	+	–	+	–	Boettcher's cells	Mouse	X-gal	110	Transcriptional regulator that binds to enhancer elements in the nucleoplasm. *CHD7* also functions as a positive regulator of ribosomal RNA biogenesis.
CIB2	Calcium- and integrin-binding family member 2	DFNB48/USH1J	+	+	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocilia	Mouse	GFP	23	Component of the tip-link region of stereocilia and interacts with *WHRN* and *MYO7A*. *CIB2* also functions as an inhibitor of calcium responses.
CLDN14	Claudin 14	DFNB29	+	+	–	+	+	+	+	–	–	–	–	+	–	+	–	–	Cuticular plate	Mouse	IF, X-gal, ISHI	60, 111	Component of tight junction complexes at the apex of the cuticular plate.
CLIC5	Chloride intracellular channel 5	DFNB102	+	+	–	–	–	–	–	–	–	–	–	–	+	–	–	–	Bottom of stereocilia	Mouse, rat	IF, GFP, EM	112, 113	Component of the chloride channels involved in chloride ion transport. *CLIC5* and *RDX* may stabilize the filamentous actin core of stereocilia.
CLPP	Caseinolytic mitochondrial matrix peptidase proteolytic subunit	PRLTS3	+	+	NA	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	Cuticular plate	Mouse	IF	114	Component of a mitochondrial ATP-dependent proteolytic complex, which is required for the stress response signaling pathway.
CLRN1	Clarin 1	USH3	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	Stereocilia, synapse of type I and 2 affarent neurons	Mouse	ISH. IF, EM	115-119	Expressed in photoreceptors and hair cell synapses and may be a component of pre-synaptic complexes in sensor cells.
COCH	Cochlin	DFNA9	–	–	–	–	–	–	–	+	–	+	–	–	–	–	+	–		Mouse, human	ISH, IHC, IF	119, 120	Extracellular matrix protein. *COCH* may contribute to the innate immune response against bacterial infection.
COL2A1	Collagen, type II, alpha 1	STL1	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–		Mouse	IF, EM	121	Structural components of the extracellular matrix of chondrocytes and the tectorial membrane.

(continued)

Table 1. (continued)

Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
COL4A3	Collagen, type IV, alpha 3	Alport syndrome	–	–	–	–	–	–	–	–	–	+	–	+	–	–	+	–	Basilar membrane, Schwann cells, spiral lamina	Human	IHC	86	Structural components of the extracellular matrix of the basilar membrane and spiral ligament.
			–	–	–	–	–	–	–	+	+	+	+	–	–	–	+	+	Basilar membrane	Mouse	IHC	122	
COL4A4	Collagen, type IV, alpha 4	Alport syndrome	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	+	Basilar membrane, spiral lamina	Mouse	IHC	122	Structural components of the extracellular matrix of the basilar membrane and spiral ligament.
COL4A5	Collagen, type IV, alpha 5	Alport syndrome	–	–	–	–	–	–	–	–	–	+	–	+	–	–	+	–	Basilar membrane, spiral lamina	Human	IHC	86	Structural components of the extracellular matrix of the basilar membrane and stria vascularis portion of the spiral ligament.
			–	–	–	–	–	–	–	+	+	+	+	–	–	–	+	+	Basilar membrane, spiral lamina	Mouse	IHC	122	
COL4A6	Collagen, type IV, alpha 6	X linked-NSHL	NA	NA	+	NA	NA	NA	NA	NA	NA	+	+	NA	NA	NA	NA	NA	Basilar membrane	Mouse	IHC	123	Structural components of the extracellular matrix of the basilar membrane and stria vascularis portion of the spiral ligament.
COL9A1	Collagen, type IX, alpha 1	STL4	–	–	–	–	–	–	–	–	–	+	–	–	–	+	+	–		Rat, mouse	IF, EM	82, 124	Structural components of the extracellular matrix of the tectorial membrane, covalently cross-linked to type II collagen.
COL9A2	Collagen, type IX, alpha 2	STL5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Cartilage-specific fibril-associated collagen. The function of this protein in the inner ear is not well known.
COL9A3	Collagen, type IX, alpha 3	AR-NSHL	–	–	–	–	–	–	–	–	–	+	–	–	–	+	+	–		Rat, mouse	IF, EM	82, 124	Structural components of the extracellular matrix of the tectorial membrane, covalently cross-linked to type II collagen.
COL11A1	Collagen, type XI, alpha 1	STL2	–	–	–	–	–	+	+	–	–	+	+	–	–	+	–	–	Greater epithelial ridge, lateral wall	Mouse	ISH	83	Structural components of the extracellular matrix of the tectorial membrane.
COL11A2	Collagen, type XI, alpha 2	DFNA13/ DFNB53/ STL3	–	–	–	–	–	+	+	–	–	+	+	–	–	–	+	–	Spiral limbus region	Mouse	ISH	84	Structural components of the extracellular matrix of the tectorial membrane.
CRYM	Crystallin, mu	AD-NSHL	–	–	–	NA	NA	NA	NA	NA	–	+	–	–	–	–	–	NA		Mouse	IF	125	Directly binds to thyroid hormone (T3) with high affinity in the presence of *NADPH*. *CRYM* and *NADPH* complex transport T3 into the nucleus and activate T3-dependent transcription.
DFNA5	Deafness, autosomal dominant 5	DFNA5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Inversely correlated with estrogen receptor gene expression. p53 induces *DFNA5* expression in response to DNA damage.
DFNB59	Pejvakin	DFNB59	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	Cochlea nuclei, kinocilium	Mouse	IF, ISH	126, 127	*DFNB59* is markedly similar to *DFNA5* and is important to the functioning of both hair cells and neurons. *PJVK* mutation causes ANSD.
DIAPH1	Diaphanous, drosophila, homolog of, 1	DFNA1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Actin polymerization protein in hair cells of the inner ear. *MITF* regulates *DIAPH1* expression.
DIAPH3	Diaphanous, drosophila, homolog of, 3	AD-ANSD1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Remodeling of cytoskeleton and may act in the elongation process of the non-branched actin filaments. *DIAPH3* directly binds to and stabilizes microtubules.

(continued)

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Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
DSPP	Dentin sialophosphoprotein	DFNA39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Small integrin-binding ligand N-linked glycoprotein family of secreted phosphoproteins, which are involved in bone mineralization.
EDN3	Endothelin 3	WS4	+	+	+	–	–	+	+	–	–	–	+	–	+	–	–	+	Boettcher's cells	Guinea pig	IF	128	*EDN3* directly binds to *EDNRB*. *EDN3-EDNRB* complex acts in the normal differentiation and development of melanocytes.
EDNRB	Endothelin receptor type B	WS4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	*EDNRB* required for normal differentiation and development of melanocytes. *SOX10* enhances the expression of *EDNRB*. *EDNRB* inhibits the Na-K transporter and activates G protein-coupled inwardly rectifying potassium channels (Kir-3).
ELMOD3	ELMO domain-containing protein 3	DFNB88	+	+	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		Rat	IF	129	ELMO domain-containing protein. *ELMOD3* has a role as a GTPase-activating protein for small GTPases.
EPS8	Epidermal growth factor receptor kinase substrate 8	AR-NSHL	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Tip of stereocilia	Mouse	IF	130	*MYO15A-WHRN-EPS8* complex has an essential role in stereocilia elongation.
ESPN	Espin	DFNB36	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocillia	Mouse	IHC	131	Directly binds to actin filaments. Actin-bundling activities of *ESPN* are not inhibited by calcium ions.
ESRRB	Estrogen-related receptor beta	DFNB35	+	+	+	+	+	+	+	–	–	+	+	+	–	–	+	–	Basilar membrane	Mouse, rat	ISH, IF	132	Estrogen-related receptor acts in epigenetic transcriptional induction at pluripotency loci during somatic cell reprogramming.
EYA1	Eyes absent homolog 1	BOR1	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	Eye	Mouse	ISH	133	Involved in the PAX-EYA-SIX regulatory pathway. *EYA1* act as a phosphorylation-dependent transcription factor or transcriptional modulator.
EYA4	Eyes absent homolog 4	DFNA10	NA	NA	+	NA	NA	+	+	+	+	–	–	–	–	–	+	+	Bony cochlea capsule	Rat	ISH	134	Involved in innate immune response regulation by modulating the phosphorylation of signal transducers for intracellular pathogens.
FOXI1	Forkhead box I 1	PDS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Transcriptional enhancer acts in the *SLC26A4* promoter. Digenic mutations of *FOXI1* and *SLC26A4* cause Pendred syndrome.
GIPC3	GIPC PDZ domain-containing family, member 3	DFNB15/ 72/95	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocilia	Mouse	IF	135	Required for postnatal maturation of hair bundles and also has potassium channel activity. *GIPC3* is required for long-term survival of hair cells and spiral ganglion.
GJB2	Gap junction protein, beta 2	DFNA3A/ DFNB1A	–	–	–	+	+	+	+	+	+	+	+	–	+	–	+	+		Rat	IF	136	Gap junction protein for potassium recirculation and the transport of other metabolites.
GJB3	Gap junction protein, beta 3	DFNA2B/ DFNB91	–	–	–	–	–	–	–	–	–	+	–	–	–	–	+	–	Auditory nerve fiber	Mouse	ISH	137	Gap junction protein gated by voltage. *GJB3* closes at low pH when exposed to long-chain alkanols.
GJB6	Gap junction protein, beta 6	DFNA3B/ DFNB1B	–	–	–	+	+	+	+	+	+	+	+	–	+	–	+	+		Rat	IF	136	Involved in the generation of the endocochlear potential (EP). *GJB6* is also required for auditory hair cell survival after the onset of hearing.
GPR98	G protein-coupled receptor 98	USH2C	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Ankle-link	Mouse	IF, EM	138	Large, calcium-binding protein expressed in the ankle link of stereocilia. *VLGR1* directly binds to *PDZD7*. *VLGR1* also expressed in the synaptic region of hair cells.

(continued)

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Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
GPSM2	G-protein signaling modulator 2	DFNB82	+	+	–	+	+	+	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	Apical surface of hair and supporting cells	Mouse	IF	52	G protein activation modulator, involved in embryonic neuroblast asymmetric cell division.
GRHL2	Grainyhead-like 2	DFNA28	–	–	–	–	–	–	–	–	–	–	+	+	–	NA	–	–	Basilar membrane	Mouse	ISH	139	Grainyhead-like transcription factor family protein. *GRHL2* has an essential role in epithelial morphogenesis and epidermal development.
GRXCR1	Glutaredoxin, cysteine-rich 1	DFNB25	+	+	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocilia	Mouse	IF, GFP	140	The glutaredoxin protein and the catalytic domain of this protein are predicted to be involved in the reversible S-glutathionylation.
GRXCR2	Glutaredoxin, cysteine-rich 2	DFNB101	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocilia bundle	NA	IF	141	Expressed in the stereocilia and has an essential role in maintaining stereocilia bundles. *GRXCR2* has a glutaredoxin domain but lacks catalytic activity.
HARS2	Histidyl-tRNA synthetase 2, mitochondrial	PRLTS2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Histidyl tRNA synthetase, a highly conserved tRNA synthetase for protein synthesis in mitochondria.
HGF	Hepatocyte growth factor	DFNB39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	*HGF/MET* signaling induces rearrangement of the actin cytoskeleton. Mutations in *HGF* cause hearing loss due to OHC degeneration and cochlea amplification loss.
HSD17B4	Hydroxysteroid (17-beta) dehydrogenase 4	PRLTS1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Enzyme involved in peroxisomal fatty acid beta-oxidation.
ILDR1	Immunoglobulin-like domain-containing receptor 1	DFNB42	+	+	–	+	+	+	–	–	–	–	–	–	–	–	–	–		Mouse	ISH	142	Involved in lipoprotein transport. *ILDR1* is expressed in the otic vesicle and lateral line organs in developing zebrafish.
KARS	Lysyl-tRNA synthetase	DFNB89	+	+	+	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Type II ganglion	Mouse	IF	143	Lysyl-tRNA synthetase, which acts in the aminoacylation of tRNA-lys in the cytoplasm and mitochondria.
KCNE1	Potassium voltage-gated channel, Isk-related family, member 1	Jervell and Lange-Nielsen syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	Heart, kidney	Mouse	IF	144	Voltage-gated potassium channel KQT-like subfamily protein. *KCNE1* is expressed on the apical surface of the marginal cells in the stria vascularis and is involved in EP generation by the endolymph, particularly in its high potassium ion concentration.
KCNJ10	Potassium inwardly rectifying channel, subfamily J, member 10	PDS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA		Mouse	ISH, IF	145	Inwardly rectifying potassium channel. The sensitivities of *KCNJ10* are controlled by intracellular pH but not extracellular pH.
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	Jervell and Lange-Nielsen syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	Heart, kidney	Mouse	IF	144	Voltage-gated potassium channel, KQT-like subfamily protein. *KCNQ1* has an important role in ion homeostasis of the endolymph, particularly in its high potassium ion concentration.
KCNQ4	Potassium voltage-gated channel, KQT-like subfamily, member 4	DFNA2A	–	+	NA	NA	–	NA	NA	NA	–	NA	–	NA	NA	–	–	NA		Mouse	ISH, IF	146, 147	Member of the voltage-gated potassium channel gene family for OHC. Alternative transcriptional variants without Ca^{2+} binding domain for auto-regulation are expressed at the basal turn of the mouse cochlea.

(continued)

Table 1. (continued)

Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
LARS2	Leucyl-tRNA synthetase 2, mitochondrial	PRLTS4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Leucyl aminoacyl-tRNA synthetases containing a mitochondrial-targeting sequence.
LHFPL5	Lipoma HMGIC fusion partner-like 5	DFNB66/67	+	+	NA	+	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tip of stereocilia	Mouse	IF	148	Tetraspan membrane protein of hair cell stereocilia and involved in the tip link complex.
LOXHD1	Lipoxygenase homology domains 1	DFNB77	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Stereocillia	Mouse	ISH, IF	43	Involved in the regulation of stereocilia elongation. Mutation of *LOXHD1* causes "fused stereocilia" and "membrane ruffling" at the apical surface of hair cells.
LRTOMT/ COMT2	Leucine-rich transmembrane and O-methyltransferase domain-containing	DFNB63	+	+	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		Mouse	IF	149	*LRTOMT* encodes 2 different reading frame proteins. Its expression is restricted to hair cells of the cochlea and vestibule, and may be involved in the maintenance of stereocilia.
MARVELD2	Tricellulin	DFNB49	+	+	NA	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA		Mouse	IF	150	Tight junction protein that contributes to the structure and function of tricellular contacts between neighboring cells.
MIR96	Micro-RNA 96	DFNA50	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		Mouse	ISH	151	Non-coding microRNA that down-regulates *MITF*, *SLC26A5*, and *PTPRQ* gene expression. *MIR96* expression is restricted to IHCs, OHCs, and spiral ganglions.
MITF	Microphthalmia-associated transcription factor	WS2A	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Important for the development of various types of neural crest-derived melanocytes. *SOX10* and *PAX3* directly regulate *MITF* gene expression.
MSRB3	Methionine sulfoxide reductase B3	DFNB74	+	+	+	NA	+	NA	NA	NA	NA	NA	–	NA	NA	NA	NA	NA	Stereocilia	Mouse	IF	152	Involved in the oxi-reduction of oxidized methionine residues. *MSRB3* is required for the repair of oxidatively damaged proteins.
MYH9	Myosin, heavy chain 9, non-muscle	DFNA17	–	+	–	+	+	+	+	+	+	+	–	+	–	–	+	+		Rat	IHC	153	*MYH9* encodes a non-muscle myosin and may be involved in actin degeneration and reorganization of the actomyosin network.
MYH14	Myosin, heavy chain 14, non-muscle	DFNA4	+	+	–	+	+	+	+	+	+	+	+	–	–	–	–	–		Mouse	IHC	154	ATP-dependent molecular motors that interact with cytoskeletal actin. *MYH14* is involved in the regulation of cytokinesis, cell motility, and cell polarity.
MYO3A	Unconventional myosin IIIA	DFNB30	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tips of stereocilia	Rat	IF	155	Myosin IIIA expression is restricted to the retina and IHCs and OHCs of the cochlea. *MYO3A* is localized in the tip density region of stereocilia and acts in the maintenance of stereocilia morphology.
MYO6	Unconventional myosin VI	DFNA22/ DFNB37	+	+	–	NA	NA	NA	NA	–	–	–	–	–	–	–	–	–	Stereocilia	Mouse, rabbit	IF	156	*MYO6* is expressed in the cuticular plate region of IHCs and OHCs. *MYO6* is involved in stereocilia formation and may have an important role in anchoring stereocilia.
MYO7A	Unconventional myosin VIIA	DFNA11/ DFNB2/ USH1B	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocilia	Mouse	IF	157	*MYO7A* encodes a component of the USH complex (including *CDH23*, *SANS*, *USH1C*, and *MYO7A*) in the tip links of stereocilia.

(continued)

Table 1. (continued)

Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
MYO15A	Unconventional myosin XVA	DFNB3	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–		Mouse, rat, guinea pig	IF	158	*MYO15A* directly binds to *WHRN* to form the *MYO15A-WHRN-EPS8* complex of stereocilia. This complex is essential for stereocilia elongation.
NDP	Norrie disease	Norrie disease	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	Capillary plexus between the Corti and the spiral ganglion	Mouse	AP	159	Cystine knot growth factor family protein (norrin). *NDP* induces the FZD4- and LRP-dependent activation of the classic Wnt signaling pathway.
OTOA	Otoancorin	DFNB22	+	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	Apical surface of the spiral limbus	Mouse	IF	160	Non-collagenous glycoproteins of the acellular gels of the inner ear. *OTOA* stabilizes the conformation of tectorial members.
OTOF	Otoferlin	DFNB9	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	Ribbon synapse	Mouse	IF	21	Correlated with afferent synaptogenesis and involved in the late step of synaptic vesicle exocytosis. *OTOF* may act as the major Ca^{2+} sensor for IHCI ribbon synapses.
OTOG	Otogelin	AR-NSHL	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	Basilar membrane, otoconial membrane	Mouse	X-gal, IF	161	N-glycosylated protein comprising the acellular membranes of the tectorial membrane.
OTOGL	Otogelin-like protein	DFNB84	+	+	–	+	+	–	+	–	+	–	–	–	+	+	–	–		Mouse	IF	88	Acellular membranes of the cochlea and vestibular system.
P2RX2	Purinergic receptor P2X, ligand-gated ion channel, 2	DFNA41	+	+	+	+	+	–	–	–	+	–	–	+	–	–	+	–		Mouse	IF	162	ATP activates *P2RX2* channels to modify OHC electromotility. Extracellular Ca^{2+} is required for the effective gating.
PAX3	Paired box 3	WS1/WS3	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	Glial cells	Mouse	X-gal	163	*SOX10* and *PAX3* strongly activate *MITF* gene expression, which is required for the differentiation and development of melanocytes.
PCDH15	Protocadherin 15	DFNB23/ USH1F	+	+	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tip-link	Mouse	IF	164	Component of the tip links and transient lateral links of stereocilia. *PCDH15* and *CDH23* directly bind to form the tip link.
PDZD7	PDZ domain-containing 7	USH2C	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Ankle-link	Mouse	IF	165	*PDZD7* encodes a component of the USH complex and is expressed in stereocilia. *PDZD7* interacts with *SANS* (*USH1G*), *GPR98*, and *USH2A*.
PNPT1	Polyribonucleotide nucleotidyltransferase 1, mitochondrial	DFNB70	+	+	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		Mouse	IF	166	Subunit of the exosome complex. *PNPT1* has 3-prime-to-5-prime exoribonuclease activity and is involved in the import of RNAs to the mitochondria.
POLR1C	Polymerase I, RNA, subunit C	TCS3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Subunit of the RNA polymerase III complex.
POLR1D	Polymerase I, RNA, subunit D	TCS2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	16-kDa subunit of mouse RNA polymerase I complex.
POU3F4	POU domain, class 3, transcription factor 4	DFNX2 (DFN3)	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–		Mouse	ISH	167	Transcription factor restrictedly expressed in the spiral ligament fibrocytes. *POU3F4* may have a role in potassium ion homeostasis.
POU4F3	POU domain, class 4, transcription factor 3	DFNA15	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–		Mouse	X-gal, GFP	168	POU family of transcription factors and is involved in the maintenance of inner ear hair cells. *POU4F3* activates *MYO7A* gene expression.

(continued)

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Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
PRPS1	Phosphoribosyl pyrophosphate synthetase 1	DFNX1 (DFN2)	+	+	+	–	–	–	+	–	–	–	–	–	–	–	–	–	Greater epithelial ridge	Mouse	ISH	169	Phosphoribosylpyrophosphate synthetase that catalyzes the phosphoribosylation of ribose 5-phosphate to 5-phosphoribosyl-1-pyrophosphate. *PNPT1* is necessary for the salvage pathways of purine and pyrimidine biosynthesis.
PTPRQ	Protein tyrosine phosphatase, receptor type, Q	DFNB84	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Basal region of stereocilia	Rat, chick, mouse, frog	IF, EM	170, 171	Protein tyrosine phosphatase receptor protein and has an important role in shaft connector formation in hair bundles. *PTPRQ* is necessary for the long-term survival of high-frequency auditory hair cells.
RDX	Radixin	DFNB24	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Stereocilia	Mouse	IF	36	Cytoskeletal protein that may be involved in anchoring actin to the plasma membrane of cochlea stereocilia.
SANS	Scaffold-containing ankyrin repeats and SAM domain	USH1G	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocilia	Rat, guinea pig	IF, GFP	172	*SANS* interacts with *USH1C*, and *MYO7A* directly. This protein is involved in hair bundle cohesion.
SEMA3E	Sema domain, immunoglobulin domain, short basic domain, secreted, 3E	CHARGE syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Encoding high-affinity proteins to receptor plexin D1. *SEMA3E* is a critical determinant of synaptic specificity in sensory motor circuits in mice.
SERPINB6	Serpin peptidase inhibitor, clade B, member 6	AR-NSHL	+	+	–	–	–	–	+	+	–	+	+	–	–	–	+	+	Lateral wall	Mouse	IF, GFP	173	*SERPINB6* encodes serpin peptidase inhibitor protein. *SERPINB6* has no effect on cochlear development but is required for cochlea homeostasis.
SIX1	SIX homeobox 1	DFNA23/ BOS3	+	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	Greater epithelial ridge	Mouse	X-gal	174	PAX-EYA-SIX regulatory pathway (*PAX3* and *EYA2* are involved in cochlea hair cells). *SIX1* has phosphorylation-dependent transcription modulation activity.
			+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Otocyst	NA	ISH	98	
SIX5	SIX homeobox 5	BOS2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	*SIX5* encodes an activator of *IGFBP5* expression, and a mutation in this gene causes Myotonic Dystrophy or BOR syndrome.
SLC17A8	Vesicular glutamate transporter 3	DFNA25	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–		Mouse, rat	IF	175, 176	Glutamate transporter protein acts in glutamate release from hair cells at the first synapse of the auditory pathway.
SLC26A4	Pendrin	DFNB4/ PDS	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	Spindle-shaped cells	Mouse	ISH, IF	177, 178	Acts as a chloride, bicarbonate, and iodide ion transporter in the spiral prominence. Pendrin also contributes to pH homeostasis and mineralization in the organ of Corti and vestibular organs.
SLC26A5	Prestin	DFNB61	–	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		Rat	IF	179	Prestin is the motor protein of cochlea OHCs and is involved in the sound amplification process.
SMAC/DIABLO	Second mitochondriai-derived activator of caspase	DFNA64	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Greater epithelial ridge	Mouse	IF	180	Regulates programmed cell death (apotosis) in specific situations or tissues.
SMPX	Small muscle protein, X-linked	DFNX4 (DFN6)	+	+	–	+	+	–	–	–	+	–	–	–	–	–	–	–	Boettcher's cells, root cells	Mouse	IF	181	*SMPX* encodes small muscle proteins that may protect the hearing organs from mechanical stress.
SNAI2	Snail family zinc finger 2	WS2D	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	Snail family of zinc finger transcription factor 2 triggers epithelial-mesenchymal transitions and developmental processes.

(continued)

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Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
SOX10	SRY (sex determining region Y)-box 10	WS4	–	–	+	+	+	+	+	+	+	–	+	+	+	–	–	+	Hair bundles	Mouse	GFP	182	*PAX3* and *SOX10* interact directly with the promoter of *MITF* and *RET* genes, which encode the central melanocyte developmental transcription factors.
STRC	Stereocilin	DFNB16	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Stereocilia	Mouse	IF	37	Associated with horizontal tip connectors and lateral links between adjacent stereocilia within OHC hair bundles.
SYNE4	Nesprin-4	DFNB76	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	Nuclear envelope	Mouse	IF	183	Contributes to microtubule-dependent nuclear positioning and necessary for the viability and normal morphology of OHCs.
TBC1D24	TBC1 domain family, member 24	DFNA65/	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–		Mouse	IF	184	*TBC1D24* coordinates Rab proteins and other GTPases for the proper transport of intracellular vesicles. *TBC1D24* directly binds to ARF6 and regulates exo- and endocytosis.
		DFNB86	+	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Stereocillia	Mouse	IF	26, 185	
TCOF1	Treacher Collins-Franceschetti syndrome 1	TCS1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	*TCOF1* has an important role in the production of mature ribosomes by the 2-prime-O-methylation of pre-rRNA. Mutations on *TCOF1* lead to apoptosis and reduced cell proliferation.
TECTA	Tectorin alpha	DFNA8/12/ DFNB21	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–		Mouse	IF	81	Encodes alpha-tectorin, one of the major non-collagenous components of the tectorial membrane.
TJP2	Tight junction protein ZO 2	DFNA51	+	+	NA	+	+	NA	NA	NA	NA	–	–	NA	NA	NA	NA	NA		Mouse	IF	54	Tight junction proteins that bind to adjacent cells in the organ of Corti. *TJP2* may act as barrier to prevent potassium ion K^+ leakage from the apical side of hair cells.
TMC1	Transmembrane channel-like protein 1	DFNA36/	+	+	+	–	+	+	+	+	–	–	–	–	–	+	+	–		Mouse	IF	186	Required for voltage-dependent mechanotransduction currents. *TMC1* is suspected of being a component of the MET channel in hair cells.
		DFNB7/11	+	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–		Mouse	ISH	38	
TMIE	Transmembrane inner ear–expressed protein	DFNB6	+	+	–	+	+	+	+	–	–	–	+	+	–	–	–	–	Stereocilia	Mouse	ISH, IF	187	*TMIE* is required for normal postnatal maturation of sensory hair cells in the cochlea, including the development of stereocilia bundles.
TMPRSS3	Transmembrane protease, serine 3	DFNB8/ 10	+	–	+	–	–	–	–	–	NA	NA	NA	NA	NA	NA	NA	NA		Mouse	IF	188	Involved in the maturation of the epithelial amiloride-sensitive sodium channel (ENaC) and K^+ channel (*KCNMA1*).
			+	+	+	–	+	+	+	+	–	+	–	–	+	–	–	+		Mouse	ISH	189	
TNC	Tenascin C	DFNA56	–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Basilar membrane, spiral lamina	Human	IF	190	Extracellular matrix protein present in the basilar membrane and osseous spiral lamina.
TPRN	Taperin	DFNB79	+	+	–	+	+	+	+	–	–	–	–	+	–	–	–	–	Tapered region of stereocilia	Mouse	IF	191	Endcodes the taparin protein, which is localized in the tapered region of each stereocilium. Taperin is required for the tapered structure of stereocilia.

(continued)

Table 1. (continued)

Gene Symbol	Gene Name	Locus	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulcus Cell	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Inter Dental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Other/Detail	Model	Method	Reference	Suspected Function (Description Survey Results)[a]
TRIOBP	TRIO and F-actin-binding protein	DFNB28	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	Rootlets of stereocilia	Mouse	IF, EM	192	Encodes the actin-binding protein and is essential for the development of rootlets that provide durable flexibility and mechanical rigidity to the stereocilia bundles.
TSPEAR	Thrombospondin-type laminin G domain and EAR repeats	DFNB98	+	+	+	NA	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	Basal region of stereocilia	Mouse	IF	193	Thrombospondin-type laminin G domain and EAR repeats-containing protein. *TSPEAR* expressed in the base of the hair bundles of inner and outer hair cells.
USH1C	Harmonin	DFNB18/ USH1C	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Hair bundles	Mouse	IF	194, 195	Scaffold protein for *CDH23*, *SANS*, and *MYO7A* complexes in the tip link of stereocillia.
USH2A	Usherin	USH2A	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tip of stereocilia ankle-link	Mouse	IF	196	Scaffold protein and forms a complex with *USH1C* and *VLGR1*. Usherin is present in the ankle links in stereocilia.
WFS1	Wolframin	DFNA6/ 14/38	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	Endoplasmic reticulum	Mouse	IF, ISH	197	Encodes the endoplasmic reticulum protein and may act as an ER calcium channel or regulator of ER calcium channel activity. *WFS1* may be involved in ER stress responses.
WHRN	Whirlin	DFNB31/ USH2D	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Tip of stereocilia ankle-link	Mouse	IF	198	Scaffolding protein that facilitates synaptic transmission in the central nervous system. *SANS*, *EPS8*, and *MYO15A* are colocalized with *WHRN* in the tip of stereocilia.

Abbreviations: BOR, branchiootorenal syndrome; EM, electron microscopy; IF, immunofluorescence; IHC, immunohistochemistry; ISH, in situ hybridization; NSHL, nonsyndromic hearing loss; PRLTS, Perrault syndrome; STL:, Stickler syndrome; TCS: Treacher Collins syndrome; USH, Usher syndrome; WS, Waardenburg Syndrome; +, expressed; –, not expressed; NA, not applicable.
[a]Suspected functions were summarized from the description in the OMIM database (http://omim.org) and each reference.

Table 2. Summary of Gene Expression Profiles of the Causative Genes and Localization of the Encoded Proteins Involved in Hereditary Hearing Loss in the Vestibular Endorgans.

Gene Symbol	Gene Name	Locus	Semicircular Canal	Utricle	Saccule	Hair Cell Type I	Hair Cell Type II	Support Cell	Transitional Epithelium	Model	Method	Reference
ACTG1	Actin gamma 1	DFNA20/26	NA	NA	NA	+	+	+	NA	Mouse, guinea pig	IF	199
ADCY1	Adenylate cyclase type 1	DFNB44	NA	+	NA	+	+	+	NA	Mouse	IF	102
BDP1	B double prime 1, subunit Of RNA polymerase III transcription initiation factor IIIB	DFNB49	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CABP2	Calcium-binding protein 2	DFNB93	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CCDC50	Coiled-coil domain-containing 50	DFNA44	NA	+	+	+	+	+	NA	Mouse	IF	105
CDH23	Cadherin-related 23	DFNB12/USH1D	+	+	+	+	+	+	+	Mouse	ISH	200, 201
CEACAM16	Carcinoembryonic antigen-related cell adhesion molecule 16	AD-NSHL	NA	NA	+	NA	NA	NA	NA	Mouse	ISH	202
CHD7	Chromodomain helicase DNA-binding protein 7	CHARGE syndrome	–	+	+	–	–	–	–	Mouse	IF	203
CIB2	Calcium- and integrin-binding family member 2	DFNB48/USH1J	NA	NA	NA	+	+	+	NA	Mouse	IF	204
CLDN14	Claudin 14	DFNB29	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CLIC5	Chloride intracellular channel 5	DFNB102	NA	NA	NA	+	+	NA	NA	Mouse	IF	113
CLPP	Caseinolytic mitochondrial matrix peptidase proteolytic subunit	Perrault syndrome 3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CLRN1	Clarin 1	USH3	NA	NA	+	+	+	NA	NA	Mouse	ISH	115
COCH	Cochlin	DFNA9	+	NA	NA	–	–	–	–	Mouse, human	IF, ISH, IHC	119, 205
COL2A1	Collagen, type II, alpha 1	Stickler syndrome	+	+	NA	NA	NA	NA	NA	Mouse	IF	81
COL4A3	Collagen, type IV, alpha 3 (Goodpasture antigen)	Alport syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL4A4	Collagen, type IV, alpha 4	Alport syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL4A5	Collagen, type IV, alpha 5	Alport syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL4A6	Collagen, type IV, alpha 6	X linked-NSHL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL9A1	Collagen, type IX, alpha 1	Stickler syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL9A2	Collagen, type IX, alpha 2	Stickler syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL11A1	Collagen, type XI, alpha 1	Stickler syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COL11A2	Collagen, type XI, alpha 2	DFNA13/DFNB53/ Stickler syndrome	+	+	+	NA	NA	NA	NA	Mouse	ISH	84
CRYM	Crystallin, mu	AD-NSHL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DFNA5	Deafness, autosomal dominant 5	DFNA5	+	NA	NA	NA	NA	NA	NA	Zebrafish	ISH	206
DFNB59	Pejvakin	DFNB59	+	+	+	NA	NA	NA	NA	Mouse	IF	126

(continued)

Table 2. (continued)

Gene Symbol	Gene Name	Locus	Semicircular Canal	Utricle	Saccule	Hair Cell Type I	Hair Cell Type II	Support Cell	Transitional Epithelium	Model	Method	Reference
DIAPH1	Diaphanous, drosophila, homolog of, 1	DFNA1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DIAPH3	Diaphanous, drosophila, homolog of, 3	AD-ANSD1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DSPP	Dentin sialophosphoprotein	DFNA39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EDN3	Endothelin 3	Waardenburg Syndrome type IV	+	+	+	–	–	–	–	Mouse	IHC	207
EDNRB	Endothelin receptor type B	Waardenburg Syndrome type IV	+	+	+	–	–	–	–	Mouse	IHC	207
ELMOD3	ELMO domain-containing protein 3	DFNB88	NA	+	+	+	+	NA	NA	Mouse	IF	129
EPS8	Epidermal growth factor receptor kinase substrate 8	AR-NSHL	NA	NA	NA	+	+	–	–	Rat, Mouse	IF	130
ESPN	Espin	DFNB36	+	+	+	+	+	NA	NA	Rat	IHC	131
ESRRB	Estrogen-related receptor beta	DFNB35	–	+	–	–	–	–	–	Mouse	ISH	132
EYA1	Eyes absent homolog 1	BOR syndrome 1	–	+	+	+	+	–	+	Mouse	ISH	208
EYA4	Eyes absent homolog 4	DFNA10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FOXI1	Forkhead box I1	Pendred syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GIPC3	GIPC PDZ domain-containing family, member 3	DFNB15/72/95	NA	NA	NA	+	+	NA	NA	Mouse	IF	135
GJB2	Gap junction protein, beta 2	DFNA3A/DFNB1A	NA	+	+	–	–	+	–	Mouse	IF	209
GJB3	Gap junction protein, beta 3	DFNA2B/DFNB91	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GJB6	Gap junction protein, beta 6	DFNA3B/DFNB1B	NA	+	+	–	–	+	–	Mouse	IF	209
GPR98 (VLGR1)	G protein-coupled receptor 98	USH2C	NA	+	NA	+	+	NA	NA	Mouse	IF	138
GPSM2	G-protein signaling modulator 2	DFNB82	NA	+	+	+	+	+	–	Mouse	IF	52
GRHL2	Grainyhead-like 2	DFNA28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GRXCR1	Glutaredoxin, cysteine RIHC 1	DFNB25	NA	+	NA	+	+	–	+	Mouse	IHC	140
GRXCR2	Glutaredoxin, cysteine RIHC 2	DFNB101	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HARS2	Histidyl-trna synthetase 2, mitochondrial	Perrault syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HGF	Hepatocyte growth factor	DFNB39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HSD17B4	Hydroxysteroid (17-beta) dehydrogenase 4	Perrault syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ILDR1	Immunoglobulin-like domain-containing receptor 1	DFNB42	NA	NA	NA	+	+	+	NA	Mouse	ISH	142
ILDR1	Immunoglobulin-like domain-containing receptor 1	DFNB42	NA	NA	+	NA	NA	NA	NA	Mouse	IHC	210
KARS	Lysyl-tRNA synthetase	DFNB89	–	–	–	+	+	+	–	Mouse	IF	143

(continued)

Table 2. (continued)

Gene Symbol	Gene Name	Locus	Semicircular Canal	Utricle	Saccule	Hair Cell Type I	Hair Cell Type II	Support Cell	Transitional Epithelium	Model	Method	Reference
KCNE1	Potassium voltage-gated channel, Isk-related family, member 1	Jervell and Lange-Nielsen syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
KCNJ10	Potassium inwardly rectifying channel, subfamily J, member 10	Pendred syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	Jervell and Lange-Nielsen syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
KCNQ4	Potassium voltage-gated channel, KQT-like subfamily, member 4	DFNA2A	–	+	+	+	+	+	NA	Mouse	IHC	211
LARS2	Leucyl-tRNA synthetase 2, mitochondrial	Perrault syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LHFPL5 (TMHS)	Lipoma HMGIC fusion partner-like 5	DFNB66/67	NA	+	+	+	+	+	NA	Mouse	IHC	14
LOXHD1	Lipoxygenase homology domains 1	DFNB77	NA	NA	+	+	+	–	NA	Mouse	ISH, IF	212
LRTOMT/ COMT2	Leucine RIHC Transmembrane and O-methyltransferase domain-containing	DFNB63	NA	+	+	+	+	+	NA	Mouse	ISH, IHC	149
MARVELD2	Tricellulin	DFNB49	NA	+	NA	+	+	+	NA	Mouse	IF	53, 150
MIR96	Micro-RNA 96	DFNA50	NA	NA	NA	+	+	-	NA	Mouse	ISH	213
MITF	Microphthalmia-associated transcription factor	Waardenburg Syndrome type IIA	–	–	–	–	–	–	–	Mouse	ISH	214
MSRB3	Methionine sulfoxide reductase B3	DFNB74	NA	NA	NA	+	+	+	NA	Mouse	IF	152
MYH9	Myosin, heavy chain 9, non-muscle	DFNA17	–	–	–	–	–	–	–	Rat	ISH	153
MYH14	Myosin, heavy chain 14, non-muscle	DFNA4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MYO3A	Unconventional myosin IIIA	DFNB30	NA	+	+	+	+	–	NA	Rat	IHC	155
MYO6	Unconventional myosin VI	DFNA22/DFNB37	NA	+	+	+	+	–	NA	Lake sturgeon, zebrafish, oscae, american shad, *Xenopus*	IHC	215
MYO6	Unconventional myosin VI	DFNA22/DFNB37	NA	+	NA	+	+	–	NA	Mouse	IHC	216
MYO7A	Unconventional myosin VIIA	DFNA11/DFNB2/ USH1B	NA	NA	NA	+	+	–	NA	Mouse, rat, guinea pig	IHC	157
MYO15A	Unconventional myosin XVA	DFNB3	NA	+	+	+	+	–	NA	Mouse, rat, guinea pig	IF	158

(continued)

Table 2. (continued)

Gene Symbol	Gene Name	Locus	Semicircular Canal	Utricle	Saccule	Hair Cell Type I	Hair Cell Type II	Support Cell	Transitional Epithelium	Model	Method	Reference
NDP	Norrie disease	Norrie disease	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
OTOA	Otoancorin	DFNB22	NA	+	+	+	+	–	NA	Mouse	IF	160
OTOF	Otoferlin	DFNB9	NA	+	NA	+	+	–	NA	Mouse	IF	217
OTOG	Otogelin	AR-NSHL	NA	+	+	–	–	–	–	Mouse	IF	218
OTOGL	Otogelin-like protein	DFNB84	NA	+	+	+	+	–	–	Mouse, zebrafish	ISH, IHC	88
P2RX2	Purinergic receptor P2X, ligand-gated ion channel, 2	DFNA41	NA	NA	NA	+	+	+	NA	Rat	GFP	219
PAX3	Paired box 3	Waardenburg syndrome type I/III	+	+	+	+	+	–	–	Mouse	X-gal	163
PCDH15	Protocadherin 15	DFNB23/USH1F	NA	+	+	+	+	–	NA	Mouse	IHC	220
PDZD7	PDZ domain-containing 7	Usher syndrome	NA	+	+	+	+	–	NA	Mouse, rat, chicken	IHC	165
PNPT1	Polyribonucleotide nucleotidyltransferase 1, mitochondrial	DFNB70	NA	NA	NA	+	NA	NA	NA	NA	NA	NA
POLR1C	Polymerase I, RNA, subunit C	Treacher Collins syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
POLR1D	Polymerase I, RNA, subunit D	Treacher Collins syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
POU3F4	POU domain, class 3, transcription factor 4	DFNX2 (DFN3)	NA	NA	NA	+	+	–	NA	Mouse	IF	221
POU4F3	POU domain, class 4, transcription factor 3	DFNA15	+	+	+	+	+	–	NA	Mouse	GFP	168
PRPS1	Phosphoribosyl pyrophosphate synthetase 1	DFNX1 (DFN2)	NA	+	NA	+	+	–	–	Murine	IHC	169
PTPRQ	Protein tyrosine phosphatase, receptor type, Q	DFNB84	NA	+	+	+	+	–	–	Mouse	IF	171
RDX	Radixin	DFNB24	NA	NA	NA	+	+	–	NA	Mouse	IF	222
SANS	Scaffold-containing ankyrin repeats and SAM domain	USH1G	NA	NA	NA	+	+	NA	NA	Guinea pig, rat	IHC	157
SEMA3E	Sema domain, immunoglobulin domain, short basic domain, secreted, 3E	CHARGE syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SERPINB6	Serpin peptidase inhibitor, clade B, member 6	AR-NSHL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SIX1	SIX homeobox 1	DFNA23	+	+	+	+	+	–	NA	Mouse	X-gal	174
SIX5	SIX homeobox 5	Alport syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SLC17A8	Vesicular glutamate transporter 3	DFNA25	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SLC26A4	Pendrin	DFNB4/Pendred syndrome	–	+	+	–	–	–	+	Mouse	ISH, IHC	177, 178
SLC26A5	Prestin	DFNB61	NA	+	+	+	+	–	NA	Mouse	ISH, IHC	223

(continued)

Table 2. (continued)

Gene Symbol	Gene Name	Locus	Semicircular Canal	Utricle	Saccule	Hair Cell Type I	Hair Cell Type II	Support Cell	Transitional Epithelium	Model	Method	Reference
SMAC/ DIABLO	Second mitochondriai-derived activator of caspase	DFNA64	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SMPX	Small muscle protein, X-linked	DFNX4 (DFN6)	+	+	NA	+	+	–	NA	Mouse	ISH	224
SNAI2	Snail family zinc finger 2	Waardenburg syndrome type IID	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SOX10	SRY (sex determining region Y)-Box 10	Waardenburg syndrome type IV	+	+	+	–	–	–	NA	Mouse	ISH	214
STRC	Stereocilin	DFNB16	NA	+	+	+	+	–	NA	Mouse	IF	37
SYNE4	Nesprin-4	DFNB76	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TBC1D24	TBC1 domain family, member 24	DFNA65/DFNB86	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TCOF1	Treacher Collins-Franceschetti syndrome 1	Treacher Collins syndrome	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TECTA	Tectorin alpha	DFNA8/12/DFNB21	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TJP2	Tight junction protein ZO 2	DFNA51	NA	+	+	–	–	+	NA	Mouse	IHC	54
TMC1	Transmembrane channel-like protein 1	DFNA36/DFNB7/11	+	+	NA	NA	NA	NA	NA	Mouse	ISH	225
TMC1	Transmembrane channel-like protein 1	DFNA36/DFNB7/11	NA	NA	NA	+	+	NA	NA	Mouse	ISH	38
TMIE	Transmembrane inner ear expressed protein	DFNB6	NA	+	+	+	+	–	–	Rat	IHC	187
TMPRSS3	Transmembrane protease, serine 3	DFNB8/ 10	NA	+	+	+	+	–	–	Mouse	ISH	189
TNC	Tenascin C	DFNA56	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TPRN	Taperin	DFNB79	NA	NA	+	+	+	–	–	Mouse	GFP	191
TRIOBP	TRIO and F-actin-binding protein	DFNB28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TSPEAR	Thrombospondin-type laminin G domain and EAR REPEATS	DFNB98	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
USH1C	Harmonin	DFNB18/USH1C	+	+	+	+	+	–	–	Mouse	IF	194
USH2A	Usherin	USH2A	NA	NA	NA	+	+	–	NA	Mouse	IF	226
WFS1	Wolframin	DFNA6/14/38	NA	NA	NA	+	+	+	NA	Mouse	ISH, IHC	197
WHRN	Whirlin	DFNB31/USH2D	NA	+	NA	+	+	–	NA	Mouse	IF	227

Abbreviations: BOR, branchiootorenal syndrome; EM, electron microscopy; IF, immunofluorescence; IHC, immunohistochemistry; ISH, in situ hybridization; NSHL, nonsyndromic hearing loss; PRLTS, Perrault syndrome; STL:, Stickler syndrome; TCS: Treacher Collins syndrome; USH, Usher syndrome; WS, Waardenburg Syndrome; +, expressed; –, not expressed; NA, not applicable.

Table 3. Summary of Gene Ontology Analysis of Each Cell Type in the Cochlea and Vestibular Endorgan.[a]

	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulucus	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Interdental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Vestibular Type1 Hair Cell	Vestibular Type 2 Hair Cell	Supporting Cell	Transitional Cell
Cell adhesion molecule	CDH23 CEACAM16 OTOGL PCDH15 PTPRQ	CDH23 CEACAM16 OTOGL PCDH15 PTPRQ		CEACAM16 OTOGL	CEACAM16 OTOGL		OTOGL	COCH	OTOGL	COCH		CDH23	CEACAM16 OTOG OTOGL	CEACAM16 TECTA OTOG OTOGL	COCH		CDH23 OTOGL PCDH15 PTPRQ	CDH23 OTOGL PCDH15 PTPRQ		
Cell junction protein	CDH23 CLDN14 MARVELD2 MYH14 MYO3A MYO6 MYO7A MYO15A TJP2	CDH23 CLDN14 MARVELD2 MYH9 MYH14 MYO3A MYO6 MYO7A MYO15A TJP2		CLDN14 GJB2 GJB6 MYH9 MYH14 TJP2	CLDN14 GJB2 GJB6 MYH9 MYH14 TJP2	CLDN14 GJB2 GJB6 MYH9 MYH14	CLDN14 GJB2 GJB6 MYH9 MYH14	GJB2 GJB6 MYH9 MYH14	GJB2 GJB6 MYH9 MYH14	GJB2 GJB3 GJB6 MYH9 MYH14	GJB2 GJB6 MARVELD2 MYH14	CDH23 CLDN14 MYH9	GJB2 GJB6	CLDN14	GJB2 GJB3 GJB6 MYH9	GJB2 GJB6 MYH9	CDH23 MARVELD2 MYO3A MYO6 MYO7A MYO15A	CDH23 MARVELD2 MYO3A MYO6 MYO7A MYO15A	GJB2 GJB6 MARVELD2 TJB2	
Cytoskeletal protein	ACTG1 CLIC5 ESPN PDZD7 RDX TRIOBP MYH14 MYO3A MYO6 MYO7A MYO15A USH1C WHRN	ACTG1 CLIC5 ESPN PDZD7 RDX TRIOBP MYH9 MYH14 MYO3A MYO6 MYO7A MYO15A USH1C WHRN		ACTG1 TRIOBP MYH9 MYH14	TRIOBP MYH9 MYH14	MYH9 MYH14	MYH9 MYH14	MYH9 MYH14	MYH9 MYH14	MYH9 MYH14	MYH14	MYH9	CLIC5		MYH9	MYH9	ACTG1 CLIC5 ESPN PDZD7 RDX MYO3A MYO6 MYO7A MYO15A USH1C WHRN	ACTG1 CLIC5 ESPN PDZD7 RDX MYO3A MYO6 MYO7A MYO15A USH1C WHRN	ACTG1	
Enzyme modulator	GPSM2 LOXHD1 MYH9 MYH14 MYO3A MYO6 MYO7A MYO15A SERPINB6 TBCID24 TMRSS3 TRIOBP	GPSM2 LOXHD1 MYH9 MYH14 MYO3A MYO6 MYO7A MYO15A SERPINB6 TBCID24 TRIOBP	TBC1D24 TMPRSS3 TRIOBP	GPSM2 MYH9 MYH14 TRIOBP	GPSM2 MYH14	GPSM2 MYH9 MYH14	MYH9 MYH14 SERPINB6	MYH9 MYH14 SERPINB6	MYH9 MYH14	MYH9 MYH14 SERPINB6	MYH14 SERPINB6	MYH9			MYH9 SERPINB6	MYH9 SERPINB6	GPSM2 LOXHD1 MYO3A MYO6 MYO7A MYO15A TMPRSS3	GPSM2 LOXHD1 MYO3A MYO6 MYO7A MYO15A TMPRSS3	GPSM2	
Membrane traffic protein	OTOF	OTOF	OTOF														OTOF	OTOF		
Defense/immunity protein	PTPRQ	PTPRQ	COL4A6				COL11A1 COL11A2	COL4A3 COL4A4 COL4A5 COL11A1 COL11A2	COL4A3 COL4A5	COL4A3 COL4A4 COL4A5 COL4A6 COL9A1 COL9A3 COL11A1 COL11A2	COL4A3 COL4A5 COL4A6 COL11A1 COL11A2	COL4A3 COL4A5		COL2A1 COL9A1 COL9A3 COL11A1	COL2A1 COL4A3 COL4A5 COL9A1 COL9A3 COL11A2	COL4A3 COL4A4 COL4A5	PTPRQ	PTPRQ		
Extracellular matrix protein	OTOA OTOGL STRC USH2A	OTOGL STRC USH2A	COL4A6	OTOGL	OTOGL		OTOGL COL11A1 COL11A2	COCH COL4A3 COL4A5 COL11A1 COL11A2	COL4A3 COL4A5 OTOGL	COCH COL4A3 COL4A5 COL4A6 COL9A1 COL9A3 COL11A1 COL11A2	COL4A3 COL4A5 COL4A6 COL11A1 COL11A2	COL4A3 COL4A5	OTOA OTOG OTOGL	COL2A1 COL9A1 COL9A3 COL11A1 OTOG OTOGL TECTA	COCH COL2A1 COL4A3 COL4A5 COL9A1 COL9A3 COL11A2 OTOA	COL4A3 COL4A5	OTOA OTOGL STRC USH2A	OTOA OTOGL STRC USH2A		
Surfactant			COL4A6				COL11A1 COL11A2	COL4A3 COL4A5 COL11A1 COL11A2	COL4A3 COL4A5	COL4A3 COL4A5 COL4A6 COL9A1 COL9A3 COL11A1 COL11A2	COL4A3 COL4A5 COL4A6 COL11A1 COL11A2	COL4A3 COL4A5		COL2A1 COL9A1 COL9A3 COL11A1	COL2A1 COL4A3 COL4A5 COL9A1 COL9A3 COL11A2	COL4A3 COL4A5				
Receptor	ESRRB P2RX2 PTPRQ TMPRSS3 USH2A	ESRRB P2RX2 PTPRQ TMPRSS3 USH2A	COL4A6 ESRRB P2RX2 TMPRSS3	ESRRB P2RX2	ESRRB P2RX2 ESRRB		ESRRB COL11A1 COL11A2	COCH COL4A3 COL4A4 COL4A5 COL11A1 COL11A2	COL4A3 COL4A5 P2RX2	COCH COL4A3 COL4A4 COL4A5 COL4A6 COL9A1 COL9A3 COL11A1 COL11A2 ESRRB	COL4A3 COL4A5 COL4A6 COL11A1 COL11A2 ESRRB	COL4A3 COL4A5 ESRRB P2RX2		COL2A1 COL9A1 COL9A3 COL11A1	COCH COL2A1 COL4A3 COL4A5 COL9A1 COL9A3 COL11A2 ESRRB P2RX2	COL4A3 COL4A4 COL4A5	P2RX2 PTPRQ TMPRSS3 USH2A	P2RX2 PTPRQ TMPRSS3 USH2A	P2RX2	

(continued)

Table 3. (continued)

	Inner Hair Cell	Outer Hair Cell	Spiral Ganglion	Pillar Cell	Supporting Cell	Hensen's Cell	Claudius' Cell	External Sulucus	Spiral Prominence	Spiral Ligament	Stria Vascularis	Reissner's Membrane	Interdental Cell	Tectorial Membrane	Spiral Limbus	Inner Sulcus Cell	Vestibular Type I Hair Cell	Vestibular Type 2 Hair Cell	Supporting Cell	Transitional Cell
Transporter	CLIC5 GPR98 LOXHD1 P2RX2 SLC17A8 TMC1	CLIC5 GPR98 LOXHD1 P2RX2 SLC26A5 TMC1 KCNQ4	COL4A6 P2RX2 SLC17A8	P2RX2	P2RX2		COL11A1 COL11A2	COL4A3 COL4A4 COL4A5 COL11A1 COL11A2 SLC26A4	COL4A3 COL4A5 P2RX2 SLC26A4	COL4A3 COL4A4 COL4A5 COL4A6 COL9A1 COL9A3 COL11A1 COL11A2	COL4A3 COL4A5 COL4A6 COL11A1 COL11A2 KCNQ1	COL4A3 COL4A5 P2RX2	CLIC5	COL2A1 COL9A1 COL9A3 COL11A1	COL2A1 COL4A3 COL4A5 COL9A1 COL9A3 COL11A2 P2RX2	COL4A3 COL4A4 COL4A5	CLIC5 GPR98 LOXHD1 P2RX2 SLC26A5 TMC1 KCNQ4	CLIC5 GPR98 LOXHD1 P2RX2 SLC26A5 TMC1 KCNQ4	P2RX2 KCNQ4	
Protease	CLPP	CLPP		CLPP	CLPP	CLPP										CLPP				
Hydrolase	CIB2 CLPP PNPT1 PTPRQ	CIB2 CLPP PNPT1 PTPRQ	PNPT1	CLPP PNPT1	CLPP CIB2	CLPP										CLPP	CIB2 PTPRQ	CIB2 PTPRQ	CIB2	
Phosphatase	CIB2 PTPRQ	CIB2 PTPRQ			CIB2												CIB2 PTPRQ	CIB2 PTPRQ	CIB2	
Calcium-binding protein	CABP2 CIB2 TMPRSS3	CABP2 CIB2 TMPRSS3	CABP2 TMPRSS3		CIB2	TMPRSS3	TMPRSS3	TMPRSS3	TMPRSS3		TMPRSS3					TMPRSS3	CIB2 TMPRSS3	CIB2 TMPRSS3	CIB2	
Signaling molecule	CLIC5 EDN3 ELMOD3 LOXHD1 TMPRSS3	CLIC5 EDN3 ELMOD3 LOXHD1 TMPRSS3	EDN3 TMPRSS3	ELMOD3	ELMOD3	EDN3 ELMOD3	EDN3 ELMOD3				EDN3		CLIC5 EDN3			EDN3	CLIC5 ELMOD3 LOXHD1 TMPRSS3	CLIC5 ELMOD3 LOXHD1 TMPRSS3		
Transcription factor	ESRRB MARVELD2 POU4F3 SIX1	ESRRB MARVELD2 POU4F3 SIX1	ESRRB PAX3 SOX10	ESRRB SOX10	ESRRB	ESRRB SOX10	ESRRB SOX10		SOX10	ESRRB POU3F4	ESRRB GRHL2 MARVELD2 PAX3 SIX1 SOX10	ESRRB GRHL2 POU3F4 SOX10	SOX10		ESRRB	SOX10	MARVELD2 PAX3 POU3F4 POU4F3 SIX1	MARVELD2 PAX3 POU3F4 POU4F3 SIX1	MARVELD2	
Nucleic acid binding	CHD7 CLIC5 ESRRB KARS PNPT1	CHD7 CLIC5 ESRRB KARS PNPT1	CHD7 ESRRB KARS PAX3 PNPT1 SOX10	CHD7 ESRRB PNPT1 SOX10	ESRRB KARS	ESRRB SOX10	ESRRB SOX10		CHD7 SOX10	BDP1 CHD7 ESRRB	BDP1 CHD7 ESRRB PAX3 SOX10	BDP1 CHD7 ESRRB SOX10	CHD7 CLIC5 SOX10		CHD7 ESRRB	SOX10	CLIC5 KARS PAX3	CLIC5 KARS PAX3	KARS	
Transmembrane receptor regulatory/ adaptor protein	EPS8 GPSM2	EPS8 GPSM2		GPSM2	GPSM2	GPSM2											EPS8 GPSM2	EPS8 GPSM2	GPSM2	
Kinase	PRPS1	PRPS1	PRPS1														PRPS1	PRPS1		
Ligase	KARS PRPS1	KARS PRPS1	KARS PRPS1														KARS PRPS1	KARS PRPS1	KARS	
Lyase	ADCY1	ADCY1								CRYM						ADCY1	ADCY1	ADCY1	ADCY1	
Oxidoreductase	CLIC5 GRXCR1 GRXCR2 MSRB3	CLIC5 GRXCR1 GRXCR2 MSRB3	MSRB3		MSRB3 GRXCR1								CLIC5				CLIC5 GRXCR1 MSRB3	CLIC5 GRXCR1 MSRB3	MSRB3	GRXCR1
Transferase	CLIC5 GIPC3 LRTOMT PNPT1 PRPS1	CLIC5 GIPC3 LRTOMT PNPT1 PRPS1	PNPT1 PRPS1 GIPC3	LRTOMT PNPT1									CLIC5				CLIC5 GIPC3 LRTOMT PRPS1	CLIC5 GIPC3 LRTOMT PRPS1	LRTOMT	
Isomerase	CLIC5	CLIC5											CLIC5				CLIC5	CLIC5		

[a]Gene ontology analyses were performed using PANTHER software as described previously.

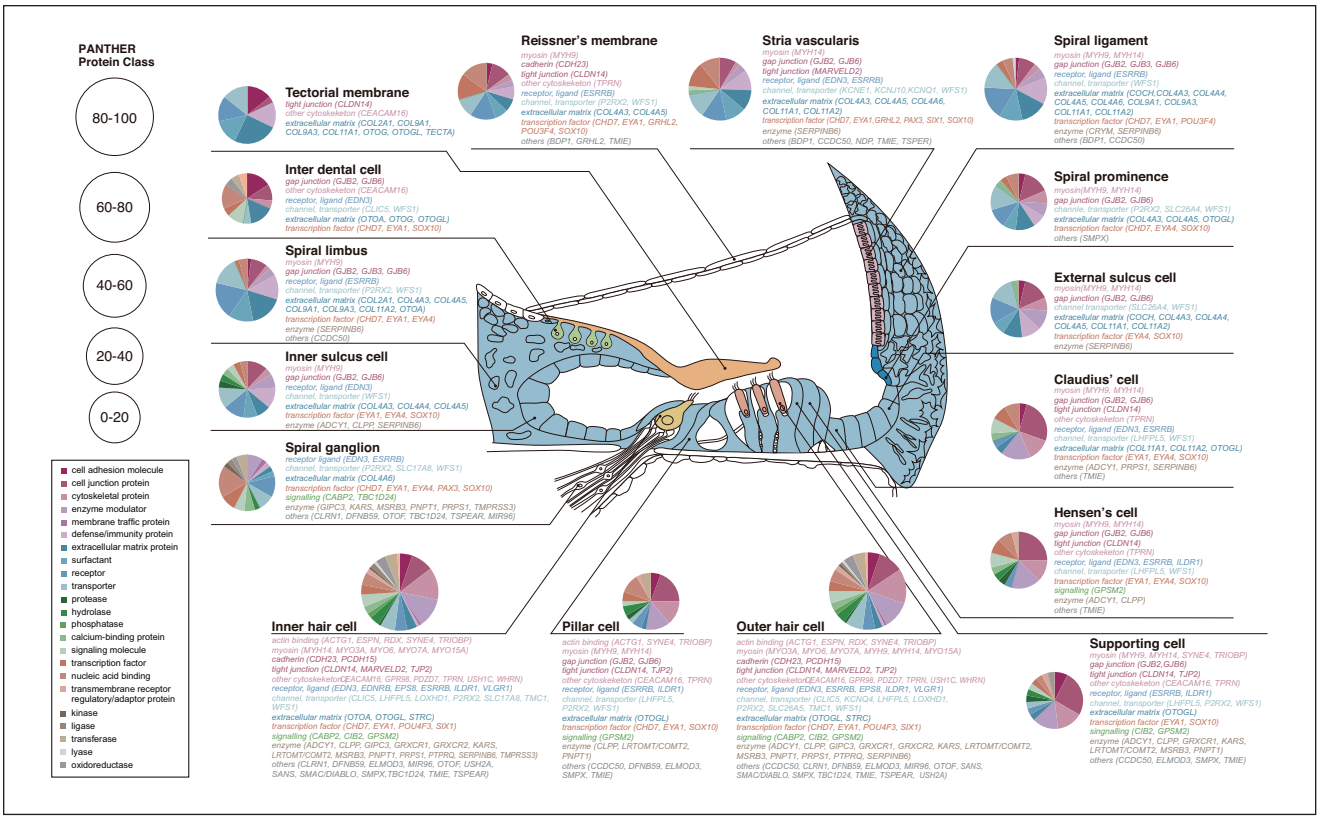


Figure 1. Gene expression profiles of the causative genes and localization of the encoded proteins involved in hereditary hearing loss in the cochlea. Pie charts indicate the results of gene ontology analysis of the gene expression profiles for each cell type.

loss.[28-42] Most of the Usher syndrome causative genes are included in this group and are expressed in the stereocilia (Figures 2A, 2B). *LOXHD1* and *GIPC3* are not components of the stereocilia; however, mutations in these genes in mice were shown to lead to degeneration of the stereocilia.[43-45] All of these genes are only expressed in the IHCs and OHCs.

The third group comprises nuclear binding protein, transcription factor, receptor, and signaling molecule genes, including *SIX1* (Sine oculis homeobox drosophila homolog 1), *POU4F3* (POU domain class 4 transcription factor 3), *EDN3* (endothelin 3), *EDNRB* (endothelin receptor type B), *EPS8* (epidermal growth factor receptor kinase substrate 8), and *GPSM2* (G-protein signaling modulator 2). These genes may have an important role in the transcription signaling pathway in IHC and OHC differentiation (Figure 3A).[46-52]

The fourth group of genes comprises genes encoding tight junction proteins, including *MARVELD2* (tricellulin), *TJP2* (tight junction protein ZO 2), and *CLDN14* (claudin 14). These genes are components of the tight junctions. *MARVELD2* is expressed only in the IHCs and OHCs, while *TJP2* is expressed in the IHCs, OHCs, pillar cells, and adjacent supporting cells, and *CLDN14* is expressed in the IHCs, OHCs, supporting cells, and Reissner's membrane. The tight junctions of these cells are believed to act as barriers that are required for normal hearing. Moreover, tricellulin proteins in the IHCs and OHCs form connections with adjacent cells and may prevent potassium ion (K^+) leakage from the apical side of hair cells.[53-55]

Outer Hair Cells Are the Center for Cochlea Amplification

OHCs in the organ of Corti are organized into 3 lines of cells that act as amplifiers of auditory signals. Similar to IHCs, OHCs also have stereocilia at the top of the cells. The OHC stereocilia are attached to the tectorial membrane; however, IHC stereocilia do not come into contact with the tectorial membrane. OHCs are electromotile, acting as an amplifier of basilar membrane vibrations. When OHCs are depolarized by K^+ ions from the stereocilia, motor proteins (prestin) located on the surface of the OHCs are shortened. As a result of the prestin movement, OHCs shrink in synchronization with basilar membrane vibrations.[56,57] As a result of this erector-evoked movement of the OHCs, basilar membrane movements are amplified, and the stereocilia of IHCs undergo more extensive swaying. This mechanism plays an important role in enhancing the dynamic range of

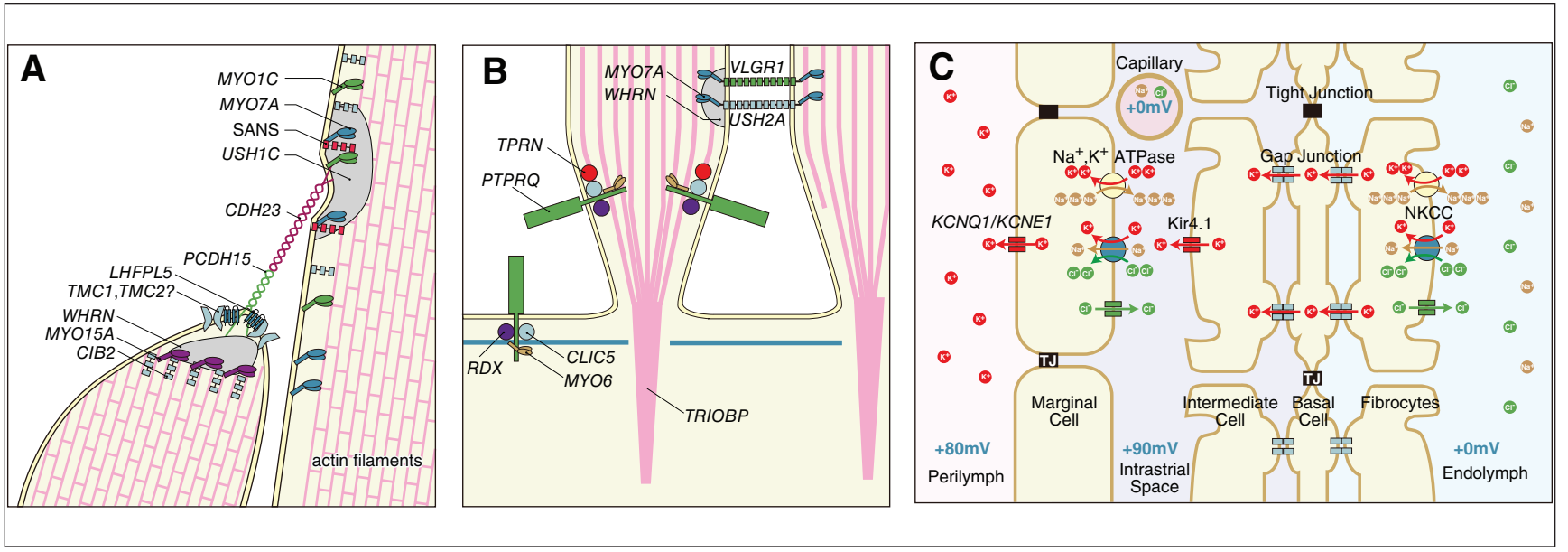


Figure 2. (A) Detailed structural components of the stereocillia tip link. Most of the Usher syndrome causative genes are expressed in the stereocilia and constructed tip link. (B) Detailed structural components of the stereocillia basal region. (C) Detailed structural components of the stria vascularis region. These figures are modified from previous reports.[9,11,113] TJ, tight junction.

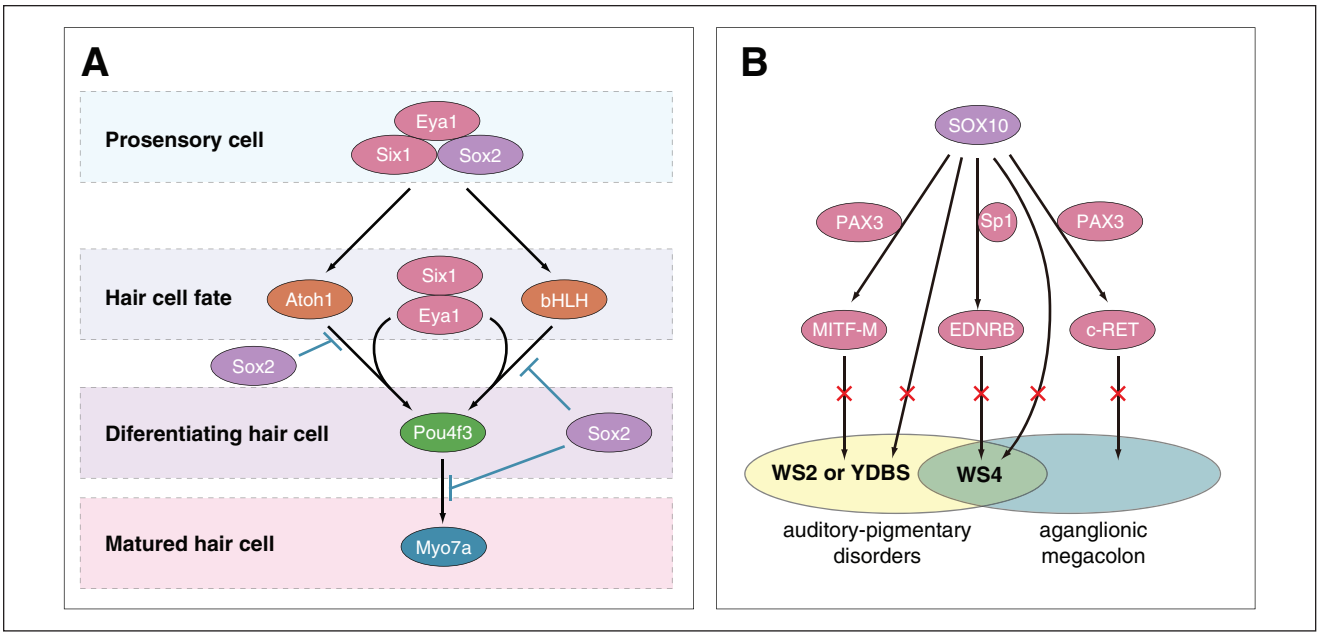


Figure 3. (A) *EYA-SIX-SOX* transcriptional pathway for hair cell differentiation. Most of the transcriptional factors expressed in hair cells are involved in this pathway. (B) *SOX-PAX-MITF* transcriptional pathway for melanocyte differentiation. Most of the transcriptional factors expressed in melanocytes in the stria vascularis are involved in this pathway. These figures are modified from previous reports.[98,99] WS, Waardenburg syndrome; YDBS, Yemenite deaf-blind hypopigmentation syndrome.

sound sensors in the IHCs, particularly for low-intensity sounds.[56,57] The movement of prestin itself does not require ATP as an energy source. Rather, changes in voltage capacity cause conformational changes in the prestin on the OHC surface membrane, thereby acting as the motor to drive these movements. OHCs are also controlled by efferent neurons, which act as a feedback system and modulate these movements.[58]

Many genes are involved in the maintenance of this unique characteristic of OHCs (Figure 1), and mutations in these genes also cause hearing loss. The gene expression profiles of OHCs are quite similar to those of IHCs, and most genes are commonly expressed in both OHCs and IHCs; however, the expression of the mechanical amplification motor protein (prestin) gene *SLC26A5* is restricted to OHCs. Three myosin motor proteins encoded by *MYO3A, MYO7A*, and *MYO15A* are expressed only in IHCs and OHCs. These genes may contribute to effective mechanical transduction and may also be involved in effective sound amplification by OHCs.

Pillar Cells Are Anchors for the Basilar Membrane and Hair Cells

Pillar cells act as the supporting cells located between IHCs and OHCs and are characterized by the presence of cross-linked actin filaments that ensure the necessary stiffness to support the hair cells on the basilar membrane and synchronize the vibration of the basilar membrane and hair cells. Pillar cells express actin gamma encoded by *ACTG1* and tight junction proteins encoded by *CLDN14* and *TJP2*.[54,59,60] The gene expression profiles of pillar cells are similar to those of hair and other supporting cells; *ACTG1* expression is only observed in hair and pillar cells.[28,52] In contrast, many types of myosin and various stereocillia components are not expressed in pillar cells. The gap junction proteins are commonly observed among the cochlea supporting and lateral wall cells, and those encoded by *GJB2* and *GJB6* are also observed in these cells.[61]

Inner Phalangeal Cells, Border Cells, and Deiters' Cells Are Neuroglial Cells in the Organ of Corti

Inner phalangeal cells, border cells, and Deiters' cells are all located adjacent to hair cells. Deiters' cells act as the supporting cells for OHCs and conform to the shape of the OHCs, while inner phalangeal cells and border cells act as the supporting cells for IHCs and conform to their shape. Furthermore, all of the aforementioned cells possess actin filaments and microtubules stretching from the basilar membrane to the reticular membrane in order to anchor the hair cells in the appropriate positions.

Another important role played by inner phalangeal and border cells is the glial cell-like uptake of the glutamate neurotransmitter, which is converted to glutamine.[62-64] After

this conversion, glutamine is transported to the hair cells, converted back to glutamate, and stored in the synaptic ribbon vesicles.[62-64]

The expression of tight junction proteins *CLDN14* and *TJP2* is expressions are only observed in hair, pillar, inner phalangeal cell, Border cell, and Deiters' cells. Methionine-R-sulfoxide reductase B3 (*MSRB3*) acts as an oxidoreductase, and its expression is only observed in hair, spiral ganglion, and inner phalangeal cell and Border and Deiters' cells.[65-72] Mutations in *MSRB3* cause DFNB74,[65-72] revealing the importance of decreasing oxidative stress in the protection of hair and nerve cells. In contrast, many types of myosin and stereocillia components are not expressed in inner phalangeal, border, or Deiters' cells. However, gap junction proteins are commonly observed among the cochlea supporting and lateral wall cells, and those encoded by *GJB2* and *GJB6* are observed in this cell type. Mutations in gap junction genes are known to cause nonsyndromic hearing loss DFNA3A/DFNB1A and DFNB1B.[66,67]

The Spiral Prominence Is the Center for Chloride, Bicarbonate, and Iodide Ion Transport

Hensen's and Claudius' cells are located adjacent to Deiters' cells. External sulcus cells and the spiral prominence are connected to the organ of Corti and stria vascularis. Most of these cells produce pendrin, which is encoded by *SLC26A4*. Pendrin acts as a chloride (Cl^-), bicarbonate (HCO_3^-), and iodide (I^-) ion transporter and is expressed in the cochlea, kidney, and thyroid gland. Mutations in *SLC26A4* result in nonsyndromic hearing loss with an enlarged vestibular aqueduct (DFNB4) and Pendred syndrome (hearing loss and goiter are the main symptoms).[68-70] Among the supporting cells, the spiral prominence strongly expresses *SLC26A4* and is believed to be responsible for maintaining Cl^- and HCO_3^- ion concentrations.

The Stria Vascularis and Spiral Ligament Are Batteries for Mechanical Transduction

The scala media of the cochlea is filled with endolymph, which has a high positive potential (+80 mV) due to the high concentration of K^+ ions (150 mM).[10,71,72] The scala vestibuli and scala tympani are filled with perilymph, which has no potential (0 mV) and a low concentration of K^+ ions (5 mM). The endocochlear potential (EP) and high concentration of K^+ ions act as an energy source for efficient mechanoelectric transduction. This unique fluid is produced by the stria vascularis and spiral ligament. The stria vascularis is composed of 3 layers of cells (marginal, intermediate, and basal cells), with narrow intrastrial spaces (IS) between the marginal and intermediate cell layers. Basal and intermediate cells are connected to each other by gap junctions and the K^+ ions of the perilymph are transported into the basal cells by the Na^+/K^+ATPase and $Na^+/K^+/2Cl^-$ co-transporter (NKCC) located on the basolateral side of the basal cells (Figure 2C). On the apical surface of the intermediate cells, *Kir4.1* encodes a potassium channel that transports K^+ ions to the IS.[10,71,72] Marginal cells have NKCC and Na^+/K^+ATPase at the basolateral surfaces and voltage-gated K^+ channels (KQT-like subfamily and ISK-related subfamily members) at the apical membranes; the genes for these channels are *KCNQ1* and *KCNE1*, respectively.[10,72] As a result of nonequivalent expression patterns on the basolateral and apical sides of the intermediate and marginal cells, K^+ ions are efficiently pumped from the perilymph to the endolymph and Na^+ ions are returned to the perilymph[10,72] (Figure 2C). This system requires ATP as an energy source, and blood vessels located in the stria vascularis supply oxygen and nutrients for ATP synthesis. The stria vascularis expresses many unique genes. *KCNQ1* and *KCNE1* are genes for the K^+ channels expressed on the apical surface of the marginal cells of the stria vascularis. Mutations in these genes cause Jervell and Lange-Nielsen syndrome, which is characterized by congenital deafness, and long QT syndrome.[73-75] Paired box gene 3 (*PAX3*), SRY-Box 10 (*SOX10*), and Endothelin 3 (*EDN3*) are expressed in the stria vascularis. *PAX3, SOX10, MITF, EDNRB*, and *EDN3* are reported to be causative genes of Waardenburg syndrome.[76-79] *PAX3* and *SOX10* encode transcriptional activator proteins and directly bind to the promoter of the *MITF, EDNRB*, and *RET* genes (Figure 3B).[78] *MITF* codes for the protein that is presumed to be a transcriptional factor associated with melanocyte differentiation.[79] In the organ of Corti, melanocytes are observed only in the stria vascularis and may have an important role in oxidoreductase activity.

The Tectorial Membrane Is a Sound Signal Enhancer

The tectorial membrane is a component of the organ of Corti and is comprised of collagens and non-collagenous glycoproteins; the membrane covers both the IHCs and OHCs. The longest OHCs stereocilia are connected to the tectorial membrane, and amplification of basilar membrane movement by the OHCs causes the endolymph to flow between the organ of Corti and tectorial membrane. As a result of this endolymph flow, IHCs more efficiently transduce sound signals.

Gene mutations associated with the tectorial membrane also causes hearing loss. Collagen, encoded by *COL2A1, COL9A1, COL9A3*, and *COL11A1*, is a

component of the tectorial membrane, and mutations in these genes appear to be related to nonsyndromic hearing loss or Stickler syndrome.[80-84] The collagen genes associated with hearing loss are not distributed in the IHCs, OHCs, or adjacent supporting cells, external sulcus cells, or the spiral prominence.[80-86] Further, no type IV collagen genes, including *COL4A3, COL4A5*, and *COL4A6*, are components of the tectorial membrane. Mutations in the type IV collagen genes cause Alport syndrome. This differential expression pattern among collagen genes might contribute to the differential roles of collagen in the hearing system. Inner ear–specific glycoproteins, coded by *TECTA, OTOG*, and *OTOGL*, are also expressed in the tectorial membrane. Mutations in *TECTA* cause DFNA8/12/DFNB21, those in *OTOG* cause nonsyndromic hearing loss, and those in *OTOGL* cause DFNB84.[87-89] Gene mutations in the tectorial membrane components can cause mild to moderate hearing loss (termed *cochlear conductive hearing loss*), and hearing aids are effective for such. This may indicate that gene mutations in the tectorial membrane components can cause a malformation of the membrane, which is required for enhancing sound signals.

Reissner's Membrane Separates the Perilymph and Endolymph

Reissner's membrane is a component of the cochlea, separating the scala vestibuli and the scala media. Reissner's membrane comprises 2 cell layers and tight junction proteins that prevent the leakage of the endolymph into the perilymph. *CLDN14*, which encodes tight junction proteins and *CDH23* are expressed in Reissner's membrane.[55,90]

Gene Expression Profiles of the Vestibular Endorgans

Our review also focused on the vestibular system. Most of the genes associated with hereditary hearing loss are also expressed in the vestibular endorgans. However, only a limited number of genes, namely, *COCH* and *SLC26A4*, have been reported to be associated with vestibular dysfunctions and/or vertigo,[91-94] and the involvement of these genes remains unclear. In the vestibular system, mechanical transduction occurs by linear and rotatory acceleration. This mechanoelectric transduction is conducted by the hair cell stereocilia of the utricle and saccule together with the crista-ampullaris of the semicircular canals. Hair cells of the vestibular endorgans are slightly different from those of the organ of Corti. Vestibular stereocilia are linked to the kinocilium, and stereocilia movement toward the kinocilium depolarizes the hair cells.

Unlike the cochlea, only a limited number of reports are available for deafness-related causative genes expressed in the vestibular endorgans. A large proportion of the causative genes for deafness are also expressed in the vestibular endorgans, with the currently available information indicating that only 2 out of 72 genes (*MITF* and *MYH9*) are restricted to the cochlea. This may reflect differences between the cochlea and vestibular endorgans (Figure 4).

The remaining genes are expressed in both the cochlea and vestibular endorgans; thus, it is difficult to explain the absence of vertigo in most patients. Possible explanations for this inconsistency are as follows: (1) other molecules compensate for the functional loss of sensory activity in the vestibular endorgans, (2) congenital vestibular dysfunction is compensated by visual and somatosensory input, and (3) the vestibular sensory system requires a lower degree of sensitivity than does the audio system. It is noteworthy that a missense mutation in *CDH23* causes DFNB12, and vertigo is not associated with the mutation. Nonsense or frameshift mutations, which have more deleterious effects on protein function, cause Usher syndrome type 1D, which is characterized by retinitis pigmentosa and vertigo. Some of these inconsistencies can be explained by the third point; however, further studies are required to elucidate the effects of mutations linked to deafness on vestibular functions.[29,95,96]

Gene Expression Profiles of Genes Causing Deafness in Other Body Parts

Some mutations in the deafness causative genes only cause hearing loss (nonsyndromic hearing loss); however, others cause syndromic hearing loss with various associated symptoms. The presence of these associated symptoms may be related to the expression profiles of the genes correlated with deafness in other parts of human body. To elucidate the gene expression profiles of genes previously reported to cause deafness, we conducted the database search summarized in Table 4. We also added information on the domain structure and protein interactions. Most of the genes known to cause deafness, including *GJB2, CDH23*, and *TECTA*, are expressed mainly in the cochlea; only a small percentage are expressed in other body parts. In contrast, most genes causing syndromic hearing loss, including *COL4A3, COL4A4, COL4A5* (Alport syndrome); *COL2A1, COL9A1, COL11A1, COL11A2* (Stickler syndrome); *PAX3* (Waardenburg syndrome); and *EYA1* (BOR syndrome), are expressed in other parts of the human body. These

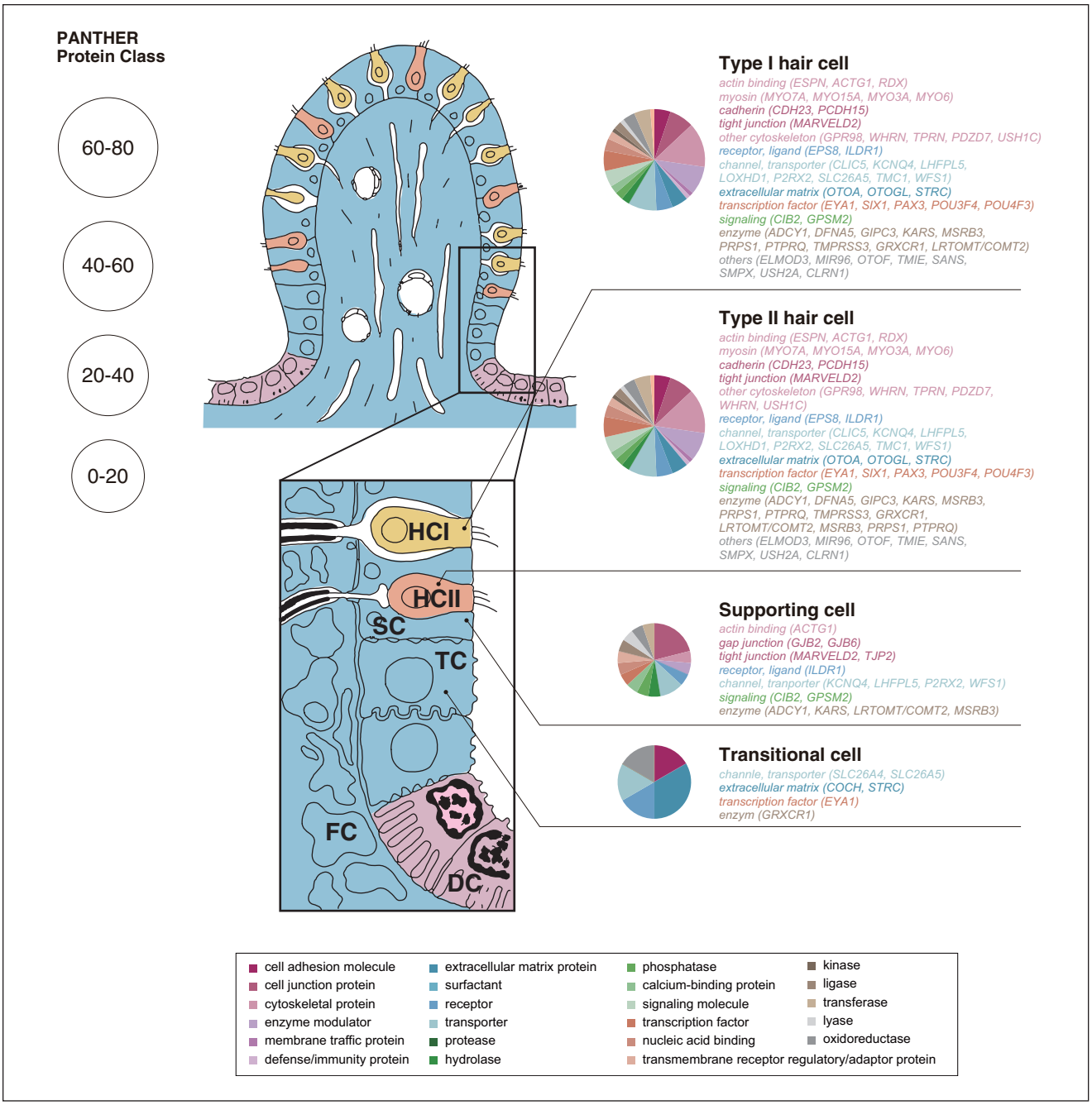
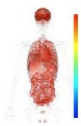
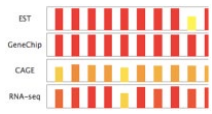
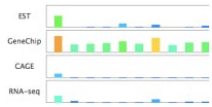
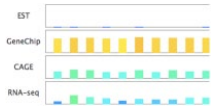
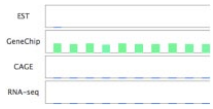


Figure 4. Gene expression profiles of the causative genes and localization of the encoded proteins involved in hereditary hearing loss in the vestibular endorgan. Pie charts indicate the results of gene ontology analysis of the gene expression profiles for each cell type.

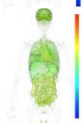
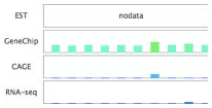
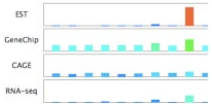
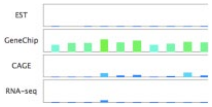
results can satisfactorily explain the presence of various symptoms in addition to hearing loss. However, many of the genes associated with nonsyndromic hearing loss are also expressed in other body parts. Further investigation is needed to elucidate the mechanisms underlying nonsyndromic hearing loss. One possible explanation of the aforementioned inconsistencies is the presence of alternative splicing variants as *OTOF* transcription variants NM_001100393 and NM_001144074 are expressed in the brain and kidney to some extent, while NM_004802 and NM_194248 are not observed in other body parts and are only expressed in the cochlea.[97]

Table 4. Summary of Gene Expression Profiles of Each Deafness Gene in Organs.

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
ACTG1 Actin, cytoplasmic 2				Itself ACTB CFL2 MLH1
ADCY1 Adenylate cyclase type 1			493 – 520 Interaction with calmodulin region 1024 – 1047 Interaction with calmodulin region	
BSND Barttin				
BDP1 Transcription factor TFIIIB component B homolog			295 – 345 Myb-like domain, 823 – 877 approximate repeat 878 – 932 repeat 2 933 – 987 3 repeat 988 – 1040 4 repeat 1041 – 1094 5 repeat 1095 – 1148 6 repeat 1149 – 1203 7 repeat 1204 – 1257 8; approximate repeat 1258 – 1327 9; approximate repeat 1 – 299 Interaction with ZBTB43 region 355 – 470 Required for phosphorylation by *CSNK2A1* region 823 – 1327 9 X 55 AA repeats region 144 – 177 coiled coil 1078 – 1103 coiled coil 1223 – 1284 coiled coil	
CABP2 Calcium-binding protein 2			78 – 113 EF-hand 1 domain 111 – 146 EF-hand 2 domain 152 – 187 EF-hand 3 domain 189 – 220 EF-hand 4 domain	
CCDC50 Coiled-coil domain-containing protein 50			63 – 130 coiled coil	OTUD7B, RIPK1, UBB
CDH23 Cadherin 23			34 – 132 Cadherin 1 domain 133 – 236 Cadherin 2 domain 237 – 348 Cadherin 3 domain 349 – 460 Cadherin 4 domain 461 – 561 Cadherin 5 domain 562 – 671 Cadherin 6 domain 672 – 784 Cadherin 7 domain 779 – 890 Cadherin 8 domain 891 – 995 Cadherin 9 domain 996 – 1102 Cadherin 10 domain 1103 – 1208 Cadherin 11 domain 1210 – 1313 Cadherin 12 domain 1314 – 1418 Cadherin 13 domain	

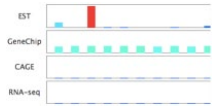
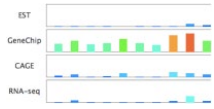
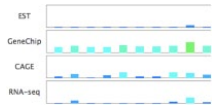
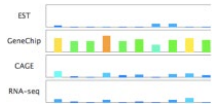
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
			1420 – 1527 Cadherin 14 domain 1529 – 1634 Cadherin 15 domain 1635 – 1744 Cadherin 16 domain 1745 – 1851 Cadherin 17 domain 1852 – 1959 Cadherin 18 domain 1960 – 2069 Cadherin 19 domain 2070 – 2174 Cadherin 20 domain 2175 – 2293 Cadherin 21 domain 2297 – 2402 Cadherin 22 domain 2403 – 2509 Cadherin 23 domain 2510 – 2611 Cadherin 24 domain 2614 – 2722 Cadherin 25 domain 2729 – 2846 Cadherin 26 domain 2847 – 2975 Cadherin 27 domain	
CEACAM16 Carcinoembryonic antigen-related cell adhesion molecule 16			133 – 218 Ig-like C2-type 1 domain 223 – 309 Ig-like C2-type 2 domain	
CIB2 Calcium- and integrin-binding family member 2			66 – 101 EF-hand 1 domain 103 – 138 EF-hand 2 domain 144 – 179 EF-hand 3 domain	
CLDN14 Claudin 14				
CLIC5 Chloride intracellular channel protein 5			260 – 400 GST C-terminal domain	SRC
COCH Cochlin			28 – 121 LCCL domain 165 – 346 VWFA 1 domain 367 – 537 VWFA 2 domain	
COL11A2 (DFNA13/DFNB53/ Stickler syndrome) Collagen alpha 2(XI) chain			57 – 228 Laminin G-like domain 399 – 447 Collagen-like 1 domain 487 – 545 Collagen-like 2 domain 546 – 590 Collagen-like 3 domain 805 – 862 Collagen-like 4 domain 863 – 899 Collagen-like 5 domain 1099 – 1156 Collagen-like 6 domain 1157 – 1172 Collagen-like 7 domain 1441 – 1499 Collagen-like 8 domain 1541 – 1735 Fibrillar collagen NC1 domain 215 – 486 Nonhelical region 487 – 1500 Triple-helical region	DDR2
COL4A6 Collagen alpha 6(IV) chain			1467 – 1691 Collagen IV NC1 domain 23 – 46 7S domain region 47 – 1463 Triple-helical region 515 – 517 Cell attachment site motif 560 – 562 Cell attachment site motif 986 – 988 Cell attachment site motif	

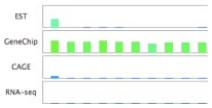
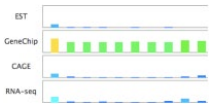
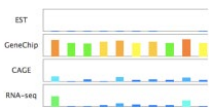
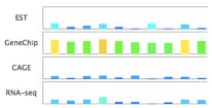
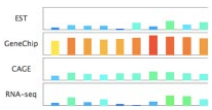
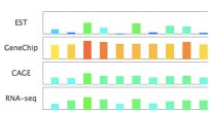
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
COL2A1 (Stickler syndrome) Collagen, type II, alpha-1			32 – 90 VWFC domain 1253 – 1487 Fibrillar collagen NC1 domain 201 – 1214 Triple-helical region 1215 – 1241 Nonhelical region (C-terminal)	
COL4A3 (Alport) Collagen, type IV, alpha-3			1445 – 1669 Collagen IV NC1 domain 29 – 42 7S domain 43 – 1438 Triple-helical region 1427 – 1444 Epitope recognized by Goodpasture antibodies region 1479 – 1557 Required for the anti-angiogenic activity of tumstatin region 1610 – 1628 Required for the anti-tumor cell activity of tumstatin region 791 – 793 Cell attachment site motif 996 – 998 Cell attachment site motif 1154 – 1156 Cell attachment site motif 1306 – 1308 Cell attachment site motif 1345 – 1347 Cell attachment site motif 1432 – 1434 Cell attachment site motif	
COL4A4 (Alport) Collagen, type IV, alpha-4			1465 – 1690 Collagen IV NC1 domain 39 – 64 7S domain 65 –1459 Triple-helical region 94 – 96 Cell attachment site motif 145 – 147 Cell attachment site motif 189 – 191 Cell attachment site motif 310 – 312 Cell attachment site motif 724 – 726 Cell attachment site motif 785 – 787 Cell attachment site motif 989 – 991 Cell attachment site motif 1212 – 1214 Cell attachment site motif	
COL4A5 (Alport) Collagen, type IV, alpha-5			1461 – 1685 Collagen IV NC1 domain 27 – 41 Nonhelical region (NC2) region 42 – 1456 Triple-helical region	
COL11A1 (Stickler syndrome) Collagen, type XI, alpha-1			71 – 243 Laminin G-like domain 442 – 490 Collagen-like 1 domain 532 – 586 Collagen-like 2 domain 583 – 641 Collagen-like 3 domain 616 – 674 Collagen-like 4 domain 643 – 699 Collagen-like 5 domain 1393 – 1450 Collagen-like 6 domain 1429 – 1487 Collagen-like 7 domain 1483 – 1541 Collagen-like 8 domain 1577 – 1805 Fibrillar collagen NC1 domain 230 – 419 Nonhelical region 420 – 508 Triple-helical region (interrupted) 509 – 511 Short nonhelical segment region 512 – 528 Telopeptide region 529 – 1542 Triple-helical region 1543 – 1563 Nonhelical region (C-terminal)	

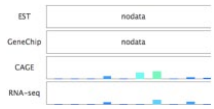
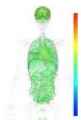
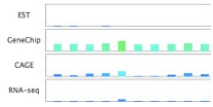
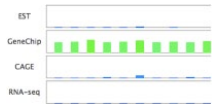
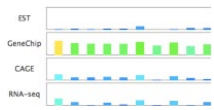
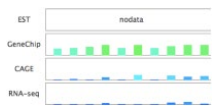
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
COL9A1 (Stickler syndrome) Collagen, type IX, alpha-1			50 – 244 Laminin G-like domain 269 – 324 Collagen-like 1 domain 325 – 356 Collagen-like 2 domain 358 – 403 Collagen-like 3 domain 416 – 472 Collagen-like 4 domain 473 – 516 Collagen-like 5 domain 587 – 643 Collagen-like 6 domain 655 – 712 Collagen-like 7 domain 713 – 755 Collagen-like 8 domain 790 – 847 Collagen-like 9 domain 848 – 899 Collagen-like 10 domain 24 – 268 Nonhelical region (NC4) 269 – 405 Triple-helical region (COL3) 406 – 417 Nonhelical region (NC3) 418 – 756 Triple-helical region (COL2) 757 – 786 Nonhelical region (NC2) 787 – 901 Triple-helical region (COL1) 902 – 921 Nonhelical region (NC1)	
COL9A2 (Stickler syndrome) Collagen, type IX, alpha-2			27 – 163 Triple-helical region 4 (COL4) 164 – 180 Nonhelical region 4 (NC4) 181 – 519 Triple-helical region 3 (COL3) 520 – 549 Nonhelical region 3 (NC3) 550 – 632 Triple-helical region 2 (COL2) 633 – 634 Nonhelical region 2 (NC2) 635 – 664 Triple-helical region 1 (COL1) 665 – 689 Nonhelical region 1 (NC1)	
CRYM Thiomorpholine-carboxylate dehydrogenase				
DFNA5 Non-syndromic hearing impairment protein				
DIAPH1 Protein diaphanous homolog 1			84 – 449 GBD/FH3 domain 583 – 764 FH1 domain 769 – 1171 FH2 domain 1194 – 1222 DAD domain	ORF, PPM1F, RHOA
DSPP Dentin sialophosphoprotein			488 – 490 Cell attachment site motif	
ELMOD3 ELMO domain-containing protein 3			170 – 324 ELMO domain	
EPS8 Epidermal growth factor receptor kinase substrate 8			327 – 488 Helicase ATP-binding domain 542 – 702 Helicase C-terminal domain 6 – 18 Nuclear localization signal motif 441 – 444 DEVH box motif	PSMC5, RAD23B, XPC

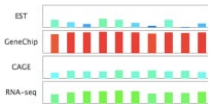
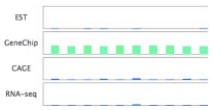
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
ESPN Espin			651 – 668 WH2 domain 756 – 830 coiled coil	
ESRRB Steroid hormone receptor			103 – 123 NR C4-type zinc finger 139 – 163 NR C4-type ziinc finger	
EYA1 Eyes absent homolog 1				
EYA4 Eyes absent homolog 4				
GIPC3 PDZ domain-containing protein GIPC3			112 – 192 PDZ domain	
GJB2 Gap junction beta 2 protein				
GJB3				
GJB6 Gap junction beta 6 protein				
GPSM2 G-protein signaling modulator 2			24 – 57 TPR 1 repeat 62 – 95 TPR 2 repeat 102 – 135 TPR 3 repeat 142 – 184 TPR 4 repeat 202 – 235 TPR 5 repeat 242 – 275 TPR 6 repeat 282 – 315 TPR 7 repeat 322 – 355 TPR 8 repeat 489 – 511 GoLoco 1 domain 544 – 566 GoLoco 2 domain 594 – 616 GoLoco 3 domain 628 – 650 GoLoco 4 domain	itself, GNAI1, NUMA1
GRHL2				

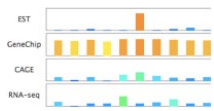
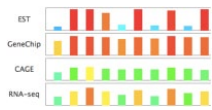
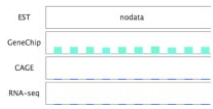
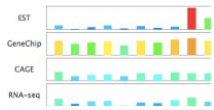
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
GRXCR1 Glutaredoxin domain-containing cysteine-rich protein 1		NA	127 – 234 Glutaredoxin domain	
GRXCR2 Glutaredoxin domain-containing cysteine-rich protein 2		NA		
HGF Hepatocyte growth factor		NA	27 – 515 Sema domain 563 – 655 IPT/TIG 1 domain 657 – 739 IPT/TIG 2 domain 742 – 836 IPT/TIG 3 domain 1078 – 1345 Protein kinase domain 1212 – 1390 Interaction with RANBP9 region 1320 – 1359 Interaction with MUC20 region	CBL, DNAJA3, EGFR, FGR, HGF, HGF, inlB (from a different organism), INPPL1, KDR, Kdr (from a different organism), LCK, LYN, MUC1, NCK1, NCK2, PIK3R1, PIK3R2, PIK3R3, PLCG1, PLXNB1, PLXNB2, PLXNB3, PTK2 (from a different organism), PTPN1, PTPN11, PTPRB, PTPRJ, SH2B3, SH2D1A, SH2D1B, SH2D2A, SH2D3C, SHB, SHC1, SHC2, SHC4, SHD, SLA2, SOCS5, SOCS6, SRC, STAP1, SYK, TEC, TENC1, TNS1, TNS, VAV3, YES1, ZAP70
ILDR1 Immunoglobulin-like domain-containing receptor 1			24 – 162 Ig-like V-type domain	
KARS Lysine-tRNA ligase				
KCNQ4 Potassium voltage-gated channel subfamily KQT member 4			546 – 650 A-domain (Tetramerization) region 610 – 645 coiled coil 283 – 288 Selectivity filter motif	
LHFPL5 Tetraspan membrane protein of hair cell stereocilia				
LOXHD1 Lipoxygenase homology domain containing protein 1			18 – 134 PLAT 1 domain 147 – 262 PLAT 2 domain 275 – 395 PLAT 3 domain 406 – 525 PLAT 4 domain 536 – 650 PLAT 5 domain	

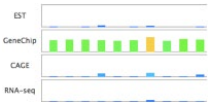
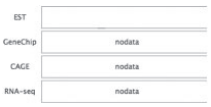
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
			744 – 862 PLAT 6 domain 897 – 1015 PLAT 7 domain 1028 – 1153 PLAT 8 domain 1182 – 1300 PLAT 9 domain 1349 – 1467 PLAT 10 domain 1480 – 1595 PLAT 11 domain 1607 – 1725 PLAT 12 domain 1738 – 1859 PLAT 13 domain 1876 – 1947 PLAT 14 domain	
LRTOMT Transmembrane O-methyltransferase		NA	139 – 140 S-adenosyl-L-methionine binding region	
MARVELD2 MARVEL domain-containing protein 2			188 – 367 MARVEL domain 466 – 490 coiled coil 524 – 548 coiled coil	
MSRB3 Methionine-R-sulfoxide reductase B3			189 – 192 Endoplasmic reticulum retention signal motif	
MYH14 Myosin 14			105 – 800 Myosin motor domain 803 – 832 IQ domain 862 – 1947 coiled coil	
MYH9 Myosin 9				CXCR4, GRB2, MEN1, NCL, SVIL
MYO15A Unconventional myosin XV			1222 – 1899 Myosin motor domain 1902 – 1924 IQ 1 domain 1925 – 1954 IQ 2 domain 1955 – 1976 IQ 3 domain 2065 – 2217 MyTH4 1 domain 2867 – 2953 SH domain 3050 – 3204 MyTH4 2 domain 3209 – 3530 FERM domain 1792 – 1799 Actin-binding region 1888 – 2029 Neck or regulatory domain region 2030 – 3530 Tail region 1323 – 1350 coiled coil	
MYO3A Myosin IIIa			21 – 287 Protein kinase domain 338 – 1053 Myosin motor domain 1055 – 1084 IQ 1 domain 1082 – 1111 IQ 2 domain 1346 – 1375 IQ 3 domain	
MYO6 Unconventional myosin VI			57 – 771 Myosin motor domain 814 – 834 IQ domain 273 – 317 Responsible for slow ATPase activity by similarity region 665 – 672 Actin-binding region	DAB2, Dab2

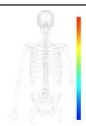
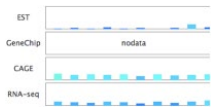
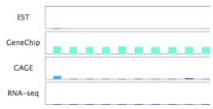
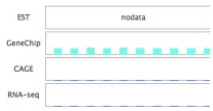
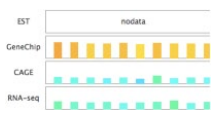
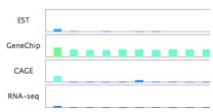
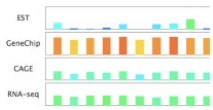
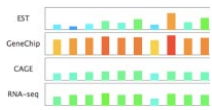
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
			782 – 810 Required for binding calmodulin region 1116 – 1118 Interaction with OPTN region 864 – 1023 coiled coil	
MYO7A Unconventional myosin VIIa			65 – 741 Myosin moto domain 745 – 765 IQ 1 domain 768 – 788 IQ 2 domain 791 – 811 IQ 3 domain 814 – 834 IQ 4 domain 837 – 857 IQ 5 domain 1017 – 1253 MyTH4 1 domain 1258 – 1602 FERM 1 domain 1603 – 1672 SH3 domain 1747 – 1896 MyTH4 2 domain 1902 – 2205 FERM 2 domain 632 – 639 Actin-binding region 858 – 935 coiled coil	
OTOA Otoancorin				
OTOF NM_001100393 NM_001144074 Otoferlin			241 – 338 C2 1 domain 404 – 514 C2 2 domain 947 – 1052 C2 3 domain 1479 – 1577 C2 4 domain 792 – 821 coiled coil	
OTOF NM_004802 NM_194248 Otoferlin			241 – 338 C2 1 domain 404 – 514 C2 2 domain 947 – 1052 C2 3 domain 1479 – 1577 C2 4 domain 792 – 821 coiled coil	
OTOGL Otogelin-like protein		NA	113 – 326 VWFD 1 domain 381 – 434 TIL 1 domain 473 – 683 VWFD 2 domain 736 – 791 TIL 2 domain 938 – 1141 VWFD 3 domain 1514 – 1734 VWFD 4 domain 2240 – 2332 CTCK domain	
P2RX2 P2X purinoceptor 2			320 – 333 Pore-forming motif region	
PCDH15 Protocadherin 15			40 – 147 Cadherin 1 domain 148 – 265 Cadherin 2 domain 278 – 395 Cadherin 3 domain 396 – 509 Cadherin 4 domain 510 – 616 Cadherin 5 domain 617 – 717 Cadherin 6 domain 719 – 819 Cadherin 7 domain 820 – 926 Cadherin 8 domain 927 – 1035 Cadherin 9 domain 1037 – 1144 Cadherin 10 domain 1145 – 1259 Cadherin 11 domain	

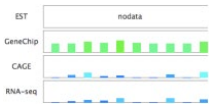
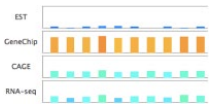
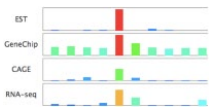
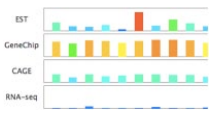
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
DFNB59 Pejvakin				
PNPT1 Polyribonucleotide nucleotidyltransferase 1, mitochondrial			605 – 664 KH domain 679 – 750 S1 motif domain	
POU3F4 POU domain, class 3, transcription factor 4			186 – 260 POU-specific domain	
POU4F3 POU domain, class 4, transcription factor 3			179 – 256 POU-specific domain 56 – 65 POU-IV box motif	
PRPS1 Ribose-phosphate pyrophosphokinase 1			212 – 227 Binding of phosphoribosylpyrophosphate region	
PTPRQ Phosphatidylinositol phosphatase			36 – 99 Fibronectin type-III 1 domain 100 – 195 Fibronectin type-III 2 domain 199 – 294 Fibronectin type-III 3 domain 350 – 438 Fibronectin type-III 4 domain 441 – 539 Fibronectin type-III 5 domain 514 – 606 Fibronectin type-III 6 domain 610 – 705 Fibronectin type-III 7 domain 710 – 799 Fibronectin type-III 8 domain 804 – 894 Fibronectin type-III 9 domain 899 – 988 Fibronectin type-III 10 domain 993 – 1093 Fibronectin type-III 11 domain 1098 – 1190 Fibronectin type-III 12 domain 1192 – 1282 Fibronectin type-III 13 domain 1287 – 1380 Fibronectin type-III 14 domain 1384 – 1470 Fibronectin type-III 15 domain 1474 – 1578 Fibronectin type-III 16 domain 1583 – 1681 Fibronectin type-III 17 domain 1686 – 1787 Fibronectin type-III 18 domain 2036 – 2292 Tyrosine-protein phosphatase domain	
RDX Radixin			5 – 295 FERM domain 60 – 63 Phosphatidylinositol binding region	ITGB2
SERPINEB6 Serpin B6			Homeobox protein SIX1	MDFI

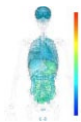
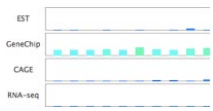
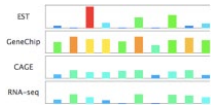
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
SIX1 Homeobox protein SIX1, Sine oculis homeobox, drosophila, homolog of, 1				
SLC17A8 Vesicular glutamate transporter 3				
SLC26A4 Pendrin			535 – 729 STAS domain	
SLC26A5 Prestin			525 – 713 STAS domain	
SMAC				
SMPX Small muscular protein				
STRC Stereocilin				
TBC1D24 TBC1 domain family member 24			47 – 262 Rab-GAP TBC domain 368 – 554 TLD domain	
TECTA Alpha-tectorin			98 – 252 NIDO domain 260 – 314 VWFC domain 321 – 540 VWFD 1 domain 597 – 650 TIL 1 domain 712 – 929 VWFD 2 domain 984 – 1036 TIL 2 domain 1099 – 1317 VWFD 3 domain 1372 – 1425 TIL 3 domain 1486 – 1694 VWFD 4 domain 1805 – 2059 ZP domain	
TJP2 Tight junction protein ZO 2			33 – 120 PDZ 1 domain 307 – 385 PDZ 2 domain 509 – 590 PDZ 3 domain 604 – 669 SH3 domain 678 – 876 Guanylate kinase-like domain 1188 – 1190 Interaction with SCRIB region	LASP1

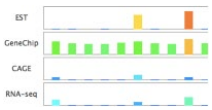
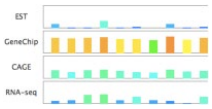
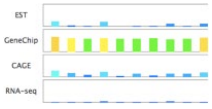
(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
TMC1 Transmembrane channel-like protein 1				
TMIE Transmembrane inner ear-expressed protein				
TMPRSS3 NM_024022 Transmembrane protease serine 3			72 – 108 LDL- receptor class A domain 109 – 205 SRCR domain 217 – 449 Peptidase S1 domain	
TMPRSS3 NM_032405 Transmembrane protease serine 3			72 – 108 LDL- receptor class A domain 109 – 205 SRCR domain 217 – 449 Peptidase S1 domain	
TNC Tenascin			118 – 145 coiled coil 174 – 186 EGF-like 1 domain; incomplete 186 – 217 EGF-like 2 domain 217 – 248 EGF-like 3 domain 248 – 280 EGF-like 4 domain 280 – 311 EGF-like 5 domain 311 – 342 EGF-like 6 domain 342 – 373 EGF-like 7 domain 373 – 404 EGF-like 8 domain 404 – 435 EGF-like 9 domain 435 – 466 EGF-like 10 domain 466 – 497 EGF-like 11 domain 497 – 528 EGF-like 12 domain 528 – 559 EGF-like 13 domain 559 – 590 EGF-like 14 domain 590 – 621 EGF-like 15 domain 625 – 715 Fibronectin type-III 1 domain 716 – 804 Fibronectin type-III 2 domain 805 – 894 Fibronectin type-III 3 domain 895 – 990 Fibronectin type-III 4 domain 991 – 1075 Fibronectin type-III 5 domain 1076 – 1165 Fibronectin type-III 6 domain 1167 – 1256 Fibronectin type-III 7 domain 1258 – 1350 Fibronectin type-III 8 domain 1351 – 1439 Fibronectin type-III 9 domain 1440 – 1531 Fibronectin type-III 10 domain 1533 – 1621 Fibronectin type-III 11 domain 1622 – 1711 Fibronectin type-III 12 domain 1712 – 1801 Fibronectin type-III 13 domain 1802 – 1888 Fibronectin type-III 14 domain 1889 – 1977 Fibronectin type-III 15 domain 1975 – 2190 Fibrinogen C-terminal domain	
TPRN Taperin				

(continued)

Table 4. (continued)

Gene Name	Image	Gene Expression Profiles (Brain, Blood, Connective Tissue, Reproductive Organs, Muscle, Digestive Organs, Liver, Lung, Kidney, Urinary Organs)	Domains	Interaction Proteins
TSPEAR Thrombospondin-type laminin G domain and EAR repeat-containing protein			58 – 277 Laminin G-like domain 313 – 358 EAR 1 repeat 359 – 408 EAR 2 repeat 411 – 460 EAR 3 repeat 463 – 512 EAR 4 repeat 513 – 570 EAR 5 repeat 573 – 622 EAR 6 repeat 624 – 668 EAR 7 repeat	
USH1C Harmonin			189 – 227 coiled coil 289 – 309 coiled coil 476 – 513 coiled coil 596 – 681 coiled coil	BET1, EXOC, NOC4L, SERTAD3
USH2A Usherin			271 – 517 Laminin N-terminal domain 518 – 574 Laminin EGF-like 1 domain 5075 – 640 Laminin EGF-like 2 domain 641 – 693 Laminin EGF-like 3 domain 694 – 746 Laminin EGF-like 4 domain 747 – 794 Laminin EGF-like 5 domain 795 – 846 Laminin EGF-like 6 domain 847 – 899 Laminin EGF-like 7 domain 900 – 950 Laminin EGF-like 8 domain 951 – 1001 Laminin EGF-like 9 domain 1002 – 1052 Laminin EGF-like 10 domain 1058 – 1146 Fibronectin type-III 1 domain 1148 – 1244 Fibronectin type-III 2 domain 1245 – 1363 Fibronectin type-III 3 domain 1364 – 1468 Fibronectin type-III 4 domain 1517 – 1709 Laminin G-like 1 domain 1714 – 1891 Laminin G-like 2 domain 1869 – 1955 Fibronectin type-III 5 domain 1957 – 2054 Fibronectin type-III 6 domain 2055 – 2144 Fibronectin type-III 7 domain 2145 – 2239 Fibronectin type-III 8 domain 2243 – 2330 Fibronectin type-III 9 domain 2331 – 2433 Fibronectin type-III 10 domain 2437 – 2531 Fibronectin type-III 11 domain 2535 – 2622 Fibronectin type-III 12 domain 2624 – 2722 Fibronectin type-III 13 domain 2726 – 2819 Fibronectin type-III 14 domain 2820 – 2923 Fibronectin type-III 15 domain	
WFS1 NM_006005 Wolframin				
WFS1 NM_001145805 Wolframin				
WHRN Whirlin			140 – 223 PDZ 1 domain 279 – 361 PDZ 2 domain 816 – 899 PDZ 3 domain	

[a]Expression profile analysis for each human organ was performed using the RefEX database as described previously.

Declaration of Conflicting Interests

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