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# Growth factor and receptor malfunctions associated with human genetic deafness

**Sadaf Naz**[1], **Thomas B. Friedman**[2]

[1]School of Biological Sciences, University of the Punjab, Lahore, Pakistan

[2]Laboratory of Molecular Genetics, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, USA 20892

## Abstract

A variety of different signaling pathways are necessary for development and maintenance of the human auditory system. Normal hearing allows for the detection of soft sounds within the frequency range of 20 to 20,000 Hz, but more importantly to perceive the human voice frequency band of 250 to 6,000 Hertz. Loss of hearing is common, and is a clinically heterogeneous disorder that can be caused by environmental factors such as exposure to loud noise, infections and ototoxic drugs. In addition, variants of hundreds of genes have been reported to disrupt processes required for hearing. Noncoding regulatory variants and variants of additional genes necessary for hearing remain to be discovered as many individuals with inherited deafness are without a genetic diagnosis, despite the advent of whole exome sequencing. Here, we discuss in detail some of these deafness-causing variants of genes encoding a ligand or its receptor. Spotlighted in this review are three growth factor-receptor-pairs EDN3/EDNRB, HGF/MET and JAG/NOTCH, which individually are necessary for normal hearing. We also offer our perspective on unanswered questions, future challenges and potential opportunities for treatments emerging from molecular genetic and mechanistic studies of deafness due to these causes.

## Graphical Abstract

**Correspondence** Sadaf Naz, School of Biological Sciences, University of the Punjab, Quaid-i-Azam Campus, Lahore, 54590, Pakistan. Tel: 92-42-99231819, naz.sbs@pu.edu.pk, Thomas B. Friedman, Laboratory of Molecular Genetics, National Institute on Deafness and Other Communication Disorders, 1F-141 Porter Neuroscience Research Center, National Institutes of Health, Bethesda, USA 20892 Tel: 302-496-7882, friedman@nidcd.nih.gov.

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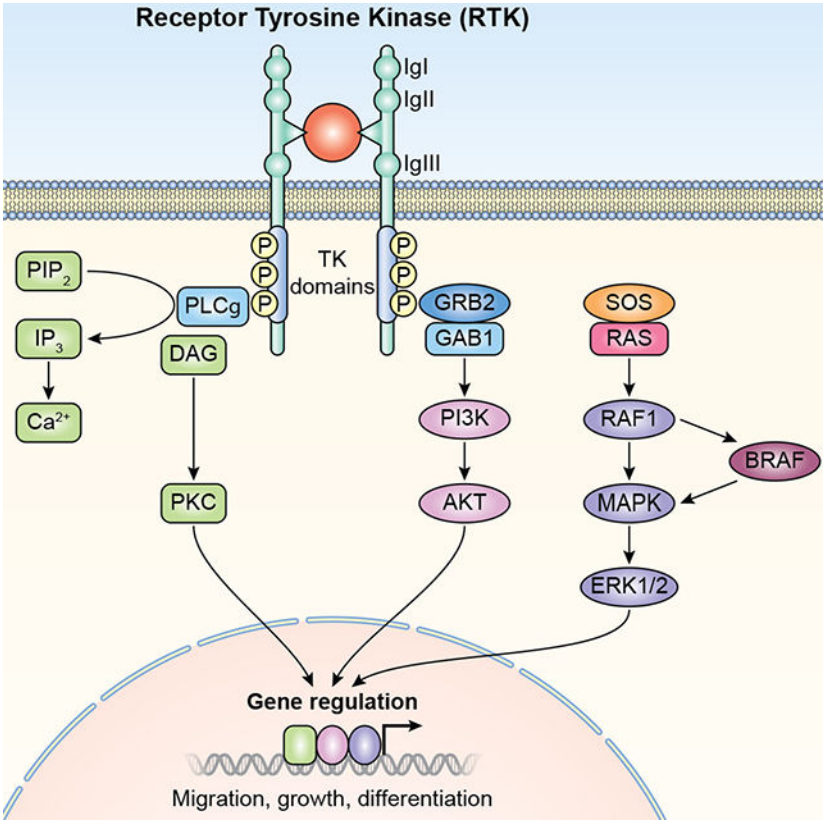


**Keywords**

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## 1 INTRODUCTION

Impaired sound detection is a prevalent deficit of older adults as well as for 1 in 500 to 1 in 2,000 young children.[1,2] Deficits in hearing often result from dysfunction of one of the complex, delicate structures or intricate signaling pathways in the inner ear.[3] Hearing loss can be conductive, sensorineural or mixed, depending on whether the defect is in the middle ear, inner ear or both, respectively (Figure 1A). The complex structure of inner ear develops from the otic placode next to the hindbrain,[4] which invaginates to form the otic vesicle (Figure 1B). This fluid-filled cyst then undergoes organogenesis to give rise to neurons of the vestibular and cochlear ganglions as well as non-sensory and sensory epithelia of the membranous labyrinth (Figure 1B). In the mature cochlea, there are three rows of sound-amplifying outer hair cells (OHCs) and a single row of inner hair cells (IHCs) responsible for mechano-chemical transduction of sound. The apical surfaces of hair cells are topped by F-actin packed stereocila (Figure 1C).[5]

Many pathogenic variants in genes encoding growth factors, receptors, co-receptors, adaptors and effectors have been identified in analyses of hearing loss in humans (Tables 1 and 2). Receptors and ligands, for example, LGR5 and BDNF, variants of which have not

been reported to cause hearing loss in humans but have important role in development of auditory system[6,7] and ligand-gated ion channel receptors, such as P2XR2[8] are not included in this review. Our focus is on variants in genes associated with human deafness. However, confidence in the evidence for pathogenicity of variants in the deafness causing genes differs. A ClinGen Hearing Loss Gene Curation Expert Panel has concluded that some are likely not bona fide pathogenic variants,[9] but rather represent coincidental co-occurrence with deafness in individual families. This appears to be the case for variants in *MYO1A*, *MYO1C*, *MYO1F* and *TSPEAR* reported in deafness.[9,10]

Here, we highlight three examples where there is robust data from human genetics and supporting data from animal models that both the receptor and its ligand, and other molecules in their signaling pathways, are necessary for hearing. When a ligand binds its receptor, a conformational change occurs in the receptor, initiating a signal propagated through second messengers.[11] Different classes of receptors can affect production of many of the same second messengers, and orchestrate development and maintenance of an organism.[12]

## 2 GROWTH FACTORS RELEVANT TO THE AUDITORY SYSTEM

Ear morphogenesis, cell fate and axis formation are established and guided by the concerted action of signaling molecules including retinoic acid, sonic hedgehog (SHH), various Wingless-related integration site (WNT) proteins, fibroblast growth factor (FGF) and bone morphogenetic protein (BMP) [reviewed in [13]]. Growth factors and cytokines necessary for the development of the ear are predominantly proteins and steroids, and less commonly, lipids. A rare example of a lipid messenger is sphingosine-1-phosphate (S1P) or lysosphingolipid,[14] a sphingolipid that binds to its S1PR2 receptor in the inner ear, which is necessary for hearing in human and mouse.[15] In addition to the classic signaling molecules involved in hearing mentioned above, NLRP3 is part of the inflammosome complex and variants cause over-production of the cytokine interleukin (IL)-1β[16] result in hearing loss.[17]

Juxtacrine signals mediated by NOTCH pathways establish the sensory epithelium, including hair cells and supporting cells.[18] In humans, WNT[19] and BMP[20] family members are required for development of the auditory system.[21] Variants of WNT3, WNT4, WNT5A, WNT7A, BMP1, BMP2, BMP4, and BMP7 (OMIM#165330, 603490, 164975, 601570, 112264 112262, 112261, 112267) result in low set ears or external ear malformations including prominent or posteriorly rotated ears, and small external auditory canals. In a few individuals, rare variants of *BMP2*, *BMP4*, *BMP7*, and *GDF6* (a BMP-class ligand) have been associated with syndromic deafness or surgically verified otosclerosis (Table 2). Variants of *NOG* encoding Noggin, which inhibits BMP signaling by blocking the ligand binding sites of the cognate receptors, also cause hearing loss in humans (Table 2). Although variants of the WNTs only lead to external ear malformations in humans,[22–26] targeted deletion of their frizzled receptors cause hearing loss in mouse[27] and are candidate genes for human deafness in individuals without a known cause. Norrin, the protein encoded by *NDP*, is a different molecule from WNT, is also a ligand of the frizzled receptor, FZ4. In humans, variants of *NDP* are associated with X-linked recessive Norrie Disease characterized by childhood onset blindness and various adult onset neurologic manifestations.[28] About 30%

to 40% of individuals with variants of *NDP* have a progressive increase in hearing thresholds (Table 2).

The growth factors *FGF3*, *FGF10*, *HGF*, *IGF1*, *JAG1, KITLG* and *TGFB1* are required for development or maintenance of hearing in humans (Table 1, Table 2). Homozygous loss of function variants of *FGF3* cause ear anomalies including labyrinthine aplasia, and microtia, accompanied by prelingual, sensorineural deafness.[29] In mouse, FGF10 is required for development of non-sensory epithelium of the inner ear.[30] Double homozygous knockouts of mouse *Ffg3* and *Fgf10* have diminutive otic vesicles, a more severe phenotype than that exhibited by single homozygous mutants of either gene.[31] Individuals with dominantly inherited pathogenic alleles of *FGF10* exhibit LADD syndrome, which is characterized by abnormalities of teeth and distal limb segments, but only 50% of cases manifest a mixed hearing loss.[32] Dominant and recessive alleles associated with deafness may have reduced penetrance and variable expressivity that can be due to modifiers in the genetic background, a supposition robustly supported by observations in mouse.[33,34] A few examples of genes with variants involved in syndromes where deafness is not a constant feature include *DVL1, DVL3*, *FGFR1*, *KIT*, *MAP3K7*, and *NDP* (Table 2). Genetic, environmental or stochastic factors responsible for reduced penetrance of deafness in syndromes due to variants of these genes remain to be discovered.

## 3 RECEPTORS RELEVANT TO AUDITORY SYSTEM

G-protein coupled receptors, receptor kinases and nuclear hormone receptors are three main classes of receptors, which respond to signaling molecules in the auditory system. Other types include enzymatic and non-enzymatic transmembrane proteins (Tables 1 and 2).

### 3.1 G-protein coupled Receptors

G-protein coupled receptors (GPCRs) have seven alpha-helical transmembrane domains with variable length intracellular N- and C-termini and intracellular and extracellular loops mediating interactions with protein partners and are coupled to multi-subunit trimeric G-proteins. Ligand binding to receptors activates multiple pathways (Figure 2A). Variants of the GPCR-encoding genes *ADGRV1*, *EDNRA*, *EDNRB* and *S1PR2* are associated with hearing loss (Tables 1 and 2). Ligand binding activates GTP hydrolysis of the G-protein catalytic unit (Figure 2A). One consequence of G-protein coupled receptor signaling is the generation of cyclic AMP (cAMP) by activation of adenylate cyclase 1 (ADCY1) (Figure 2A). A nonsense variant of *ADCY1* was reported to cause hearing loss in humans and zebrafish morphants of *Adcy1b* have a hearing loss due to hair cell dysfunction.[35] The inner ear morphology and hearing status of mice with a targeted disruption of *Adcy1*[36] or a spontaneous retrotransposon disruption of *Adcy1* (*brl*)[37] have not been reported.

Cyclic GMP (cGMP) is generated from GTP by guanylyl cyclase in response to ligand binding to G-protein coupled receptors. cGMP activates cGMP-dependent protein kinases. One such kinase is PRKG1, which is expressed in sensory cells and neurons of the mouse inner ear where it protects against noise induced hearing loss.[38] *PDE1C*, which encodes phosphodiesterase 1C, and hydrolyzes cGMP and cAMP, is important for $Ca^{+2}$ homeostasis

(Figure 2A). Variants of human *PDE1C* are associated with dominantly inherited hearing loss DFNA74 (Table 1).

Regulators of G-protein coupled receptor signaling required for normal hearing include GPRASP2 and GPSM2 (Table 2). GPRASP2 regulates post-endocytic sorting of G-protein coupled receptors by binding to their C-termini.[39,40] GPSM2, together with its partner GNAI3, are both expressed asymmetrically at the apical surface of hair cells, and control localization of kinocilia.[41] GPSM2 interacts with the α-subunits of G-proteins, (including GNAI3), and modulates their activation.[42] Additionally, GPSM2 and GNAI3 are both normally enriched in a narrow compartment at the tips of the tallest row stereocilia.[43,44] A conditional deficiency of GPSM2 or GNAI3 in the mouse inner ear results in stereocilia that are shortened by ~40% and ~25%, respectively.[45] Consistent with these results in mice, variants of human *GPRASP2* and *GPSM2* have been found to cause deafness (Table 2). The accumulation of GPSM2 and GNAI3 along with WHRN and EPS8 at the tips of stereocilia requires MYO15A, a motor protein. In the absence of MYO15A, WHRN and EPS8 fail to accumulate at the stereocilia tips. These data suggest that MYO15A transports a large complex of proteins to locations where they regulate actin polymerization dynamics of both stereocilia in post-mitotic hair cells and neuronal growth cones.[45]

### 3.1A EDN3 and EDNRB signaling

Endothelin EDN3 is synthesized as pre-pro-endothelin and then cleaved by endothelin-converting enzyme to a 21-residue peptide.[46] Endothelins are vasoconstrictors that participate in epithelial-mesenchymal interactions and are also important for melanocyte differentiation. In the inner ear, melanocytes develop from neural crest cells, some of which migrate into the intermediate cell layer of the stria vascularis and are necessary for establishing the endocochlear potential, which drives sound transduction.[47] EDN3 binds to EDNRA or EDNRB, that transmit signals through Gαq/α11 G-protein subunits.[47] One consequence is activation of phospholipase C which hydrolyses phoshphatidylinositol into second messengers diacylglycerol (DAG) and inositol 1,4,5 triphosphate (IP3). IP3 releases $Ca^{2+}$ from endoplasmic reticulum. DAG and $Ca^{2+}$ together activate Protein Kinase C (PKC) (Figure 2A). PKC then activates mitogen-activated protein kinase (MAPK) pathway, phosphorylating cAMP response element binding protein (CREB).[48] CREB binds to cAMP response element (CRE) DNA sequence of *MITF*,[48] a transcription factor required for development of melanocytes.

Variants of either human *EDNRB* or *EDN3* are associated with Waardenburg syndrome types 4A and 4B, respectively.[49,50] WS4 is chacterized by sensorineural hearing loss, hair, skin and eye pigmentary abnormalities and Hirschsprung's disease (Table 2) chacterized by a deficiency of ganglion cells of the distal colon and consequently muscles in the colon fail to peristaltically move stool leading to obstructions. EDNRB also has a distinct but unknown role for normal spiral ganglion function as *Ednrb* knockout mice undergo degeneration of spiral ganglion neurons.[51] The time course of *Ednrb* expression in SGNs, exactly when SGN death occurs and also which of the three SGN subtypes (1a, 1b, or 1c) are lost in *Ednrb* mutants remains to be studied.

### 3.2 Receptor Tyrosine Kinases

Receptor Tyrosine Kinases (RTK) are single-pass transmembrane proteins with extracellular immunoglobulin-like domains and other regions of variable lengths that interact with growth factors and trigger cell growth and differentiation. The intracellular region has tyrosine kinase activity and docking sites for scaffold proteins (Figure 2B). Variants of human RTKs *FGFR1*, *FGFR2*, *FGFR3*, *IGF1*, *KIT*, *MET* and *ROR1* are associated with hearing loss (Table 1, Table 2). RTKs mediate signaling through RAS/RAF/MAPK/ERK pathways (Figure 2B). Regulatory proteins of RTKs are important for signaling in the inner ear including a family of mitogen-activated protein kinase kinase kinases, BRAF and RAF1 that regulate RAS/RAF/MAPK/ERK signal transduction (Figure 2B). BRAF phosphorylates MAP3K1[52], and RAF1 is the principal component of MAPK pathway.[53,54] The importance of BRAF and RAF1 for normal hearing is demonstrated by the fact that some of their variants are associated with LEOPARD syndromes 3 and 2 and Noonan Syndrome 5, respectively (Table 2), which are separately characterized by disparate anomalies of heart, skin, genitalia or skeleton. RAS-related GTPase RIT1 regulates p38 MAPK-dependent signaling cascades[55] and variants of *RIT1* (OMIM #609591) are also associated with low set ears in humans,[56] pointing to the importance of RIT1 for both the morphogenesis and function of the outer ear.

Effectors of RTK signaling participating in hearing include CCDC50, EPS8, EPS8L2 among others, variants of which are associated with hearing loss DFNA44, DFNB102 and DFNB106, respectively (Table 1). *CCDC50* encodes YMER, which inhibits EGFR down-regulation [57] and negatively regulates NF-kB signaling pathway.[58,59] In the inner ear, EGFR signaling is important for proliferation of supporting cells.[60] The epidermal growth factor receptor pathway substrate 8 (EPS8) and epidermal growth factor receptor pathway substrate 8-like protein 2 (EPS8L2) are also required for hearing.[61,62] EPS8 is part of N-methyl-d-aspartate (NMDA) receptor complex,[63] which controls transduction of signals from RAS to RAC. EPS8L2 acts by stimulating RAC (GTPase)-guanine nucleotide exchange factor activity of SOS1.[64] In the inner ear, EPS8 and EPS8L2 are components of an electron-dense complex of proteins at the tips of hair cell stereocilia, as visualized by transmission electron microscopy. By virtue of their actin remodeling activity, they are important for elongation and maintenance of the precise lengths of stereocilia.[64–68]

**3.2A Hearing requires HGF and MET signaling—**Hepatocyte growth factor (HGF) is secreted by mesenchymal cells, binds the MET receptor, and regulates epithelial cell development and motility by activating a variety of downstream signaling pathways.[69] Like many genes, human *HGF* and mouse *Hgf* encode multiple alternative transcripts, most of which have not been well studied.[70] The importance of identifying and then studying the function of each alternative transcript of a gene was recently highlighted when an alternatively spliced microexon in cytohesin 1 (*CYTH1*), a gene encoding a guanidine exchange factor, was shown to be necessary for spatially restricting HGF-MET signaling.[71]

In 40 large families from Pakistan segregating deafness, the phenotype was linked to markers for the *DFNB39* locus on chromosome 7. Homozygosity was detected for either a non-coding, evolutionarily conserved three base pair deletion or an overlapping ten base pair

deletion in the 3′ UTR of a short alternative splice isoform of *HGF* of unknown function.[70] The presence of recognizable pathogenic variants in all of other exons and conserved sequences in the *DFNB39* interval was excluded by sequencing. Yet, the possibility remains that the non-coding 3bp and 10bp deletions of *HGF* are in linkage disequilibrium with the real deafness-causing variant in the *DFNB39* interval. The pathogenicity of these noncoding variants may be addressed by knocking in the identical 3bp or 10bp deletions in mouse *Hgf*. Nevertheless, there is compelling evidence from mouse that a wild type HGF expression level in the inner ear is necessary for normal hearing.[70] In mouse, body-wide excessive expression of HGF from a *Hgf* transgene results in deafness. Additionally, a homozygous inner ear conditional knockout of *Hgf* causes deafness, indicating that the titer of HGF must be tightly regulated for normal hearing, and that too much or too little HGF is incompatible with normal hearing.[70] During inner ear development, HGF is required for proper incorporation of neural crest cells into the intermediate cell (middle) layer of the stria vascularis (Figure 1C) in mice.[72] The stria maintains an endocochlear potential of +80 to +120 millivolts and a high concentration of potassium (154 millimolar) that bathes the apical surface of hair cells and which is necessary for mechano-transduction of sound by inner hair cells (Figure 1C).

The HGF receptor MET was also demonstrated genetically to be necessary for hearing. In mouse, a complete loss of MET function results in embryonic lethality and zebrafish *met* morphants have reduced neuromast-derived hair cells.[73] Zebrafish neuromasts resemble vertebrate inner ear sensory epithelia. In nine affected members of a human family, a predicted damaging missense variant p.(Phe841Val) of MET, located in the IPT4 domain of all MET isoforms, is associated with recessively inherited, nonsyndromic severe hearing loss.[74] The IPT3 and IPT4 domains constitute a high-affinity HGF binding surface of MET. A second homozygous missense variant p.(Phe1186Cys) of MET is associated with arthrogryposis and deafness in two siblings,[75] providing independent support for the conclusion that MET is required for normal hearing. It seems likely that these two damaging missense variants permit residual MET function required for embryonic development but disrupt a function of MET necessary for hearing.

The HGF-stimulated MET signaling pathway has numerous branches (Figure 2B). Variants of some of the genes encoding components of this signaling cascade are also associated with deafness in human or mouse. GAB1 is a component of a multi-subunit scaffold for various RTKs including IGF1 and MET (Figure 2B). A homozygous, hypomorphic missense variant of *GAB1*, p.(Gly116Glu), is associated with nonsyndromic hearing loss DFNB26 segregating in a family with eight affected individuals.[76] Unexpectedly, seven normal hearing individuals in this family were also homozygous for the p.(Gly116Glu) variant. These non-penetrant individuals (but none of the affected individuals) also carry a missense variant p.(Arg544Gln) of EEF1AKNMT (also called METTL13) [76] at the dominant modifier locus *DFNM1* of DFNB26 deafness. METTL13 (methyltransferase 13) is a predicted methyltransferase and is hypothesized to suppress *GAB1*-related deafness although the mechanism by which this might act is unknown. Interestingly, GAB1 and sprouty (SPRY2) interact with METTL13. SPRY2 down-regulates receptor tyrosine kinases and is also required for hearing in mouse.[77] Taken together, it is clear that HGF/MET/GAB1/SPRY2

signaling is crucial for the auditory system, although how this is mediated is not yet fully understood.

### 3.3 Other Enzymatic transmembrane receptors

In addition to RTK, two types of receptors expressed in the ear have intrinsic enzymatic activity, serine/threonine kinases and receptor tyrosine phosphatases. Receptor serine/threonine kinases are single-pass transmembrane proteins with a serine/threonine kinase domain (types I, II and III). Types I and II exist as homodimers. Type III receptors act as co-receptors by presenting the ligand to the other two classes (Figure 3A). *ACVR1* encodes a type I serine/threonine kinase receptor and variants cause hearing loss in some individuals with fibrodysplasia ossificans progressiva, a connective tissue disorder (Table 2).

The receptor tyrosine phosphatases are a subclass of transmembrane protein tyrosine phosphatases (PTPase). PTPRQ is a type III receptor-like protein-tyrosine phosphatase (Figure 3B) that preferentially dephosphorylates and regulates levels of phosphatidylinositol 1,4,5-trisphosphate, PIP3,[78] by dephosphorylating it to PIP2, which is further dephosphorylated to IP3 (Figure 3B). Signaling through PIP3 is important for survival, proliferation, and the subcellular architecture of diverse cellular types. Several dominant and recessive variants of human *PTPRQ* are associated with hearing loss in human (Table 1) and mouse.[79] In the inner ear, PTPRQ contributes to hair-bundle shaft connectors, which modulate spacing of stereocilia,[79] while rootlets of stereocilia develop postnatally and function to anchor stereocilia into the actin-rich cuticular plate. It remains to be determined whether PTPRQ also functions as a receptor in the inner ear.

### 3.4 Non-enzymatic Receptors

Transmembrane receptors with no known intrinsic enzymatic activity include ILDR1, NOTCH, TNFRS11A and SLITRK6 (Figure 4A–4D). ILDR1 is a receptor having an immunoglobulin-like extracellular domain (Figure 4A). In zebrafish, *ildr1b* morphants exhibit hearing loss and have a significantly reduced expression of *fgf3*, *fgf10*, and *fgfr1*, disrupting migration of the lateral line primordium.[80] In mouse, *Ildr1* is expressed in the small intestine and regulates fat-stimulated cholecystokinin secretion.[81] Variants of human *ILDR1* are associated with nonsyndromic deafness DFNB42 inherited as a recessive trait (Table 1), a phenotype that is recapitulated in mouse homozygous for a deletion of *Ildr1*.[82,83] It remains to be determined if deaf human subjects with biallelic pathogenic variants of *ILDR1* alleles have an additional clinically relevant phenotype involving a disruption of cholecystokinin secretion. In the mouse inner ear, ILDR1 is necessary for retention of marvel domain-containing protein 2 (MARVELD2)-originally named tricellulin encoded by *TRIC*- at the tricellular tight junctions.[83] Human deafness-causing equivalent knock-in variants of mouse *Marveld2* are also deaf.[84] It is not known if there is a ligand for ILDR1 in the inner ear. Perhaps in the sensory epithelium of the inner ear, ILDR1 just functions as a structural protein at the tricellular junction between three epithelial cells.

**3.4A. JAG/NOTCH signaling—**Signaling through NOTCH receptors determines cell fates during development.[85] NOTCH receptors interact with membrane bound ligands JAG and DLL that are present on adjacent cells (Figure 4B). Signaling induced by binding of

NOTCH or JAG results in cleavage of the NOTCH receptor, which then translocates to the nucleus and alters transcription of target genes, some of which are important for hearing, such as HES1 (Figure 4B).[86,87] Variants of the human genes encoding JAG1, and NOTCH2 and NOTCH3 receptors cause syndromes involving hearing loss (Table 2). In the cochlea of a *Jag1* p.(Gly289Asp) heterozygous mouse, referred to as *headturner*, the number of outer hair cells is reduced by 33% with a slight increase in the number of inner hair cells. However, these mice are not deaf.[88] In contrast, mice with a deletion of *Jag1* or *Notch2* limited to neural crest cells have malformed stapes and incus, and have a mild to moderate hearing loss.[89]

### 3.5 Nuclear Hormone Receptors

Nuclear hormone receptors are cytoplasmic proteins. Binding to ligand activates the receptors, which then translocate to the nucleus where they regulate target gene transcription (Figure 4E). Nuclear hormone receptors required for hearing in human include *ESRRB*, *ESRRG* and *THRB* (Table 1, Table 2). Studies of conditional knockout mice have shown that ESRRB controls expression of many genes encoding transporters and ion channels, such as *Atp1b2*, *Kcnq1*, *Kcne1*, which are all important for inner ear function,[90] specifically in strial marginal cells. One consequence of the absence of ESRRB in mouse is a partial transformation of strial marginal cells into epithelial cells.[90]

Repressors of nuclear hormone receptors also play a role in audition. TBL1X and TBL1Y are members of WD40 repeat-containing protein family and act as repressors of nuclear hormone receptors. They are important for ear development and hearing.[91,92] TBL1X and TBL1Y are components of nuclear receptor co-repressor (NCOR) complex which is required for Tri-iodothyronine (T3)-regulated gene expression.[93] This regulation is important since thyroid hormone T3 and its receptor THRB play a role in cochlear development by controlling expression of genes necessary for hearing, which include *KCNQ4* and *SLC26A5*.[94]

### 3.6 CO-RECEPTORS

Heparan sulfate proteoglycans are required for dimerization of some receptor tyrosine kinases including FGFR and EGFR.[95] In addition, there are many proteins, which function as co-receptors. For example, the low-density lipoprotein (LDL) receptor-related proteins serve as co-receptors to frizzled proteins during canonical WNT signaling and their variants are associated with hearing loss.[96–98] LRP5/6 is a WNT co-receptor in vertebrates,[99] and *Lrp5* knockdown in zebrafish with morpholinos reduces the number of supporting cells and hair cells.[98] Additionally, variants of human *LRP5* cause either nonsyndromic hearing loss (Table 1) or sensorineural hearing loss in patients with dominantly inherited osteosclerosis (Table 2).

## 4 CONCLUSION

The development of the auditory system requires multiple precisely orchestrated biochemical events. Genetic studies of hundreds of genes necessary for audition have uncovered several pathways important for normal hearing. Based initially upon studies of

animal model, growth factors are now being explored for treatment of noise and ototoxic induced deafness and age related hearing loss,[100–109] and some of these are currently in clinical trials.[110,111] For example, topical application of IGF1 to the middle ear was used to treat sudden sensorineural hearing loss in humans, and some treated individuals showed improvements of 10 dB to 30 dB for tested frequencies as compared to controls.[103,112] Hair cell regeneration in response to application of growth factors and by inhibition of specific signaling pathways is also being explored.[113] For example, an inhibitor of NOTCH signaling is in phase II clinical trial for treatment of sensorineural moderate to severe hearing loss.[21] As signaling pathways are involved with differentiation, proliferation, maintenance and regeneration processes, greater understanding of the *in vivo* ligands, receptors, protein partners and the modulation of their expression may provide opportunities to rebuild a properly patterned and functional adult human inner ear.

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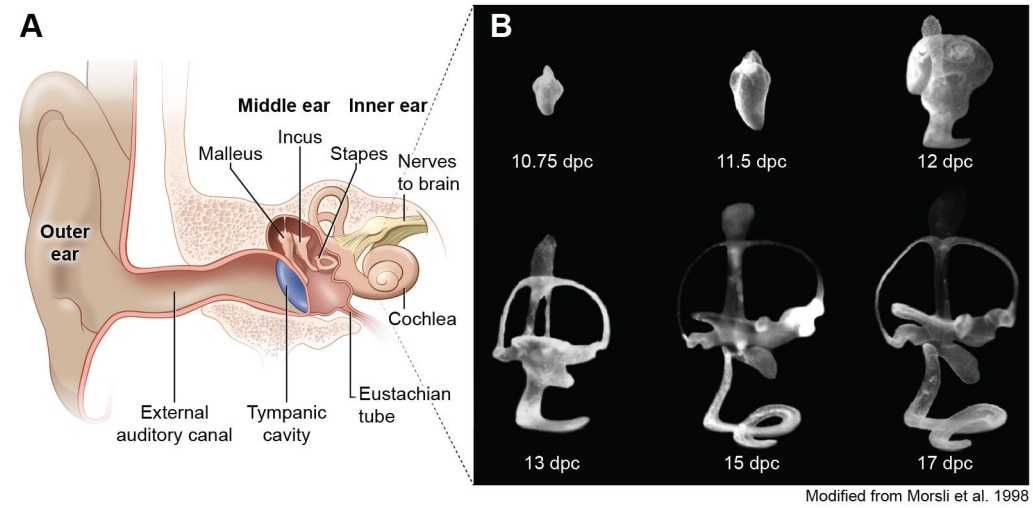


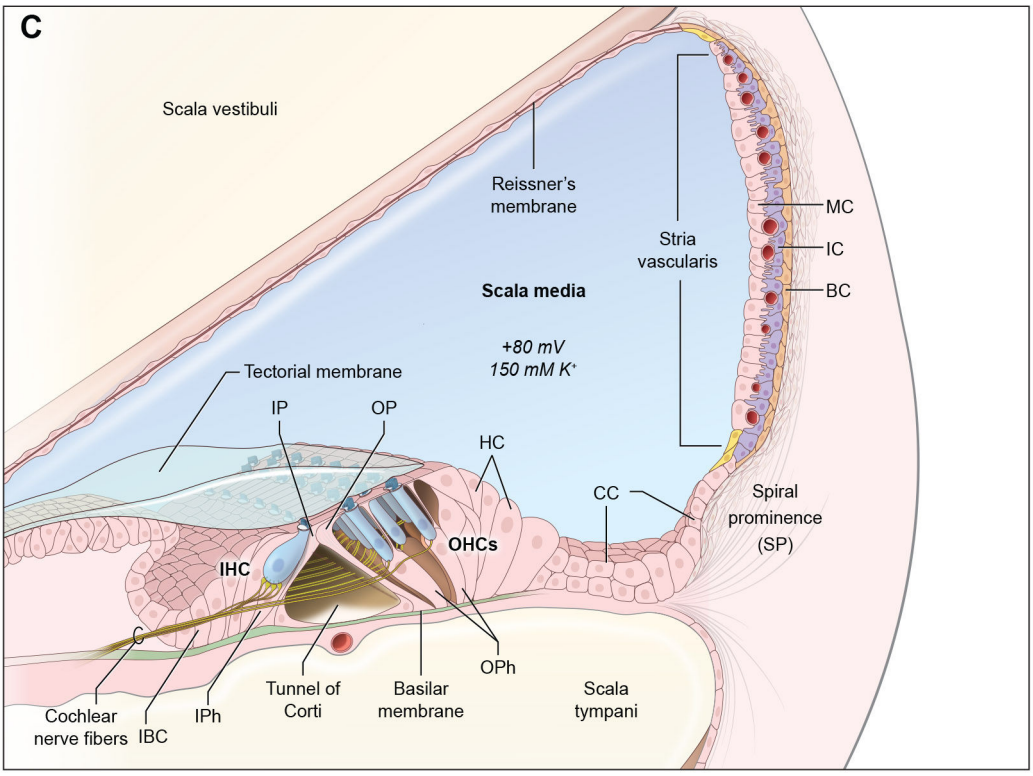


**FIGURE 1.**

Development and structure of the ear. (A) Structure of the human ear showing its three main parts, outer, middle and inner ear. (B) Paint-filled mouse membranous labyrinths at embryonic days 10.75 days-postcoitum to postnatal day 1 (P1). Lateral views are shown. Scale bar, 200 μm. (C) Diagram of a cross-section of the cochlea. The roof of the cochlear duct is formed by two layers of flattened cells comprising Reissner's membrane, while the base is formed by the basilar membrane, which separate the cochlear duct (scala media) from the scala vestibuli and the scala tympani. The three rows of outer hair cells, one row of inner hair cells and different types of supporting cells and the stria vascularis are shown. IHC; Inner Hair Cells, OHC, Outer Hair Cells, IP, Inner Pillar cells, OP; Outer Pillar Cells,

HC; Hensen’s Cells, CC; Claudius Cells, BC; Basal Cells, IC; Intermediate cells, MC; Marginal Cells, IBC; inner border cells.

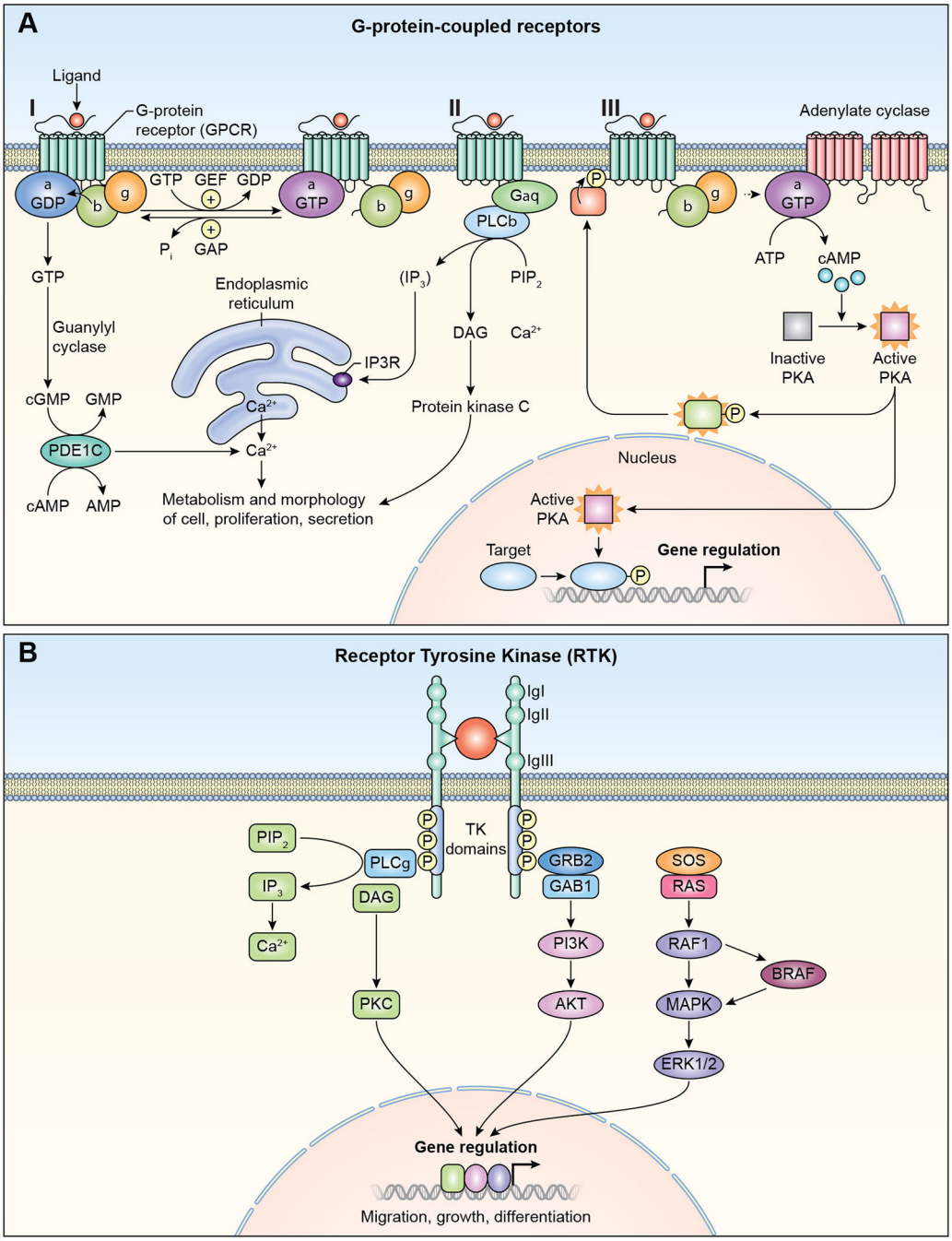


**FIGURE 2.**

GPCR and RTK signaling pathways. (A) G-protein Coupled Receptors (GPCR). I. The receptors are coupled to the C-terminus of heterotrimeric G-proteins. G-proteins are composed of α, β, and γ subunits. GPCRs activate signaling through multiple pathways. II. Phospholipase C, (PLC), phosphatidylinositol signaling pathway. Diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) are generated by cleavage of phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) by phospholipase C. $IP_3$ releases calcium ions from endoplasmic reticulum. Diacylglycrol remains bound to the plasma membrane. Both

diacylglycerol and calcium ions act together activate Protein Kinase C (PKC). PKC phosphorylates multiple cytoplasmic proteins that regulate cellular activity. III. Cyclic AMP signaling pathway. Cyclic AMP is a second messenger. GPCR activates adenylate cyclase, which converts ATP to cyclic AMP (cAMP). cAMP activates protein Kinase A (PKA), which then phosphorylates different proteins and transcription factors. PKA translocates to nucleus and controls gene transcription of target genes. IP3R, inositol trisphoshphate receptor, GEF; guanidine exchange factor, P; Phosphate. (B) Receptor Tyrosine Kinase (RTK). Ligand binding causes receptor dimerization and autophosphorylation. Signaling via RTK can take place through phospholipase C pathway, left side of figure (also see Figure 2A). GRB2 with other associated proteins such as GAB1, is bound to RTK. The activated receptor phosphorylates SOS1 and other guanine nucleotide exchange factors (GEF), and members of RAS, RHO and RAF, which are tethered to membranes. Signals are further propagated through the MAPK/ERK pathway to regulate gene expression. PI3K; phosphoinositide 3- kinase, Akt; Protein Kinase B.

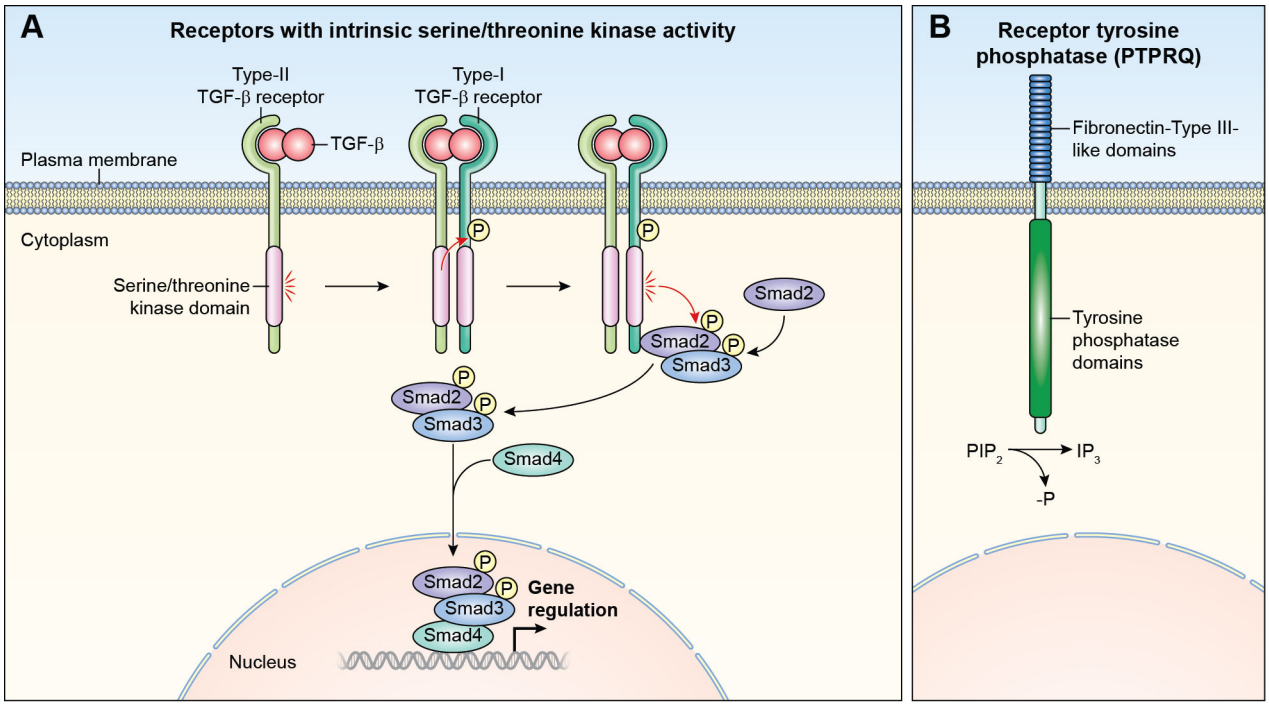


**FIGURE 3.**

Other receptors with intrinsic enzymatic activity (A) Receptor serine/threonine kinase. A ligand of the TGFB superfamily or the BMP superfamily, binds first to a type II receptor, which in turn phosphorylates the type I receptor and leads to their dimerization. The activated receptor complex phosphorylates the SMAD family proteins. Phosphorylation of SMAD proteins disassociates them from the receptor complex. Bound SMADS translocate to the nucleus and form complexes with DNA regulatory proteins inhibiting or activating transcription of target genes. (B) Receptor tyrosine phosphatase. PTPRQ dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PIP3) to PIP2. (See Figure 2B for details of signaling via PIP2).

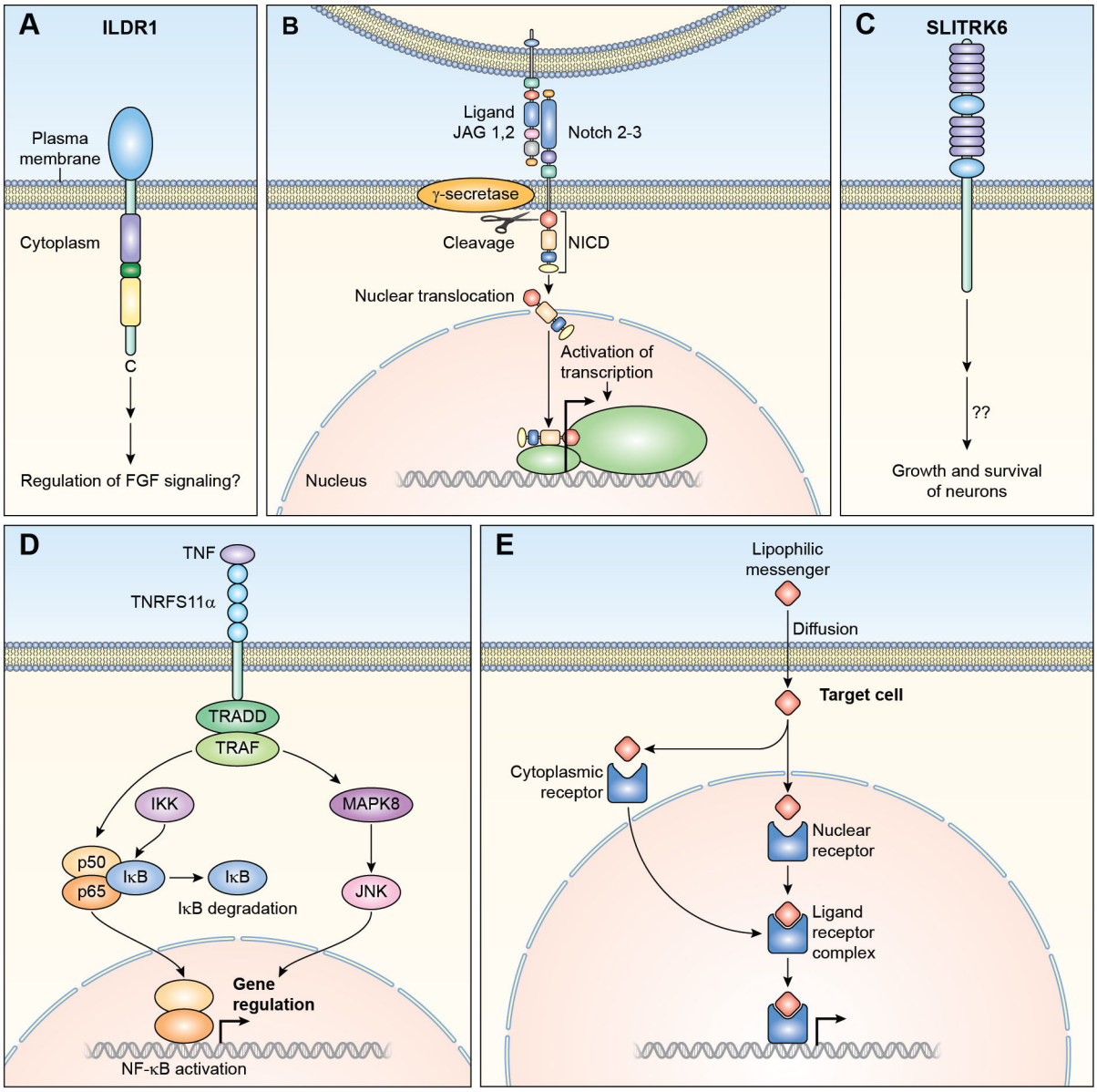


**FIGURE 4.**

Non-enzymatic receptors (A) ILDR1 has an extracellular immunoglobin like domain and intracellular cysteine and arginine regions. Both of these are separated by a dileucine motif. Signaling through this receptor in the inner ear remains to be elucidated. (B) NOTCH receptors bind to transmembrane ligands such as JAG1. As a result of binding, NOTCH is proteolytically cleaved by γ-secretase releasing the intracellular domain of the protein (NICD), which translocates to the nucleus forming complexes with other proteins and regulate transcription of target genes. (C) SLITRK6 is a transmembrane receptor with leucine rich repeats in its extracellular domain. The mechanism of signaling through SLITRK6 is unknown. (D) TRADD and TRAFF are adapters of TNRFS receptors and participate in downstream signaling. Binding of TNF to its receptors activates either MAPK8/JNK or NF-kB (NFKB1), which is sequestered in the cytoplasm by IKB. The

activation of NFKB1 by receptor binding activates a kinase (IKK) which phosphorylates IKB at specific serine residues. IKB is then ubiquitinated and degraded by the proteasome. Free NFKB1 translocates to the nucleus and regulates transcription. The second signaling pathway involves MAPK8/JNK. MAPK8 phosphorylates a number of transcription factors which modulate transcription of specific genes. (E) Ligand binding to nuclear hormone receptors cause dimerization and translocation to the nucleus. Receptor-DNA binding controls transcription of targeted genes involved in a variety of cellular activities including ion transport and proliferation. IKB; nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha, IKK; IKB Kinase.

## TABLE 1

Growth factors, receptors and related proteins implicated in nonsyndromic hearing loss

| Gene | OMIM | Description; cellular location | Protein/alias | Function | HL type | Locus† |
|---|---|---|---|---|---|---|
| *ADCY1* | 103072 | Adenylate Cyclase 1; transmembrane | ADCY1/AC1 | Generates the second messenger cAMP | Prelingual, sensorineural, bilateral, profound | *DFNB44* |
| *CCDC50* | 611051 | Coiled Coil Domain-Containing protein 50; cytoplasmic | CCDC50/ YMER/ C3ORF6 | Inhibits downregulation of EGFR/Effector of EGF mediated signaling | Postlingual, progressive, sensorineural, mid-frequency> | *DFNA44* |
| *DCDC2* | 605755 | Double Cortin Domain-Containing protein 2; cytoplasmic | DCDC2/RU2/ RU2S | Inhibits WNT signaling | Prelingual, sensorineural, profound | *DFNB66* |
| *ELMOD3* | 615427 | ELMO/ced12 Domain-containing protein 3; cytoplasmic | ELMOD3/ RBED1 | GTPase-activating protein (GAP) for small GTPases | Prelingual, mixed, severe to profound | *DFNB88* |
| *EPS8* | 600206 | Epidermal growth factor receptor Pathway Substrate 8; cytoplasmic | EPS8 | Elongation of stereocilia by actin remodeling | Prelingual, sensorineural, bilateral, profound | *DFNB102* |
| *EPS8L2* | 614988 | Epidermal growth factor receptor Pathway Substrate 8-Like protein 2; cytoplasmic | EPS8L2 | Maintenance of stereocilia, actin remodeling | Childhood onset, progressive, bilateral, sensorineural, moderate to profound | *DFNB106* |
| *ESRRB* | 602167 | EStrogen-Related Receptor, Beta; cytoplasmic | ESRRB/ ESRL2/ERR2 | Epithelial cell fate, development of the stria vascularis | Prelingual or postlingual, sensorineural, bilateral, severe to profound | *DFNB35* |
| *GAB1* | 604439 | GRB2-Associated Binding protein 1; cytoplasmic | GAB1 | Mediator of HGF, IGF1 signaling | Prelingual, bilateral, sensorineural, profound | *DFNB26* |
| *GIPC3* | 608792 | GIPC PDZ domain-containing family, member 3; cytoplasmic | GIPC3/GAIP C-terminus-interacting protein 3 | Predicted to modulate WNT signaling | Prelingual, bilateral, sensorineural, severe to profound | *DFNB15/ DFNB72/ DFNB95* |
| *GRAP* | 604330 | Growth factor Receptor-bound protein 2 (Grb2)-related Adaptor Protein; cytoplasmic | GRAP | Activates RAS signaling | Prelingual, bilateral, sensorineural, severe to profound | *DFNB114* |
| *HGF* | 142409 | Hepatocyte Growth Factor; secreted | HGF/SF | Incorporation of neural crest cells into the stria vascularis | Prelingual, sensorineural, bilateral, moderate to severe or severe to profound | *DFNB39* |
| *IFNLR1* | 607404 | Interferon-Lambda Receptor 1, transmembrane | IFNLR1/ IL28RA | Functions in Jak/STAT pathway | Postlingual, sensorineural, bilateral, progressive, moderate to profound | *DFNA2C* |
| *ILDR1* | 609739 | Immunoglobulin-Like Domain-containing Receptor 1; transmembrane and cytoplasmic | ILDR1 | Structural role at the tricellular tight junctions; receptor role in the inner ear unknown | Prelingual, sensorineural, bilateral, moderate to profound or severe to profound | *DFNB42* |
| *KITLG* | 184745 | KIT Ligand; transmembrane and secreted | KITLG/KL/ KITL/MGF/S CF/SF | Proliferation, migration from the neural crest, differentiation of melanoblasts | Prelingual, sensorineural, unilateral or asymmetric | *DFNA69* |

| Gene | OMIM | Description; cellular location | Protein/alias | Function | HL type | Locus† |
|---|---|---|---|---|---|---|
| *LRP5* | 603506 | Low density lipoprotein Receptor-related Protein 5; transmembrane | LRP5/ LRP7/LR3 | Co-receptor during WNT signaling | Sensorineural, progressive, childhood onset, bilateral, low and mid frequency | -, recessive |
| *MET* | 164860 | Mesenchymal EpithelialTransition factor; transmembrane | MET/HGFR | Incorporation of neural crest cells into the stria vascularis | Prelingual, sensorineural, bilateral, severe | *DFNB97* |
| *NLRP3* | 606416 | NLR family, Pyrin domain-containing 3; cytoplasmic | NLRP3/ CIAS1/ NALP3/ PYPAF1/ AII/AVP Receptor-Like | Leads to events which end in production of cytokine IL-1β | Postlingual, bilateral, progressive | *DFNA34* |
| *PDE1C* | 602987 | Phosphodiesterase 1C; cytoplasmic | PDE1C/ HCAM3 | Regulates levels of second messengers cAMP and cGMP | Postlingual, progressive, bilateral, mild to profound | *DFNA74* |
| *PTPRQ* | 603317 | Protein-Tyrosine Phosphatase, Receptor-type, Q; transmembrane and cytoplasmic | PTPRQ/ PTPGMC1 | Receptor role unknown, structural role as shaft connector | Sensorineural, variable onset, progressive, bilateral, mild to moderate | *DFNA73* |
| *PTPRQ* | 603317 | Protein-Tyrosine Phosphatase, Receptor-type, Q; transmembrane and cytoplasmic | PTPRQ/ PTPGMC1 | Receptor role unknown, structural role as shaft connector | Sensorineural, childhood onset, progressive, bilateral, moderate to profound | *DFNB84A* |
| *ROR1* | 602336 | Receptor tyrosine kinase-like Orphan Receptor 1; transmembrane | ROR1/ NTRKR1 | Innervation of auditory hair cells in response to WNT5A signaling | Prelingual, bilateral, sensironeural, profound, auditory neuropathy, | *DFNB108* |
| *S1PR2* | 605111 | Sphingosine-1-Phosphate Receptor 2; transmembrane & cytoplasmic | S1PR2/EDG5/ S1P2 | Development of stria vascularis | Congenital, sensorineural, bilateral, profound | *DFNB68* |

†DFNA, dominant hearing loss, DFNB, recessive hearing loss, OMIM, Online Mendelian Inheritance in Man (https://www.omim.org/). A comprehensive source of gene expression data in mouse and zebrafish auditory systems are available on the gEAR Portal, https://umgear.org/.

## TABLE 2

Growth factors, receptors and related proteins implicated in syndromic hearing loss

| Gene | OMIM | Description; cellular location | Protein/alias | Function | Hearing loss type | Locus; mode of inheritance |
|---|---|---|---|---|---|---|
| *ACVR1* | 102576 | ACtiVin a Receptor, type I; transmembrane | ACVR1/ ACVRLK2/ ALK2 | General role as receptor for Activin, BMP or TGFB mediated SMAD signaling | Variable age of onset, conductive or sensorineural, mild to severe | Fibrodysplasia ossificans progressiva; dominant |
| *ADGRV1* | 602851 | ADhesion G protein-coupled Receptor V1; transmembrane | ADGRV1/ GPR98/ MASS1/ VLGR1/ KIAA0686 | Receptor function unknown, component of stereocilia ankle links | Sensorineural, bilateral, progressive, moderate to severe | Usher syndrome 2C; recessive |
| *BMP2* | 617877 | Bone Morphogenetic Protein 2, secreted | BMP2/ BMP2A | Endochondral ossification | External ear malformations, conductive | Short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies; dominant |
| *BMP2* | 617877 | Bone Morphogenetic Protein 2, secreted | BMP2/ BMP2A | Endochondral ossification | Conductive | Otosclerosis |
| *BMP4* | 112262 | Bone Morphogenetic Protein 4; secreted | BMP4/ BMP2B/ BMP2B1 | Specification of sensory and nonsensory regions of cochlea | Conductive | Otosclerosis |
| *BMP4* | 112262 | Bone Morphogenetic Protein 4; secreted | BMP4/ BMP2B/ BMP2B1 | Specification of sensory and nonsensory regions of cochlea | Sensorineural, mild to moderate | Stickler syndrome and renal dysplasia; dominant |
| *BMP7* | 112267 | Bone Morphogenetic Protein 7; secreted | BMP7/OP1 | Specifies tonotopic axis in developing inner ear | Sensorineural, bilateral, moderate | Ocular, brain, ear, palate, and skeletal anomalies; dominant |
| *BRAF* | 164757 | v-RAF murine sarcoma viral oncogene homologue B1; cytoplasmic, cell membrane, nuclear | BRAF/ BRAF1/ RAFB1 | Regulator of MAPK/ERK signaling pathway | Outer ear malformation, sensorineural | LEOPARD syndrome 3; dominant |
| *DVL1* | 601365 | Dishevelled 1, cytoplasmic | DVL1/DVL | Functions downstream of WNT signaling | Outer ear malformation, conductive or sensorineural | Robinow syndrome, autosomal dominant 2; dominant |
| *DVL3* | 601368 | Dishevelled 3, cytoplasmic | DVL3 | Functions downstream of WNT signaling | Rare ear malformation and hearing loss | Robinow syndrome, autosomal dominant 3; dominant |
| *EDN3* | 131242 | Endothelin 3, secreted | EDN3/ET3 | Development of neural crest and its cell lineages | Sensorineural, Mild to profound, unilateral or bilateral | Waardenburg syndrome, type 4B, WS4B; dominant or recessive |
| *EDNRA* | 131243 | Endothelin Receptor, type A; transmembrane | EDNRA/ETA/ ETRA | Development of neural crest and its cell lineages | Outer ear malformation, childhood onset, conductive, moderate | Mandibulofacial dysostosis with alopecia; dominant |

| Gene | OMIM | Description; cellular location | Protein/alias | Function | Hearing loss type | Locus; mode of inheritance |
|---|---|---|---|---|---|---|
| *EDNRB* | 131244 | Endothelin Receptor, type B; transmembrane | EDNRB/ETB/ ETBR | Development of neural crest and its cell lineages | Sensorineural, mild to profound, unilateral or bilateral | Waardenburg syndrome, type 4A, WS4A, WS1, WS2; dominant and recessive Waardenburg syndrome, type 2A, WS2A; dominant; ABCD syndrome; recessive |
| *ESRRG* | 602969 | EStrogen Related Receptor Gamma, nuclear | ESRRG/ ERR3 | Unknown | Prelingual, sensorineural, bilateral, mild to moderate | Hearing loss with mild intellectual disability; recessive |
| *FGF3* | 164950 | Fibroblast Growth Factor 3, secreted | FGF3/INT2 | Induction of inner ear fate | Outer and inner ear anomalies, prelingual, sensorineural, profound | Congenital deafness, inner ear agenesis, microtia, microdontia; recessive |
| *FGF10* | 602115 | Fibroblast Growth Factor 10; secreted | FGF10 | Specification of nonsensory regions of inner ear | Outer ear malformation, conductive, sensorineural or mixed hearing loss | LADD syndrome; dominant |
| *FGFR1* | 136350 | Fibroblast Growth Factor Receptor 1; transmembrane | FGFR1/ FLT2/FLG | Early cell proliferation of cochlea, differentiation of sensory epithelium | Outer ear malformation in some, unilateral | Kallmann syndrome 2; dominant |
| *FGFR2* | 176943 | Fibroblast Growth Factor Receptor 2; transmembrane | FGFR2/TK14 | Essential for inner ear morphogenesis | Outer ear malformations may be present, prelingual or postlingual, conductive or sensorineural or mixed, bilateral mild to severe | Apert syndrome, Crouzon syndrome CFD1; LADD syndrome; Saethre-Chotzen Syndrome, Pfeiffer syndrome type 3; Dominant |
| *FGFR3* | 134934 | Fibroblast Growth Factor Receptor 3; transmembrane | FGFR3 | Controls fate of supporting cells in organ of Corti | Sensorineural or mixed, mild to moderate | CATSHL syndrome, LADD syndrome, Muenke syndrome, SADDAN; dominant or recessive |
| *GDF6* | 601147 | Growth/ Differentiation Factor 6; secreted | GDF6/ CDMP2 | Growth of cartilage elements, SMAD signaling | Outer ear malformation, conductive or sensorineural, mild to moderate | Klippel-Feil syndrome 1; dominant multiple synostoses syndrome, dominant |
| *GNAI3* | 139370 | Guanine Nucleotide-binding protein, Alpha-Inhibiting activity polypeptide 3; cytoplasmic | GNAI3/ G protein | Mediator of signaling involving G protein-coupled endothelin receptor | Outer ear malformation, conductive or sensorineural, mild to moderate | Auriculocondylar syndrome 1; dominant |
| *GPRASP2* | 300969 | G Protein-coupled Receptor-Associated Sorting Protein 2; cytoplasmic | GPRASP2/ GASP2 | Turnover of G-protein-Coupled Receptors | External ear malformations, congenital or progressive, bilateral, mixed hearing loss, moderate to profound | DFNX7, Deafness X-linked 7, recessive |
| *GPSM2* | 609245 | G Protein Signaling Modulator 2; cytoplasmic | GPSM2/LGN/ PINS | Asymmetric localization of kinocilia in | Prelingual, sensorineural, bilateral, severe to profound | Chudley-McCullough Syndrome; recessive |

| Gene | OMIM | Description; cellular location | Protein/alias | Function | Hearing loss type | Locus; mode of inheritance |
|---|---|---|---|---|---|---|
| | | | | postmitotic hair cells | | |
| *IGF1* | 147440 | Insulin-like Growth Factor I; secreted | IGF1/IGFI/ Somatomedin C | Postnatal differentiation and maturation of cochlea and central auditory neurons | Sensorineural, prelingual, bilateral, profound | Insulin-like growth factor I deficiency; recessive |
| *IGF1R* | 147340 | Insulin-like Growth Factor I Receptor; transmembrane | IGF1R | Postnatal differentiation and maturation of cochlea and central auditory neurons | Bilateral, profound | Insulin-like growth factor I, resistance to; dominant |
| *JAG1* | 601920 | JAGged 1; transmembrane | JAG1/JAGL1 | Patterning of the organ of Corti, outer hair cell number | Mild to severe, mixed, mid-frequency | Deafness, congenital heart defects, and posterior embryotoxon; dominant |
| *KIT* | 164920 | V-KIT Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue; transmembrane | KIT/SCFR | Proliferation, migration from the neural crest, differentiation of melanoblasts | Prelingual, sensorineural, profound | Piebaldism (Woolf's syndrome); dominant |
| *KITLG* | 184745 | KIT Ligand; trasmembrane and secreted | KITLG/KL/ KITL/MGF/SCF/SF | Proliferation, migration from the neural crest, differentiation of melanoblasts | Congenital, stable unilateral and asymmetric hearing loss | Waardenburg syndrome, type 2; dominant |
| *LRP2* | 600073 | Low density lipoprotein Receptor-related Protein 2; transmembrane | LRP2/ Glycoprotein 330/ megalin | Endocytic receptor, Development of ear | Outer ear malformation, sensorineural, severe to profound | Donnai-Barrow syndrome; recessive |
| *LRP4* | 604270 | Low density lipoprotein Receptor-related Protein 4; transmembrane | LRP4/ MEGF7 | Causes narrowing of foramina of the cranial nerves which leads to hearing loss | Hearing loss present, but no details provided | Sclerosteosis 2, recessive |
| *LRP5* | 603506 | Low density lipoprotein Receptor-related Protein 5; transmembrane | LRP5/ LRP7/LR3 | Co-receptor during WNT signaling | Sensorineural, | Osteosclerosis, dominant |
| *MAP3K7* | 602614 | Mitogen-Activated Protein Kinase kinase kinase 7; cytoplasmic | MAP3K7/ TAK1 | Mediator of TGFB and BMP signaling | Outer and inner ear malformations, conductive. bilateral | Cardiospondylocarpofacial syndrome; dominant |
| *MET* | 164860 | Mesenchymal EpithelialTransition factor; transmembrane | MET/HGFR | Incorporation of neural crest cells into the stria vascularis | Prelingual, sensorineural, bilateral, severe to profound | Deafness with arthrogryposis and distinctive facial features; recessive |
| *NDP* | 300658 | Norrin cystine knot growth factor; secreted | NDP/Norrin | Vascularization of cochlea with particular importance in stria vascularis and spiral ganglion, binds to Frizzled receptors | Sensorineural, postlingual, childhood or adult onset, bilateral, progressive, mild to profound | Norrie Disease; X-linked recessive |

| Gene | OMIM | Description; cellular location | Protein/alias | Function | Hearing loss type | Locus; mode of inheritance |
|---|---|---|---|---|---|---|
| *NLRP3* | 606416 | NLR family, Pyrin domain-containing 3; cytoplasmic | NLRP3/ CIAS1/ NALP3/ PYPAF1/ Cryopyrin | Leads to events which end in production of cytokine IL-1β | Postlingual, sensorineural, bilateral, progressive, severe | CINCA syndrome, Muckle-Wells syndrome; dominant |
| *NOG* | 602991 | NOGgin, mouse homologue of; secreted | NOG | Inhibits signaling by GDF6, BMP, and TGFB | Stapes ankylosis, conductive, rarely sensorineural, progressive | Multiple synostoses syndrome 1; dominant |
| *NOTCH2* | 600275 | Drosophila homolog of Notch, 2; transmembrane | NOTCH2 | Patterning of the organ of Corti | Childhood onset, conductive, rarely sensorineural, mild to moderate | Hajdu-Cheney syndrome; dominant |
| *NOTCH3* | 600276 | Drosophila homolog of Notch, 3; transmembrane | NOTCH3 | Patterning of the organ of Corti | Outer ear malformation, conductive or mixed, bilateral, moderate | Lateral meningocele syndrome; dominant |
| *NSD1* | 606681 | Nuclear receptor-binding Su-var, enhancer of zeste, and trithorax Domain protein 1; nuclear | NSD1/ ARA267 | unknown | Childhood onset, otitis media, conductive | Sotos syndrome 1; dominant |
| *PTPN11* | 176876 | Protein-Tyrosine Phosphatase, Nonreceptor-type, 11; cytoplasmic | PTPN11/ PTP2C/SHP2 | Mediates signaling by HGF, EGF through activation of RAS/MAPK pathways | Outer ear malformation, Childhood or adult onset, sensorineural or mixed, unilateral or bilateral, mild to profound | Noonan syndrome 1, LEOPARD syndrome 1; dominant |
| *RAF1* | 164760 | v-Raf-1 Rapidly Accelerated Fibrosarcoma murine leukemia viral oncogene homologue 1, cytoplasmic | RAF1/CRAF | Secondary signal transducer for receptor tyrosine kinase via RAS/MAPK pathways | Outer ear malformation, childhood or adult onset,sensorineural or mixed, unilateral or bilateral, mild to profound | Noonan Syndrome 5, LEOPARD syndrome 2; dominant |
| *ROBO1* | 602430 | Roundabout, drosophila, homolog of 1; transmembrane | ROBO1/ SAX3 | Axon guidance receptor | Sensorineural, profound | combined pituitary hormone deficiency; recessive |
| *SEMA3E* | 608166 | SEMAphorin 3E; secreted | SEMA3E/ SEMAH/ KIAA0331 | Cell migration, neural crest and otic placode induction | Outer and inner ear malformations, prelingual, mixed or sensorineural, progressive, severe or profound | CHARGE syndrome; dominant |
| *SLITRK6* | 609681 | SLIT- and NTRK-like family, member 6; transmembrane | SLITRK6 | Survival and innervation of sensory neurons | Sensorineural or auditory neuropathy spectrum syndrome, prelingual, bilateral moderate to profound | Deafness and myopia; recessive |
| *SMAD4* | 600993 | Mothers Against Decapentaplegic, drosophila, homolog of, 4; cytoplasmic | SMAD4/ MADH4/ DPC4 | Mediator of signaling of BMP and TGFB superfamily members | Outer ear malformations, early onset, mixed | Myhre syndrome; dominant |
| *TBL1X* | 300196 | Transducin-Beta-Like 1, X-linked | TBL1X/ TBL1/EBI | Component of the nuclear corepressor (NCOR) complex | Mild hearing loss | X-linked |

| Gene | OMIM | Description; cellular location | Protein/alias | Function | Hearing loss type | Locus; mode of inheritance |
|---|---|---|---|---|---|---|
| *TBL1Y* | 400033 | Transducin-Beta-Like 1, Y-linked | TBL1Y | Component of the nuclear corepressor NCOR complex | Sensorineural, adult onset, bilateral, mild to severe | Deafness, Y-linked 2; Y-linked |
| *TBL1XR1* | 608628 | Transducin-Beta-Like 1 Receptor 1; nuclear | TBL1XR1/ TBLR1/ IRA1/C21 | General function in WNT signaling and component of the nuclear corepressor (NCOR) complex | Outer ear malformation, prelingual, unilateral or bilateral, Conductive | Pierpont syndrome; dominant |
| *TGFB1* | 190180 | Transforming Growth Factor, Beta-1; secreted | TGFB1, TGFB | Proliferation of mesenchymal and epithelial cell types | Conductive or sensorineural, bilateral, moderate | Camurati-Engelmann disease; dominant, Otosclerosis |
| *TGFB1* | 190180 | Transforming Growth Factor, Beta-1; secreted | TGFB1, TGFB | Proliferation of mesenchymal and epithelial cell types | Conductive | Otosclerosis |
| *THRB* | 190160 | Thyroid Hormone Receptor Beta; nuclear | THRB/ ERBA2/ ERBAβ | Maturation of auditory system | Prelingual, sensorineural, bilateral, severe | Thyroid hormone resistance, autosomal recessive; recessive |
| *THRB* | 190160 | Thyroid Hormone Receptor Beta; nuclear | THRB/ ERBA2/ ERBAβ | Maturation of auditory system | Sensorineural, variable degree | Thyroid hormone resistance; dominant |
| *TNFRSF11A* | 603499 | Tumor Necrosis Factor Receptor SuperFamily, member 11A; transmembrane | TNFRSF11A/ RANK/ ODFR/OSTS | Role in auricular ossification, stimulates NF-kappaB signaling | Conductive or mixed, progressive, bilateral, mild to moderate | Paget disease of bone 2, early-onset; dominant |
| *TNFRSF11A* | 603499 | Tumor Necrosis Factor Receptor SuperFamily, member 11A; transmembrane | TNFRSF11A/ RANK/ ODFR/OSTS | Role in auricular ossification, stimulates NF-kappaB signaling | Prelingual, mixed, bilateral, mild to moderate, or profound | Osteolysis, familial expansile, dominant |
| *TNFRSF11B* | 602643 | Tumor Necrosis Factor receptor superfamily, member 11b; secreted | TNFRSF11B/ OPG/OCIF | Regulates NF-kappaB signaling as a decoy receptor ligand for TNFRS11A | Sensorineural, prelingual, bilateral, profound | Paget disease of bone 5, juvenile onset; recessive |

OMIM, Online Mendelian Inheritance in Man