NIH Public Access
Author Manuscript
Front Biosci. Author manuscript; available in PMC 2013 June 17.

Published in final edited form as:
Front Biosci. ; 17: 2213–2236.

Autosomal recessive nonsyndromic deafness genes: a review

Duygu Duman[1] and **Mustafa Tekin**[1,2]

[1]Division of Genetics, Department of Pediatrics, Ankara University School of Medicine, Dikimevi, Ankara, 06100, Turkey

[2]Department of Human Genetics and Institute for Human Genomics, 1501 NW 10th Avenue, Miami, FL, 33136, USA

Abstract

More than 50 percent of prelingual hearing loss is genetic in origin, and of these up to 93 percent are monogenic autosomal recessive traits. Some forms of genetic deafness can be recognized by their associated syndromic features, but in most cases, hearing loss is the only finding and is referred to as nonsyndromic deafness. To date, more than 700 different mutations have been identified in one of 42 genes in individuals with autosomal recessive nonsyndromic hearing loss (ARNSHL). Reported mutations in *GJB2*, encoding connexin 26, makes this gene the most common cause of hearing loss in many populations. Other relatively common deafness genes include *SLC26A4, MYO15A, OTOF, TMC1, CDH23*, and *TMPRSS3*. In this report we summarize genes and mutations reported in families with ARNSHL. Founder effects were demonstrated for some recurrent mutations but the most significant findings are the extreme locus and allelic heterogeneity and different spectrum of genes and mutations in each population.

Keywords

Consanguinity; Deafness; Founder effects; Gene; Inner ear; Non syndromic hearing loss; Recurrent mutations; Allelic heterogeneity; Review

2. INTRODUCTION

Congenital or prelingual hearing loss occurs in approximately 1 in 500 infants and is caused by genetic factors in at least 50% of cases (1). Hereditary hearing loss can be classified according to inheritance type, age at onset, audiological characters, vestibular phenotype, and responsible genetic locus. Additional findings are present in 20–30% of cases, who are referred to as having syndromic deafness. Genetic hearing loss is a largely monogenic phenotype. Autosomal recessive transmission occurs in 77–93% of cases and is typically prelingual, while autosomal dominant hearing loss accounts for about 10–20% of cases and is most often postlingual. X-linked or mitochondrial inheritance is observed in the remaining cases.

Biallelic mutations in 42 different genes have so far been reported for autosomal recessive nonsyndromic hearing loss (ARNSHL), which explains more than 50% of families with this type of deafness in many populations. More than 80 loci have been mapped to different chromosomal loci, which are referred to as DFNB followed by a number consequently given

Send correspondence to: Mustafa Tekin, Department of Human Genetics, 1501 NW 10th Avenue, Miami, FL, 33136, USA, Tel: 305-243-2381, Fax: 305-243-2703, mtekin@med.miami.edu.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

when a locus was first reported. Mutations in *GJB2*, encoding connexin 26, are the most commonly identified cause of sensorineural hearing loss in many populations.

An overall summary of mutations reported in 42 genes is seen in Table 1. Since parental consanguinity and large family size facilitate usage of linkage with autozygosity mapping, most of the currently recognized deafness genes have been discovered in countries with these characteristics such as Pakistan, Tunisia, Iran, Palestine, India, and Turkey. Mutations have been reported in few families for many genes and their worldwide distribution is largely unknwon. Recurrent mutations were reported in some deafness genes but only few were detected in more than one population. Founder effects were demonstrated for some of these recurrent mutations and multiple origins were shown in some others. Because of different population characteristics of each country, mutation distribution is highly heterogeneous among populations.

The purpose of this article is to provide an overall summary of 42 ARNSHL genes and reported mutations. We group genes according to proposed functions of protein products in hearing physiology.

3. GENES IMPLICATED IN COCHLEAR HOMEOSTASIS

3.1. Gap junctions

Cochlear gap junctions, especially connexin 26 (Cx26) and 30 (Cx30), have been implicated in the maintenance of K^+ homeostasis in the inner ear (2,3). It is likely that gap junctions in the inner ear have more complex physiological roles including trafficking of second messengers and generation of the endocochlear potential. *GJB2* (Gap Junction Protein Beta-2) (MIM 220290) was the first gene in which mutations were reported to cause ARNSHL in 1997 (4). Although mutations in *GJB3* (MIM 603324) and *GJB6* (MIM 604418) were subsequently discovered, *GJB2* remains the most common cause of hereditary deafness in many populations.

3.1.1. *GJB2* and *GJB6* (DFNB1)—Initially ARNSHL was mapped to the DFNB1 locus in two consanguineous families from Tunisia (5). The *GJB2* gene, encoding Cx26, and the *GJB6* gene, encoding Cx30, reside in close proximity to one another in the DFNB1 locus (4,6). Mutations in *GJB2* were later discovered and were shown to cause up to 50% of cases with ARNSHL in Caucasian populations while their frequency is much lower in some other parts of the world (7,8,9). *GJB2* mutations can also cause autosomal dominant nonsyndromic hearing loss (ADNSHL) (4), and autosomal dominantly inherited Keratitis-Ichthyosis-Deafness (MIM 148210), (10,11), Vohwinkel (MIM 124500) (12,13), Bart-Pumphrey (MIM 149200) (13,14) syndromes and Palmoplantar Keratoderma-Deafness (MIM 148350). More than 200 different mutations have been identified in this single coding exon gene and recurrent mutations, almost specific to a population, have been observed (Human Gene Mutation Database Professional Edition, accessed in June 2010). The c. 35delG mutation is the most frequent pathogenic variant in the majority of Caucasian populations and may account for up to 70% of all *GJB2* mutations (15). The c.35delG carrier frequency, however, differs significantly between European populations, highest frequency being in the Southeastern Europe (16). Other frequent mutations in specific populations are c.167delT in Ashkenazi Jews (17), c.235delC in Japanese (18), p.W24X in Indians (19) and European gypsies (20), and IVS1+1G>A in Mongolians (9). Genotyping close SNPs suggested the presence of ancient founders for many of these common mutations. Heterozygote advantage and assortative mating have also been proposed as potential explanations for the common occurrence of *GJB2* mutations (21).

NIH-PA Author Manuscript

Although mutations in *GJB6* have been implicated as the cause of hearing loss, only one point mutation, p.T5M, associated with ADNSHL has so far been reported. Four large deletions were identified in cases with ARNSHL. The first deletion, del (GJB6-D13S1830), is 309 kb in size (6,22), and is relatively frequent in France, Spain, and Israel. Analysis of haplotypes associated with this deletion revealed a single founder in Ashkenazi Jews and also suggested a common founder for countries in western Europe (7,23). The size of the second deletion, del (GJB6-D13S1854), is 232 kb, which showed a common origin in Spain, the United Kingdom, and Italy by haplotype analysis (22). These two deletions occur upstream of GJB2 and truncate GJB6, but it is likely that they cause hearing loss because they abolish GJB2 expression (6,22). The third deletion was found in one patient and extended at least 920 kb removing the three connexin genes, GJA3 (MIM 121015), *GJB2*, and *GJB6* (24). Finally, a deletion of 131.4 kb has recently been identified in one family with ARNSHL who carried only a single *GJB2* mutation. This deletion, del (chr13:19, 837, 344–19, 968, 698), does not involve coding sequences of *GJB2* or *GJB6*, yet segregates with hearing loss suggesting the presence of distant *GJB2* and *GJB6* cis-regulatory elements (25). A limited number of *GJB6* missense mutations cause an inherited autosomal dominant skin disorder, hidrotic ectodermal dysplasia (Clouston syndrome) (MIM 129500), which is sometimes associated with hearing loss (26).

3.1.2. *GJB3*—The *GJB3* gene encoding the gap junction protein connexin 31 was initially mapped to chromosome 1p35– p33 and heterozygous mutations were shown to cause ADNSHL (27). Similar to *GJB2*, *GJB3* mutations have been reported to cause ARNSHL and a skin disorder, erythrokeratodermia variabilis (MIM 133200), as well. Biallelic *GJB3* mutations causing ARNSHL have been reported once in two families in which patients were compound heterozygote for two different *GJB3* mutations (28). Digenic inheritance of nonsyndromic deafness caused by mutations in *GJB2* and *GJB3* has recently been reported. Two different missense mutations (p.N166S and p.A194T) of *GJB3* were found in compound heterozygosity with the c.235delC and c.299delAT mutations of *GJB2* in three simplex families from China (29).

3.2. Tight junctions

Tight junctions play important roles for making a barrier between different compartments of the organ of Corti. The apical membranes of the sensory hair cells and supporting cells are interconnected by complex bicellular tight junctions. Among members of these tight junctions, mutations of *CLDN14* (MIM 605608) cause deafness in humans. In addition to the selective permeability of bicellular tight junctions, which helps to maintain the distinct ionic composition of compartments separated by epithelial barriers, the passage of solutes and ions is also assumed to occur through the tricellular region, which has a unique architecture at the point where three epithelial cells contact one another. Tricellulin is a member of these proteins and mutations in *TRIC* (MIM 610572) cause deafness in humans as well. Despite their important roles in hearing physiology only few families have so far been reported to have mutations in genes coding for different tight junctions.

3.2.1. *CLDN14* (DFNB29)—The DFNB29 locus was initially mapped to chromosome 21q22.1 by linkage analysis in two large consanguineous Pakistani families segregating profound congenital deafness and mutations were identified in the *CLDN14* gene, encoding Claudin 14 (30). Claudin 14 is one of the members of the claudin family which is expressed in the supporting cells of the organ of Corti, sensory epithelium of the vestibular system, liver and kidney. It has been hypothesized that the absence of Claudin 14 from tight junctions in the organ of Corti leads to altered ionic permeability of the paracellular barrier of the reticular lamina and that prolonged exposure of the basolateral membranes of outer

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

hair cells to high potassium concentrations may be the cause of the death of hair cells (31). Only one additional patient from Greece was later reported (32).

3.2.2. *TRIC* (DFNB49)—The *TRIC* (*MARVELD2*) gene which encodes tricellulin, maps to chromosome 5 (33). Tricellulin is a component of tight junctions, a tricellular tight junctions protein, which plays a key role in the formation of barriers between tricellular contacts of epithelial cells throughout the body. In the inner ear, the protein is present in tricellular junctions of the reticular lamina of the organ of Corti. Five different homozygous mutations of *TRIC* in 11 Pakistani families were demonstrated (34,35). One splice site mutation, IVS4+2T>C, was reported in six Pakistani families (34,35).

3.3. Other genes

3.3.1. *SLC26A4* (DFNB4) (MIM 605646)—A large consanguineous family from India with congenital profound ARNSHL initially showed linkage to chromosome 7q31 where Pendred syndrome (deafness and goiter- MIM 274600) gene, *SLC26A4*, was residing (36,37). Affected individuals were found to be homozygote for a missense mutation involving a conserved residue in *SLC26A4* (36). Enlargement of the vestibular aqueduct (EVA) (MIM 600791) is present in almost all individuals with Pendred syndrome or DFNB4 deafness (38), although it can also be present as an isolated finding together with sensorineural hearing loss.

The *SLC26A4* gene encodes pendrin, which is a transmembrane anion exchanger that belongs to the solute carrier 26 family and exchanges chloride, iodide, bicarbonate and formate. It is expressed in different tissues, including thyroid, kidney, and inner ear. In the cochlea, it is found in the apical membrane of outer sulcus and spiral prominence epithelial cells that border the endolymph, in the spiral ganglion and in supporting cells (39). Pendrin knockout mice are profoundly deaf, exhibiting bulged endolymphatic spaces of the inner ear with striking similarity to the pathology observed in humans (40). *SLC26A4* mutations may account for as much as 10% of hereditary deafness in diverse populations (41). Each ethnic population has a different and diverse mutation spectrum, with one or few prevalent founder mutations (41,42). In northern Europe, four mutations are found quite frequently (p.L236P, p.T416P, p.E384G and IVS8 + 1G > A) (43). Recently, it has been reported that the *SLC26A4* promoter contains a key transcriptional regulatory element that binds *FOXI1* (MIM 601093), a transcriptional activator of the gene (44) and digenic inheritance was reported with either *FOXI1* or *KCNJ10* (MIM 602208) (45).

3.3.2. *ESRRB* (DFNB35) (MIM 608565)—The *ESRRB* gene encodes the estrogen-related receptor protein beta, a member of the nuclear hormone receptor family of transcription factors. These proteins share a zinc finger DNA binding domain and a ligandbinding domain. *ESRRB* is expressed in the spiral limbus, supporting cells, Reissner's membrane, stria vascularis, spiral ligament, nerve fibers and spiral ganglion cells, but it is notably absent from sensory cells. Studies in mice homozygous for the targeted deletion of *Esrrb* have confirmed that the protein is essential for the development of marginal cells and a functional stria vascularis, as evidenced by disturbed endolymph production, aberrant inner-ear fluid homeostasis, and hearing loss in these mutant mice (46). In humans, it is likely that *ESRRB* is required for these processes. The *ESRRB* gene was mapped to 14q24.3 by fluorescence *in situ* hybridization. Five different homozygous mutations have so far been reported (47,48).

3.3.3. *BSND* (DFNB73) (MIM 606412)—The *BSND* gene encodes barttin, an essential beta subunit for the chloride channels CLCNKA (MIM 602024) and CLCNKB (MIM 602023). Heteromers formed by the chloride channels and barttin are crucial for renal salt

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

reabsorption and potassium recycling in the inner ear (49). Biallelic mutations in this gene cause Bartter syndrome with sensorineural deafness (50). A homozygous missense mutation in BSND was reported in four Pakistani families with ARNSHL mapped to the DFNB73 locus. Homozygote individuals did not have clinical findings of Bartter syndrome suggesting that the identified mutation was a hypomorphic allele (51).

4. GENES INVOLVED IN CELLULAR ORGANIZATION

4.1. Myosins

Myosins are actin-based molecular motors that regulate several processes, such as rearrangement of the actin cytoskeleton, regulation of tension of actin filaments and transport of organelles (52). Myosin superfamily is subdivided into conventional and unconventional myosins. Conventional myosins form filaments and regulate contractility of actin filaments, while the function of unconventional myosins is more varied and includes crucial cellular roles such as vesicle trafficking and endocytosis. Different myosins are classified by the degree of sequence similarity of the conserved catalytic motor (head) domain (53). Unconventional myosins also have binding sites for proteins on their C-terminal tails and they may take cargo proteins to their target sites in the cell. Nonmuscle cells express several different unconventional myosins, and some are essential for hearing. Mutations in five unconventional myosins (IA, IIIA, VI, VIIA and XVA) have been reported to cause deafness, sometimes with vestibular dysfunction. Each myosin probably has a hair-cell-specific function, as gene-specific mutations cause distinguishable hair cell phenotypes.

4.1.1. *MYO3A* (DFNB30) (MIM 606808)—Myosin IIIA is found at the tips of developing stereocilia surrounding the tip density region, a molecular compartment of stereocilia tips that may be the site of actin polymerization and operation of the mechanoelectrical transduction apparatus. Myosin IIIA is also found further down the shaft of the stereocilia (54). Myosin IIIA expression has been demonstrated in human retina (55), and murine expression was shown in cochlea, where it was restricted to the neurosensory epithelium, especially to inner and outer hair cells (56). Myosin IIIa was recently reported to interact with espin, another deafness protein, and when coexpressed, they lead to stereocilia elongation and hence may work together to regulate stereocilia length (57).

Genome-wide linkage analysis of the hearing loss segregating in an Israeli family showed linkage to chromosome 10p12-p11, which contained *MYO3A* (56). Surprisingly three different *MYO3A* mutations were identified to segregate with late-onset, progressive ARNSHL in the Israeli family. Hearing loss started during the second decade (56). No other families with *MYO3A* mutations have been reported.

4.1.2. *MYO6* (DFNB37) (MIM 600970)—Myosin VI is in a class of myosins that move toward the minus end of actin filaments, in the opposite direction that other characterized myosins move (58). Its unique function suggests that myosin VI may facilitate the removal of molecular components that are released by treadmilling at the taper of the stereocilium (59). Myosin VI is expressed in the cytoplasm of the hair cells, with increased levels in the cuticular plate and to some extent in the stereocilia (60, 61).

Mutations in the murine *Myo6* lead to fusion of stereocilia at their base and underlie deafness in the Snell's waltzer (sv) mouse (62). In humans, biallelic mutations in *MYO6* cause congenital, profound ARNSHL while heterozygous missense mutations cause ADNSHL with a milder phenotype and a later onset, secondary to a dominant-negative mechanism of action (63). In one family, a dominant *MYO6* mutation leads to a combination of ADNSHL and hypertrophic cardiomyopathy and prolongation of the QT

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

interval (MIM 606346) (64). The DFNA22 locus linked to 6q13 was originally described in an Italian family, with a missense mutation in the motor domain of myosin VI (p.C442Y) (65). In recent years, additional mutations have been found in Belgian (63) and Danish (66) families. Recessive mutations in *MYO6* have been found in three Pakistani families (67). In addition to deafness, vestibular dysfunction and mild facial dysmorphism were present in one family.

4.1.3. *MYO7A* (DFNB2) (MIM 276903)—*MYO7A* encodes myosin VIIA, which is ubiquitously expressed in many epithelial tissues including the inner ear and retina. Mutations in *MYO7A* are associated with Usher syndrome type 1B (USH1B) (MIM 276900) and ARNSHL (DFNB2) as well as ADSNHL (DFNA11) (68,69). More than 200 mutations in myosin VIIa (MYO7A) have been reported but most of them cause Usher syndrome type I, which is characterized by congenital, bilateral, profound sensorineural hearing loss, vestibular areflexia, and adolescent-onset retinitis pigmentosa.

Two mouse mutants carrying *Myo7a* mutations have been described: the recessive mutant shaker-1 (sh1) and the dominant mutant Headbanger (Hdb). sh1 mutants show hyperactivity, head-tossing and circling due to vestibular dysfunction, together with dysfunction and progressive degeneration of the organ of Corti. In Hdb mice, outer hair cell stereocilia form O instead of V shapes and many inner hair cell stereocilia fuse and elongate, forming giant stereocilia (70). Both vestibular dysfunction and deafness might result from a defective morphogenesis of the hair cell stereocilia, the highly specific mechanical properties of which are critical for the mechanotransduction process (71). Myosin VIIA participates in opsin transport through the connecting cilium to the outer segment of the photoreceptor cell (72), which may be the critical cellular process disrupted by USH1B mutations of *MYO7A*. Myosin VIIA has a conserved NH2-terminal motor domain followed by a variable number of light-chain binding (IQ) motifs and a highly divergent tail like other myosins. The motor domain allows interactions with actin filaments and makes this protein an actin-based molecular motor. The tail domain contains a coiled-coil domain for homodimer formation and a FERM domain, which may allow attachment to the plasma membrane. Vezatin, harmonin and SANS interact with myosin VIIA through binding with the tail domain.

The DFNB2 locus was initially mapped by a genome search to 11q13.5 in a consanguineous family from Tunisia segregating nonsyndromic, profound deafness (73). The *MYO7A* gene was the second DFNB gene discovered. Four mutations of *MYO7A* have been reported to cause ARNSHL (68, 69, 71, 75, 76), and based on their nature and location, it is difficult to explain the absence of the retinal phenotype in individuals with DFNB2 deafness. The Tunisian family used to define the DFNB2 locus was first diagnosed with hearing loss and vestibular dysfunction and seven years later, affected persons were also found to have mild retinitis pigmentosa (77). This phenotypic variability seen in families segregating recessive mutations of *MYO7A* may be due to a combination of allelic, environmental, and genetic background differences.

4.1.4. *MYO15A* (DFNB3) (MIM 602666)—A genome-wide homozygosity mapping strategy initialy identified a locus (DFNB3) on chromosome 17p11.2 for ARNSHL segregating in a Balinese village of 2,200 residents (78,79). This locus was confirmed in two Indian families (79). On the basis of conserved chromosomal synteny, the autosomal recessive mouse deafness mutant shaker-2 was proposed as the homologue of DFNB3 (79). The shaker-2 mouse has a mutation in the *Myo15* gene causing the substitution of a tyrosine for a conserved cysteine in the motor domain (80) another shaker-2 allele was a deletion of the last six exons of *Myo15A* (81). Full-length human *MYO15A* is expressed in a number of tissues in addition to the inner ear (82). In the shaker-2 mouse, the presence of very short stereocilia, and a long abnormal actin-containing structure that projects from the base of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

auditory hair cells, suggested that myosin XV is necessary for actin organization in hair cells (80,81). Studies of the mouse mutants shaker-2 and whirler have shown that myosin XVA interacts with whirlin and moves it to the stereocilia tip links. A number of *MYO15A* mutations have been reported in different populations suggesting that *MYO15A* is a relatively common cause of ARNSHL following the initial discovery in 1998 (82).

4.2. Other genes

4.2.1. *ESPN* (DFNB36) (MIM 606351)—The linkage interval on chromosome 1p36.3 referred to as DFNB36 contains *ESPN*, a gene known to cause deafness and vestibular dysfunction in the jerker mouse (83). *ESPN* codes for the espin protein, which is an actin-bundling protein present in the parallel actin bundle of the stereocilia of cochlear and vestibular hair cells (84). Espin consists of a C-terminus responsible for bundling actin, a WH-2 actin monomer-binding domain (85), and a variable N-terminus determined by the specific isoform.

In humans, mutations in *ESPN* were found to cause ARNSHL with vestibular areflexia but without eye symptoms (86) and were also found to cause ADNSHL without vestibular involvement (87). Two homozygous *ESPN* frameshift mutations were detected in two Pakistani families with autosomal recessive deafness and vestibular areflexia (86) and one frameshift mutation in a Moroccan family with autosomal recessive deafness without vestibular involvement (88).

4.2.2. *SLC26A5* (DFNB61) (MIM 604943)—Prestin, encoded by *SLC26A5* is another member of the carrier 26 family of anion exchangers. The protein is expressed abundantly in the outer hair cells and plays a key role in their voltage dependent cell-length variation. Variations in the outer hair cell plasma membrane potential cause conformational rearrangements of prestin, which drive cellular contraction and elongation movements (89). Prestin is more highly conserved among mammalian species than any other protein in its family, demonstrating 95% amino acid identity between mouse and human, compared to an average of 86% for the group (90). Prestin also appears to have a role beyond the outer hair cells since *SLC26A5* transcripts are found in heart, spleen, brain, and testis (91).

Homozygous prestin knockout mice display a 40–60 dB hearing loss (92). Two sequence variations were suggested to be associated with hearing loss in humans. In an initial study homozygous IVS2-2A>G variant in *SLC26A5* was identified as the cause of ARNSHL in two Caucasian families (93). This sequence variation was suspected of disrupting the splicing of *SLC26A5* exon 3, which contains the prestin ATG start codon, thereby disrupting prestin protein production (93). The same mutation was found in the heterozygous state in seven patients with varying degrees of hearing loss, which suggests an interaction of *SLC26A5* with additional modifier genes (93). However, carrier frequency of this variant was found to be 4.1% among Caucasian controls, precluding its involvement in hereditary hearing loss (94). Recently, another variant, p.R150Q, was reported in one hearing impaired patient and his normal hearing father, suggesting the p.R150Q variant is not sufficient to cause hearing loss (95).

4.2.3. *TRIOBP* (DFNB28) (MIM 609761)—The TRIO and filamentous actin binding protein encoded by *TRIOBP* colocalizes with F-actin along the length of the stereocilia and is thought to be involved in actin cytoskeletal organization (96). TRIOBP forms were demonstrated in resilient rootlets of hair cell stereocilia (97) Nine mutations in *TRIOBP* have been identified in Indian, Pakistani, and Palestinian families with ARNSHL (96,98). Eight mutations were truncating and one mutation was a missense change.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

4.2.4. *RDX* (DFNB24) (MIM 179410)—Radixin is part of the ezrin/radixin/moesin family which consists of three closely related proteins that function as cross-linkers between plasma membranes and actin filaments (99). Screening of three Pakistani families with markers from the region containing *RDX*, 11q23, led to the identification of one frameshift, one nonsense, and one missense mutations in this gene (100). A homozygous splice site mutation was reported in an Iranian family (101).

4.2.5. *WHRN* (DFNB31) (MIM 607928)—Homozygosity mapping in a consanguineous Palestinian family from Jordan mapped a locus (DFNB31) for prelingual, profound hearing impairment to chromosome 9q32–q34 containing the *WHRN* gene (102). Whirlin localized to the tips of mouse stereocilia and its expression is a critical and dynamic organizer for stereocilia elongation and actin polymerization (103). Whirlin is an important scaffolding protein in the Usher protein complex and links many different proteins. It is transiently expressed in stereocilia tips during elongation in both inner and outer hair cells and is also found at the base of stereocilia. In the recessive mouse mutant whirler (wi), *Whrn* mutations cause deafness and vestibular dysfunction due to impaired stereocilia elongation (104). In humans, *WHRN* mutations cause profound ARNSHL and Usher syndrome type IID (102). In the family in whom DFNB31 was originally identified a homozygous nonsense mutation was found (105).

4.2.6. *USH1C* (DFNB18) (MIM 605242)—Prelingual, profound, nonsyndromic sensorineural deafness segregating in a large, consanguineous Indian family was initially mapped by a genome-wide search to chromosome 11p15.1–p14 (106), encompassing the region for Usher syndrome type 1C (USH1C) (107). *USH1C* was cloned, by serologic expression cloning and was designated PDZ73, from a metastatic colon cancer cDNA expression library (108). The *USH1C* gene encodes a PDZ domain-containing protein, harmonin. Harmonin was shown to bind to otocadherin and to interact with myosin VIIA suggesting a functional unit underlying the formation of a coherent hair cell bundle (109,110). Two recessive mouse mutants, deaf circler (dfcr) and deaf circler 2 Jackson (dfcr-2J), carry Ush1c mutations and show deafness and circling behaviour (111). Studies of dfcr indicate that harmonin b is essential for stereocilia development. The protein also plays an important role in mechanoelectrical transmission (109).

Mutations in *USH1C* also cause ARNSHL at the DFNB18 locus. Whether the phenotype is one of nonsyndromic deafness or Usher syndrome depends on the expression pattern and splicing of the different *USH1C* isoforms. Mutations causing Usher syndrome are all truncating and occur in constitutive exons present in both the eye and cochlea. Missense mutations in alternatively spliced exons cause nonsyndromic hearing loss, as these exons are absent in the eye (112).

4.2.7. *CDH23 (DFNB12)* (MIM 605516)—Allelic mutations of *CDH23* cause both nonsyndromic deafness *DFNB12* (110) and *USH1D* (MIM 601067) (113,114,115). *CDH23* encodes cadherin 23 and is expressed in the sensory hair cells and in the Reissner's membrane. In the developing hair cells, the protein is a component of transient lateral links between neighbouring stereocilia and is believed to play an essential role in cohesion of stereocilia during hair bundle development. Cadherin 23 is also a component of the tip links and kinocilial link in the mature hair cell (116).

A genotype-phenotype relationship for *USH1D* and *DFNB12* was proposed where some amino acid replacements in cadherin 23 were presumed to be hypomorphs, causing partial loss of function and nonsyndromic deafness, whereas more disabling mutations and functional null alleles of *CDH23* cause retinitis pigmentosa and vestibular dysfunction as well as deafness (114). The largest *CDH23* isoform consists of 69 exons encoding a deduced

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

3354 amino acid protein. It is predicted to have one transmembrane spanning region that divides cadherin 23 into a large extracellular domain with 27 EC domains and a cytoplasmic domain of 268 amino acids showing no similarity to any known protein (113,114). The unique cytoplasmic domain contains one alternatively spliced exon encoding 35 amino acids (114). *CDH23* exon 68 is expressed preferentially in the inner ear and not in the brain or retina (109,110). In the photoreceptor layer of the retina the cytoplasmic domain of cadherin 23 (lacking exon 68) has an internal and a C-terminal PDZ-binding ligand sequence that can form a complex with two PDZ domains (PDZ1 and PDZ2) of harmonin (110), a macromolecular organizer encoded by *USH1C*, the gene underlying Usher syndrome type 1C, and nonsyndromic deafness *DFNB18* (117,118,119).

5. GENES CODING FOR TECTORIAL MEMBRANE ASSOCIATED PROTEINS

5.1. *TECTA* (DFNB21) (MIM 602574)

The *TECTA* gene encodes α-tectorin, an extracellular protein constituent of the tectorial membrane and the otolithic membrane in the cochlea and vestibular system, respectively (127). The protein is mainly expressed during development of the tectorial membrane and contains several protein-protein interaction domains including an N-terminal entactin G1-like domain, three full and two partial von Willebrand factor type D repeats, and a C-terminal zona pellucida domain (128). α-tectorin is believed to interact with itself and with other extracellular matrix proteins including β-tectorin and several collagens (128).

Families with ADNSHL and ARNSHL have been reported to carry mutations in *TECTA*. Homozygosity for functional null alleles of *TECTA* at the *DFNB21* locus causes recessive, prelingual, severe-to-profound stable hearing loss with a flat or shallow U-shaped audiometric configuration (129). Heterozygous mutations in *TECTA* (DFNA8/12) can cause either stable or progressive hearing loss depending on their location within the gene and with dominant negative effect (130). Tecta null mice are deaf because the tectorial membrane is detached completely from the organ of Corti; consequently, vibrations of the basilar membrane associated with the traveling wave do not lead to deflection of outer hair cell or inner hair cell stereocilia (131).

5.2. *COL11A2* (DFNB53) (MIM 120290)

A genome-wide scan carried out in a consanguineous Iranian family with nonsyndromic, prelingual, profound hearing loss identified a novel locus on 6p21.3 (DFNB53) (132) which contained the *COL11A2* gene associated with ADNSHL (133). Type XI collagen A2 (COL11A2) is the component of the tectorial membrane and is essential for maintaining the interfibrillar spacing and fibril diameter of type II collagen. Type II collagen is composed of three α-chain polypeptide subunits (α1, α2 and α3), each transcribed from a different gene (*COL11A1*, *COL11A2*, and *COL2A1*). Mutations in *COL11A2* cause ADNSHL and ARNSHL in addition to different forms of osteochondrodysplasia such as Stickler syndrome and otospondylomegaepiphyseal dysplasia. Only one homozygous mutation (p.P621T) in an Iranian family has been associated with ARNSHL (132).

5.3. *STRC* (DFNB16) (MIM 606440)

The *STRC* gene, which encodes stereocilin, is expressed in the sensory hair cells and is associated with the stereocilia, the stiff microvilli forming the structure for mechanoreception of sound stimulation (134). Stereocilin and otoancorin share C-terminal sequence homology, suggesting that both may function to anchor the tectorial membrane to organ of Corti cell structures (135). The *STRC* gene was dentified on chromosome 15q15, within the candidate region for DFNB16 (134). The *STRC* gene is tandemly duplicated, with the coding sequence of the second copy interrupted by a stop codon in exon 20 (134). Two

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

frameshift mutations and a large deletion were identified in two families affected by ARNSHL (134).

5.4. *OTOA* (DFNB22) (MIM 607038)

The *OTOA* gene encodes otoancorin, which is an inner ear-specific glycosylphosphatidylinositol-anchored protein that is found on the apical surface of non-sensory cells, where they contact the tectorial membrane (136). Mutations in the *OTOA* gene, encoding otoancorin, were shown to be associated with ARNSHL (136). Otoancorin shares weak homology with megakaryocyte potentiating factor/mesothelin precursor. Otoancorin is located at the interface between the apical surface of the inner ear sensory epithelia and their overlying acellular gels. In the cochlea, otoancorin is detected at two attachment zones of the tectorial membrane, a permanent one along the top of the spiral limbus and a transient one on the surface of the developing greater epithelial ridge. In the vestibule, otoancorin is present on the apical surface of nonsensory cells, where they contact the otoconial membranes and cupulae (136).

Genomic sequencing of *OTOA* in one Palestinian family with moderate-to-severe prelingual sensorineural hearing loss identified a homozygous point mutation at a splice donor site (136). A large genomic deletion and a homozygous missense mutation of *OTOA* were identified in two Palestinian families and the carrier frequency of the *OTOA* genomic deletion was 1% (137).

6. GENES IMPLICATED IN NEURONAL TRANSMISSION

6.1. *OTOF* (DFNB9) (MIM 603681)

The *OTOF* gene coding for otoferlin was identified as the gene responsible for the recessive deafness DFNB9. It was mapped by a genomewide search to chromosome 2p23–p22 in a consanguineous Lebanese family (138). Otoferlin is a member of the mammalian ferlin family of membrane-anchored cytosolic proteins. All ferlins contain six calcium-binding C2 domains and are involved in vesicle membrane fusion. The protein is essential for exocytosis and neurotransmitter release at the inner hair cell ribbon synapse (139). Alternatively spliced *OTOF* transcripts combined with the use of several different translation initiation sites result in multiple short and long isoforms of the protein (140,141).

OTOF mutations cause prelingual, profound ARNSHL, which initially may be accompanied by auditory neuropathy (142). Auditory neuropathy is characterized by the presence of otoacoustic emission responses in the absence of auditory brainstem responses (141). In the Spanish population, p.Q829X is the most common and founder *OTOF* mutation identified and ranks as the third most common cause of ARNSHL in this ethnic group (142,143). A founder *OTOF* mutation, p.E1700Q, was identified in 23% of the studied East Asian patients with auditory neuropathy (144). Some mutations reported to be involved in temperature-dependent auditory neuropathy (145–147).

6.2. *PJVK* (DFNB59) (MIM 610219)

Pejvakin, encoded by *PJVK*, is found in spiral ganglion neurons and may play a role in action potential propagation or intracellular trafficking. These possible functions have been suggested by the observation that the two missense mutations initially identified in *PJVK* cause auditory neuropathy in both humans and Dfnb59 knock-in mice (148). The Dfnb59 knock-in mice had only an auditory defect whereas the other mouse model with auditory defects 'sirtaki' displayed both auditory and vestibular defects (149). DFNB59 was the first reported gene that leads to deafness via neuronal dysfunction along the auditory cascade

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(148). Exon organization between the *PJVK* and *DFNA5* genes throughout the region of similarity is identical, indicating that these two genes share a common origin (148).

Eight mutations have been found in the *PJVK* gene (74, 148–152). The p.R183W mutation was found in three Iranian families with nonsyndromic deafness due to a neuronal defect and in a Turkish family without transiently evoked otoacoustic emissions (148,151). Haplotype analysis did not suggest a founder effect for the Turkish and Iranian families with the mutation. Other mutations were found in individual families.

7. GENES IMPLICATED IN CELL GROWTH, DIFFERENTIATION, AND SURVIVAL

7.1. *HGF*(DFNB39) (MIM 142409)

The *HGF* gene was mapped to 7q11.2-q21 by *in situ* hybridization (153). The protein and mRNA were found for both hepatocyte growth factor and its receptor (MET) present in third trimester placentas, suggesting that HGF serves as a paracrine mediator to control placental development and growth (154). Mice were generated with a conditional knockout of *Hgf* in the inner ear and observed morphologic defects of the inner ear not seen in littermate controls, including a disorganized tectorial membrane onto which the Reissner membrane was collapsed, thin and flattened stria vascularis with occasional clumps of cellular proliferation, hypoplastic spiral ganglion, and outer hair cell degeneration throughout the organ of Corti (155).

In Pakistani and Indian families with autosomal recessive profound prelingual deafness mapping to DFNB39 three mutations in the *HGF* gene were identified: a synonymous substitution in exon and a 3-bp and a 10-bp deletion in an intron (155). The synonymous substitution was shown to affect splicing *in vitro*, and the two deletions occur in a highly conserved sequence that is part of the 3-prime untranslated region of a previously undescribed short isoform of *HGF*.

7.2. *SERPINB6* (DFNB91)

A consanguineous Turkish family with five affected members with moderate to severe ARNSHL was mapped to 6p25.2 and a truncating mutation in *SERPINB6*, segregating with the phenotype was found in this family (156). SERPINB6 is an intracellular protease inhibitor that is expressed in hair cells and proposed to protect inner ear cells during stress against proteases.

8.GENES WITH OTHER or UNKNOWN FUNCTIONS

8.1. *TMC1* (DFNB7) (MIM 606706)

A locus for prelingual, severe to profound hearing impairment was mapped to chromosome 9q13–q21 in two consanguineous families from India defining the DFNB7 locus (157). *TMC1* is predicted to encode a multipass transmembrane protein with no similarity to proteins of known function. Expression analyses of *TMC1* detected transcripts in human fetal cochlea and mouse inner and outer cochlear hair cells as well as in neurosensory epithelia of the vestibular organs (158). *Tmc1* mutations were also identified in the recessive deafness (dn) and dominant Beethoven (Bth) mouse mutant strains segregating hearing loss and postnatal hair cell degeneration, indicating that Tmc1 is required for postnatal hair cell development or maintenance (158,159). The TMC1 protein is predicted to contain six transmembrane domains and to have cytoplasmic orientation of N and C termini (158).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Mutations in human *TMC1* cause both ARNSHL and ADNSHL. The recessive mutations all cause severe-to-profound hearing loss. The dominant mutations have been reported in two North-American families; both families segregated mutations at amino acid position 572, suggesting that this amino acid position may be a mutational hot spot (160). *TMC1* mutations seem a rather common cause of recessive deafness in Indian, Pakistani, Turkish, and Tunisian families (158, 161, 162). One mutation, c.100C > T (p.R34X) seems especially frequent as a cause of ARNSHL (163) and has been shown to have arisen from two founders (164).

8.2. *TMIE* (DFNB6) (MIM 607237)

Tmie was first discovered as the mutant gene causing the spinner phenotype in affected mice, with hearing loss and vestibular dysfunction due to neuroepithelial defects in the inner ear (165). The 156-amino-acid human protein showed no similarity to other known proteins and was predicted to contain an N-terminal signal site peptide and at least one transmembrane domain (165,166). The study of the recessive mouse mutant spinner (sr) carrying a mutation in *Tmie* suggests that the gene is required during maturation of sensory cells and is involved in the development or maintenance of stereocilia bundles. As the stereocilia of outer hair cells of spinner mice are shortened, Tmie might influence actin filament dynamics in the normal hair bundle or alternatively play a role in the organization of cytoskeleton-membrane interactions in sensory hair cells (165).

In humans, mutations in *TMIE* cause autosomal recessive severe-to-profound hearing loss (166). Homozygous insertion, deletion, and three missense mutations were described in five families from Pakistan and India resulting in autosomal recessive hearing loss linked to DFNB6 locus on 3p21 (166). Three additional families from Pakistan, one from Jordan and eight from Turkey with ARNSHL were later reported to have homozygous *TMIE* mutations (167, 168). The p.R84W mutation was common for one Indian and eight Turkish families (166, 168). Haplotype analysis in the Turkish families showed that the mutation arose in a single founder.

8.3. *TMPRSS3* (DFNB8/10) (MIM 605511)

TMPRSS3 is a member of the Type II Transmembrane Serine Protease family, a class of membrane-bound proteolytic enzymes that mediate a variety of biological processes, and encodes a protease that also contains low-density lipoprotein receptor class A and scavenger receptor cysteine rich domains. The gene has been implicated in cancer biology and also has an important role in the auditory system. It is expressed in the neuron bodies of the spiral ganglion, the stria vascularis and the epithelium of the organ of Corti. While the function of the protein is unknown, a role in mechanoelectric transduction is possible through regulation of ENaC (amiloride-sensitive) sodium channel activity and therefore cochlear sodium concentration (169).

In a Pakistani family with the childhood-onset form of deafness designated DFNB8, Scott *et al.* (170) identified a splice site mutation in intron 4, resulting in a 4-bp insertion in the mRNA and a frameshift. In a Palestinian family with the congenital form of deafness designated DFNB10, they identified a mutation consisting of an 8-bp deletion and insertion of 18 complete beta-satellite repeat monomers, which are normally present in tandem arrays of up to several hundred kilobases on the short arms of acrocentric chromosomes. Several mutations have been identified to date that cause the DFNB8/10 forms of deafness. Most affected persons have severe-to-profound hearing loss, but age of onset, severity and rate of progression are variable and no genotype-phenotype correlation has been established (171).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

8.4. *LHFPL5 (TMHS)* (DFNB67) (MIM 609427)

The human *LHFPL5* (lipoma HMGIC fusion partnerlike 5) gene was mapped to the DFNB67 locus on chromosome 6 in the region homologous to mouse chromosome 17 (172). *LHFPL5* encodes the tetraspan membrane protein of hair cell stereocilia and was recently discovered in the recessive mouse mutant hurry-scurry (hscy), in which recessive *Tmhs* mutations cause hearing loss and vestibular dysfunction (173).

Mutations in the human *TMHS* are the cause of profound ARNSHL without vestibular dysfunction (174). Three missense and two truncating mutations were reported in five families from Turkey, Pakistan and Palestine (74,172,174). Tlili *et al.* (175) mapped the form of autosomal recessive nonsyndromic sensorineural deafness segregating in a large consanguineous Tunisian family (DFNB66) to chromosome 6p22.3-p21.2. But no *LHFPL5* mutation was identified in the DFNB66 family.

8.5. *LRTOMT* (DFNB63) (MIM 612414)

Autosomal recessive nonsyndromic deafness locus DFNB63 was found to be linked at chromosome 11q13.2-q13.3 (176,177,178). In the candidate region for DFNB63 on chromosome 11q13, a fusion gene was identifed and named *LRTOMT*. Analysis of corresponding clones isolated from a human liver cDNA library showed five alternatively spliced transcripts of *LRTOMT* that were widely expressed (179). The *LRTOMT* gene contains 10 exons. Exons 5, 7, and 8 have dual reading frames. *LRTOMT* has two alternative reading frames and encodes two different proteins, LRTOMT1 and LRTOMT2, that differ by translation start codons. When translation starts in exon 3, the encoded protein has a predicted transmembrane domain, two leucine-rich repeats, and is named LRTOMT1. Translation beginning in exon 5 produces LRTOMT2, which is predicted to have a catechol-O-methyltransferase domain. Depending on the use of an alternative acceptor splice site in exon 8, LRTOMT2 may have a predicted transmembrane helix (179).

In affected members of four unrelated families with DFNB63 from Turkey, Tunisia, and Pakistan four different homozygous mutations were identified in the *LRTOMT* gene (179). A homozygous nonsense mutation was identified in one of 192 deaf Iranian families by direct sequencing the five exons of the *LRTOMT* gene (180).

8.6. *LOXHD1*(DFNB77) (MIM 613072)

Mouse *Loxhd1* was cloned, and identified human *LOXHD1* by database analysis (181). *In situ* hybridization detected Loxhd1 expression in the developing mouse inner ear, but not in any other tissue. By genomic sequence analysis, the *LOXHD1* gene was mapped to chromosome 18q12-q21 (181). One nonsense mutation in *LOXHD1* was identified in affected members of a five-generation consanguineous Iranian family segregating a progressive form of autosomal-recessive nonsyndromic hearing loss (DFNB77) (181).

8.7. *TPRN* (DFNB79) (MIM 613354)

Using targeted genome capture and sequence analysis, *TPRN* as the gene mutated in DFNB79, was identified in a form of autosomal recessive nonsyndromic deafness linked to chromosome 9q34.3 (182). RT-PCR detected *TPRN* expression in human fetal cochlea and in all mouse tissues examined (183). Immunohistochemical analysis detected Tprn in the sensory epithelia of the mouse organ of Corti and vestibular end organs and, to a lesser extent, in Reisner membrane and the spiral ligament. In the organ of Corti, Tprn localized within the supporting cells and inner ear hair cell stereocilia, where it localized to the taper region of each stereocilium (182).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In affected members of four consanguineous Pakistani families with DFNB79, four different homozygous truncating mutations in the *TPRN* gene were identified (182). In affected members of a large consanguineous Moroccan family and a Dutch family with DFNB79 were found homozygous loss of function mutations in the *TPRN* gene (183).

8.8. *PTPRQ* (DFNB84) (MIM 603317)

PTPRQ belongs to the type III receptor-like protein-tyrosine phosphatase (PTPase) family. PTPRQ has low activity against phosphotyrosine, but is active against phosphatidylinositol phosphates that are involved in the regulation of survival, proliferation, and subcellular architecture (184). The complete characterization of the human *PTPRQ* gene was reported and identified four different splice variants (185). Quantitative PCR analysis using a fragment encoding the intracellular region of PTPRQ detected expression in all but two human fetal tissues tested, with highest expression in fetal kidney, followed by fetal lung and fetal cochlea (185).

In a consanguineous Palestinian kindred with ARNSHL, DFNB84 locus on chromosome 12, which includes the *PTPRQ* gene was identified (74). Sequencing of *PTPRQ* in affected individuals revealed the c.1285C>T mutation, leading to p.Q429X (186). In affected members of two unrelated families with ARNSHL with vestibular dysfunction, one nonsense and one missense homozygous mutations in the exon 19 of the *PTPRQ* gene were identified (185).

8.9. *GRXCR1*(DFNB25) (MIM 613283)

The *GRXCR1* gene was mapped to chromosome 4p13 (187). The mouse pirouette (pi) locus, containing the *Grxcr1* gene, was mapped to a region of mouse chromosome 5 that shares syntenic homology with human chromosome 4 (188). The human *GRXCR1* was cloned, which encoded a deduced 290-amino acid protein containing a putative glutaredoxin catalytic domain and a cysteine-rich C-terminal region (187). Quantitative PCR detected high *GRXCR1* expression in fetal cochlea, moderate expression in adult testis, low expression in fetal heart and adult duodenum and brain, and little to no expression in other adult and fetal tissues examined (187).

In three sibs from a nonconsanguineous Dutch family, one sporadic Dutch patient and affected members of two consanguineous Pakistani families with autosomal recessive nonsyndromic hearing loss (DFNB25) mapping to 4p13, were identified one missense, one nonsense, and two splice site mutations in the *GRXCR1* gene that cosegregated with deafness (187).

8.10. *PDZD7* (MIM 612971)

In a boy with congenital nonsyndromic deafness, born to consanguineous parents, a homozygous reciprocal translocation was identified. The 10q24.3 breakpoint disrupted the open reading frame of the C and D isoforms of PDZD7. This observation suggests that the PDZD7 gene causes ARNSHL and because of its interactions with Usher syndrome proteins, mutations in PDZD7 might be associated with Usher syndrome (189)

8.11. GPSM2 (DFNB82) (MIM 613557)

In a large consanguineous Palestinian family with prelingual, bilateral, severe, nonsyndromic sensorineural deafness Shahin et al. (74) found linkage to a 3.1-Mb region on chromosome 1p13.3 which they designated DFNB82. In affected members of family with DFNB82, Walsh et al. (190) identified a homozygous p.R127X mutation in the GPSM2 gene. The second truncating mutation, p.Q562X, was identified via autozygosity mapping in a consanguineous Turkish family (191)

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

8.12. MSRB3 (DFNB74) (MIM 613719)

By genomewide linkage analysis of three consanguineous Pakistani families with autosomal recessive profound deafness, Waryah et al. (192) identified a locus, termed DFNB74, on chromosome 12q14.2-q15. In affected members of six consanguineous Pakistani families, including the three families previously reported by Waryah et al. (192) with autosomal recessive DFNB74, Ahmed et al. (193) identified the p.C89G mutation in the MSRB3 gene. The affected individuals in two other families were homozygous for a transition mutation (c. 55T>C), which results in a nonsense mutation (p.Arg19X) in alternatively spliced exon 3, encoding a mitochondrial localization signal. This finding suggests that DFNB74 deafness is due to a mitochondrial dysfunction (193).

8.13. ILDR1 (DFNB42) (MIM 609739)

ILDR1 encodes immunoglobulin-like domain containing receptor 1, a putative transmembrane receptor of unknown function. ILDR1 gene was mapped to chromosome 3q21.1 and was determined to contain 8 exons (194). By genomewide analysis of a Pakistani family with nonsyndromic deafness, Aslam et al. identified a 21.6-cM candidate disease locus, termed DFNB42, on chromosome 3q13.31-q22.3 (195). A homozygous nonsense mutation was identified in ILDR1 as the cause of hearing loss. To date affected individuals of 11 families with nonsyndromic hearing loss from Pakistan and Iran were found to have ILDR1 mutations including missense, nonsense, frameshift, and splice-site mutations as well as a start codon mutation in the family that originally defined the DFNB42 locus (196)

8.14.GIPC3(DFNB15/72/95) (MIM 608792)

Autosomal recessive nonsyndromic deafness loci DFNB15 (197, 198), DFNB72 (199, 200) and DFNB95 (201) were all located at chromosome 19p13.3-p13.1. The GIPC3 gene was also mapped to chromosome 19p13.3 (202). One homozygous frameshift and six different homozygous missense mutations were found in GIPC3 in the affected individuals from seven ARSNHL families of Indian and Pakistan origin.

Acknowledgments

This study was supported by NIH- National Institute on Deafness and Other Communication Disorders with grant R01DC009645.

REFERENCES

1. Morton CC, Nance WE. Newborn hearing screening—a silent revolution. N Engl J Med. 2006; 354:2151–2164. [PubMed: 16707752]
2. Kikuchi T, Kimura RS, Paul DL, Takasaka T, Adams JC. Gap junction systems in the mammalian cochlea. Brain Res Brain Res Rev. 2000; 32:163–166. [PubMed: 10751665]
3. Wangemann P. K+ cycling and the endocochlear potential. Hear Res. 2002; 165:1–9. [PubMed: 12031509]
4. Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, Mueller RF, Leigh IM. Connexin 26 mutations in hereditary nonsyndromic sensorineural deafness. Nature. 1997; 387:80–83. [PubMed: 9139825]
5. Guilford P, Ben Arab S, Blanchard S, Levilliers J, Weissenbach J, Belkahia A, Petit C. A non-syndrome form of neurosensory, recessive deafness maps to the pericentromeric region of chromosome 13q. Nat Genet. 1994; 6:24–28. [PubMed: 8136828]
6. del Castillo I, Villamar M, Moreno-Pelayo MA, del Castillo FJ, Alvarez A, Telleria D, Menendez I, Moreno F. A deletion involving the connexin 30 gene in nonsyndromic hearing impairment. New Eng J Med. 2002; 346:243–249. [PubMed: 11807148]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

7. Seeman P, Bendova O, Raskova D, Malikova M, Groh D, Kabelka Z. Double heterozygosity with mutations involving both the *GJB2* and *GJB6* genes is a possible, but very rare, cause of congenital deafness in the Czech population. Ann Hum Genet. 2005; 69:9–14. [PubMed: 15638823]

8. Oguchi T, Ohtsuka A, Hashimoto S, Oshima A, Abe S, Kobayashi Y, Nagai K, Matsunaga T, Iwasaki S, Nakagawa T, Usami S. Clinical features of patients with *GJB2* (connexin 26) mutations: severity of hearing loss is correlated with genotypes and protein expression patterns. J Hum Genet. 2005; 50:76–83. [PubMed: 15700112]

9. Tekin M, Xia XJ, Erdenetungalag R, Cengiz FB, White TW, Radnaabazar J, Dangaasuren B, Tastan H, Nance WE, Pandya A. *GJB2* mutations in Mongolia: complex alleles, low frequency, and reduced fitness of the deaf. Ann Hum Genet. 2010; 74:155–164. [PubMed: 20201936]

10. Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryynänen M, Jabs EW, Bale SJ, DiGiovanna JJ, Uitto J, Russell L. Missense mutations in *GJB2* encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. Am J Hum Genet. 2002; 70:1341–1348. [PubMed: 11912510]

11. Yotsumoto S, Hashiguchi T, Chen X, Ohtake N, Tomitaka A, Akamatsu H, Matsunaga K, Shiraishi S, Miura H, Adachi J, Kanzaki T. Novel mutations in *GJB2* encoding connexin-26 in Japanese patients with keratitisichthyosis-deafness syndrome. Br J Dermatol. 2003; 148:649–653. [PubMed: 12752120]

12. Common JE, Bitner-Glindzicz M, O'Toole EA, Barnes MR, Jenkins L, Forge A, Kelsell DP. Specific loss of connexin 26 expression in ductal sweat gland epithelium associated with the deletion mutation del(GJB6-D13S1830). Clin Exp Dermatol. 2005; 30:688–693. [PubMed: 16197390]

13. Richard G, Brown N, Ishida-Yamamoto A, Krol A. Expanding the phenotypic spectrum of Cx26 disorders: Bart- Pumphrey syndrome is caused by a novel missense mutation in *GJB2* . J Invest Dermatol. 2004; 123:856–863. [PubMed: 15482471]

14. Alexandrino F, Sartorato EL, Marques-de-Faria AP, Steiner CE. G59S mutation in the *GJB2* (connexin 26) gene in a patient with Bart-Pumphrey syndrome. Am J Med Genet. 2005; 136:282–284. [PubMed: 15952212]

15. Snoeckx RL, Huygen PL, Feldmann D, Marlin S, Denoyelle F, Waligora J, Mueller-Malesinska M, Pollak A, Ploski R, Murgia A, Orzan E, Castorina P, Ambrosetti U, Nowakowska-Szyrwinska E, Bal J, Wiszniewski W, Janecke AR, Nekahm-Heis D, Seeman P, Bendova 0, Kenna MA, Frangulov A, Rehm HL, Tekin M, Incesulu A, Dahl HH, du Sart D, Jenkins L, Lucas D, Bitner-Glindzicz M, Avraham KB, Brownstein Z, del Castillo I, Moreno F, Blin N, Pfister M, Sziklai l, Toth T, Kelley PM, Cohn ES, Van Maldergem L, Hilbert P, Roux AF, Mondain M, Hoefsloot LH, Cremers CW, Lopponen T, Lopponen H, Parving A, Gronskov K, Schrijver I, Roberson J, Gualandi F, Martini A, Lina-Granade G, Pallares-Ruiz N, Correia C, Fialho G, Cryns K, Hilgert N, Van de Heyning P, Nishimura CJ, Smith RJ, Van Camp G. *GJB2* mutations and degree of hearing loss: a multicenter study. Am J Hum Genet. 2005; 77:945–957. [PubMed: 16380907]

16. Gasparini P, Rabionet R, Barbujani G, Melchionda S, Petersen M, Brondum- Nielsen K, Metspalu A, Oitmaa E, Pisano M, Fortina P, Zelante L, Estivill X. High carrier frequency of the 35delG deafness mutation in European populations. Eur J Hum Genet. 2000; 8:19–23. [PubMed: 10713883]

17. Morell RJ, Kim HJ, Hood LJ, Goforth L, Friderici K, Fisher R, Van Camp G, Berlin CI, Oddoux C, Ostrer H, Keats B, Friedman TB. Mutations in the connexin 26 gene (*GJB2*) among Ashkenazi Jews with nonsyndromic recessive deafness. N Engl J Med. 1998; 339:1500–1505. [PubMed: 9819448]

18. Ohtsuka A, Yuge I, Kimura S, Namba A, Abe S, Van Laer L, Van Camp G, Usami S. *GJB2* deafness gene shows a specific spectrum of mutations in Japan, including a frequent founder mutation. Hum Genet. 2003; 112:329–333. [PubMed: 12560944]

19. Maheshwari M, Vijaya R, Ghosh M, Shastri S, Kabra M, Menon PSN. Screening of families with autosomal recessive non-syndromic hearing impairment (ARNSHI) for mutations in *GJB2* gene: Indian scenario. Am J Med Genet. 2003; 120A:180–184. [PubMed: 12833397]

20. Alvarez A, del Castillo I, Villamar M, Aguirre LA, Gonzalez-Neira A, Lopez-Nevot A, Moreno-Pelayo MA, Moreno F. High prevalence of the W24X mutation in the gene encoding connexin-26

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

(*GJB2*) in Spanish Romani (gypsies) with autosomal recessive non-syndromic hearing loss. Am J Med Genet. 2005; 137A:255–258. [PubMed: 16088916]

21. Arnos KS, Welch KO, Tekin M, Norris VW, Blanton SH, Pandya A, Nance WE. A comparative analysis of the genetic epidemiology of deafness in the United States in two sets of pedigrees collected more than a century apart. Am J Hum Genet. 2008; 83:200–207. [PubMed: 18656178]
22. del Castillo FJ, Rodriguez-Ballesteros M, Alvarez A, Hutchin T, Leonardi E, de Oliveira CA, Azaiez H, Brownstein Z, Avenarius MR, Marlin S, Pandya A, Shahin H, Siemering KR, Weil D, Wuyts W, Aguirre LA, Martín Y, Moreno-Pelayo MA, Villamar M, Avraham KB, Dahl HH, Kanaan M, Nance WE, Petit C, Smith RJ, Van Camp G, Sartorato EL, Murgia A, Moreno F, del Castillo I. A novel deletion involving the connexin-30 gene, del(GJB6-d13s1854), found in trans with mutations in the GJB2 gene (connexin-26) in subjects with DFNB1 non-syndromic hearing impairment. J Med Genet. 2005; 42:588–594. [PubMed: 15994881]
23. del Castillo I, Moreno-Pelayo MA, del Castillo FJ, Brownstein Z, Marlin S, Adina Q, Cockburn DJ, Pandya A, Siemering KR, Chamberlin GP, Ballana E, Wuyts W, Maciel-Guerra AT, Alvarez A, Villamar M, Shohat M, Abeliovich D, Dahl HH, Estivill X, Gasparini P, Hutchin T, Nance WE, Sartorato EL, Smith RJ, Van Camp G, Avraham KB, Petit C, Maciel-Guerra FM, oreno AT, Alvarez A, Villamar M, Shohat M, Abeliovich D, Dahl HH, Estivill X, Gasparini P, Hutchin T, Nance WE, Sartorato EL, Smith RJ, VanCamp G, Avraham KB, Petit C, Moreno F. Prevalence and evolutionary origins of the del (GJB6-D13S1830) mutation in the DFNB1 locus in hearing-impaired subjects: a multicenter study. Am J Hum Genet. 2003; 73:1452–1458. [PubMed: 14571368]
24. Feldmann D, Le Maréchal C, Jonard L, Thierry P, Czajka C, Couderc R, Ferec C, Denoyelle F, Marlin S, Fellmann F. A new large deletion in the DFNB1 locus causes nonsyndromic hearing loss. Eur J Med Genet. 2009; 52:195–200. [PubMed: 19101659]
25. Wilch E, Azaiez H, Fisher RA, Elfenbein J, Murgia A, Birkenhäger R, Bolz H, da Silva-Costa SM, del Castillo I, Haaf T, Hoefsloot L, Kremer H, Kubisch C, Le Marechal C, Pandya A, Sartorato EL, Schneider E, Van Camp G, Wuyts W, Smith RJ, H K. Friderici, Anovel DFNB1 deletion allele supports the existence of a distant cis-regulatory region that controls *GJB2* and *GJB6* expression. Clin Genet. 2010; 78:267–274. [PubMed: 20236118]
26. Lamartine J, Essenfelder GM, Kibar Z, Lanneluc I, Callouet E, Laoudj D, Lemaître G, Hand C, Hayflick SJ, Zonana J, Antonarakis S, Radhakrishna U, Kelsell DP, Christianson AL, Pitaval A, DerKaloustian V, Fraser C, Blanchet-Bardon C, Rouleau GA, Waksman G. Mutations in *GJB6* cause hidrotic ectodermal dysplasia. Nat Genet. 2000; 26:142–144. [PubMed: 11017065]
27. Xia JH, Liu CY, Tang BS, Pan Q, Huang L, Dai HP, Zhang BR, Xie W, Hu DX, Zheng D, Shi XL, Wang DA, Xia K, Yu KP, Liao XD, Feng Y, Yang YF, Xiao JY, Xie DH, Huang JZ. Mutations in the gene encoding gap junction protein b-3 associated with autosomal dominant hearing impairment. Nat Genet. 1998; 20:370–373. [PubMed: 9843210]
28. Liu XZ, Xia XJ, Xu LR, Pandya A, Liang CY, Blanton SH, Brown SDM, Steel KP, Nance WE. Mutations in connexin31 underlie recessive as well as dominant non-syndromic hearing loss. Hum Molec Genet. 2000; 9:63–67. [PubMed: 10587579]
29. Liu XZ, Yuan Y, Yan D, Ding EH, Ouyang XM, Fei Y, Tang W, Yuan H, Chang Q, Du LL, Zhang X, Wang G, Ahmad S, Kang DY, Lin X, Dai P. Digenic inheritance of non-syndromic deafness caused by mutations at the gap junction proteins Cx26 and Cx31. Hum Genet. 2009; 125:53–62. [PubMed: 19050930]
30. Wilcox ER, Burton QL, Naz S, Riazuddin S, Smith TN, Ploplis B, Belyatseva I, Ben-Yosef T, Liburd NA, Morell RJ, Kachar B, Wu DK, Griffith AJ, Riazuddin S, Friedman TB. Mutations in the gene encoding tight junction claudin-14 cause recessive deafnessDFNB29. Cell. 2001; 104:165–172. [PubMed: 11163249]
31. Ben-Yosef T, Belyantseva IA, Saunders LT, Hughes ED, Kawamoto K, Van Itallie CM, Beyer LA, Halsey K, Gardner DJ, Wilcox ER, Rasmussen J, Anderson JM, Dolan DF, Forge A, Raphael Y, Camper SA, Friedman TB. Claudin 14 knockout mice,a model for autosomal recessive deafness DFNB29, are deaf due to cochlear hair cell degeneration. Hum. Molec.Genet. 2003; 12:2049–2061. [PubMed: 12913076]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

32. Wattenhofer M, Reymond A, Falciola V, Charollais A, Caille D, Borel C, Lyle R, Estivill X, Petersen MB, Meda P, Antonarakis SE. Different mechanisms preclude mutant CLDN14 proteins from forming tight junctions *in vitro* . Hum. Mutat. 2005; 25:543–549. [PubMed: 15880785]
33. Ikenouchi J, Furuse M, Furuse K, Sasaki H, Tsukita S, Tsukita S. Tricellulin constitutes a novel barrier at tricellular contacts of epithelial cells. J Cell Biol. 2005; 171:939–945. [PubMed: 16365161]
34. Riazuddin S, Ahmed ZM, Fanning AS, Lagziel A, Kitajiri S, Ramzan K, Khan SN, Chattaraj P, Friedman PL, Anderson JM, Belyantseva IA, Forge A, Riazuddin S, Friedman TB. Tricellulin is a tight-junction protein necessary for hearing. Am J Hum Genet. 2006; 79:1040–1051. [PubMed: 17186462]
35. Chishti MS, Bhatti A, Tamim S, Lee K, McDonald ML, Leal SM, Ahmad W. Splice-site mutations in the *TRIC* gene underlie autosomal recessive nonsyndromic hearing impairment in Pakistani families. J Hum Genet. 2008; 53:101–105. [PubMed: 18084694]
36. Li XC, Everett LA, Lalwani AK, Desmukh D, Friedman TB, Green ED, Wilcox ER. A mutation in *PDS* causes non-syndromic recessive deafness. Nat Genet. 1998; 18:215–217. [PubMed: 9500541]
37. Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet. 1997; 17:411–422. [PubMed: 9398842]
38. Phelps PD, Coffey RA, Trembath RC, Luxon LM, Grossman AB, Britton KE, Kendall-Taylor P, Graham JM, Cadge BC, Stephens SG, Pembrey ME, Reardon W. Radiological malformations of the ear in Pendred syndrome. Clin Radiol. 1998; 53:268–273. [PubMed: 9585042]
39. Yoshino T, Sato E, Nakashima T, Teranishi M, Yamamoto H, Otake H, Mizuno T. Distribution of pendrin in the organ of corti of mice observed by electron immunomicroscopy. Eur Arch Otorhinolaryngol. 2006; 263:699–704. [PubMed: 16703388]
40. Everett LA, Belyantseva IA, Noben-Trauth K, Cantos R, Chen A, Thakkar SI, Hoogstraten-Miller SL, Kachar B, Wu DK, Green ED. Targeted disruption of mouse Pds provides insight about the inner-ear defects encountered in Pendred syndrome. Hum Mol Genet. 2001; 10:153–161. [PubMed: 11152663]
41. Park HJ, Shaukat S, Liu XZ, Hahn S, Naz S, Ghosh M, Kim HN, Moon SK, Abe S, Tukamoto K, Riazuddin S, Kabra M, Erdenetungalag R, Radnaabazar J, Khan S, Pandya A, Usami SI, Nance WE, Wilcox ER, Riazuddin S, Griffith AJ. Origins and frequencies of *SLC26A4* (PDS) mutations in East and South Asians: glogal implications for the epidemiology of deafness. J Med Genet. 2003; 40:242–248. [PubMed: 12676893]
42. Van Hauwe P, Everett LA, Coucke P, Scott DA, Kraft ML, Ris-Stalpers C, Bolder C, Otten B, de Vijlder JJ, Dietrich NL, Ramesh A, Srisailapathy SC, Parving A, Cremers CW, Willems PJ, Smith RJ, Green ED, Van Camp G. Two frequent missense mutations in pendred syndrome. Hum Mol Genet. 1998; 7:1099–1104. [PubMed: 9618166]
43. Coyle B, Reardon W, Herbrick JA, Tsui LC, Gausden E, Lee J, Coffey R, Grueters A, Grossman A, Phelps PD, Luxon L, Kendall-Taylor P, Scherer SW, Trembath RC. Molecular analysis of the PDS gene in Pendred syndrome. Hum Mol Genet. 1998; 7:1105–1112. [PubMed: 9618167]
44. Yang T, Vidarsson H, Rodrigo-Blomqvist S, Rosengren SS, Enerback S, Smith RJH. Transcriptional control of SLC26A4 is involved in Pendred syndrome and nonsyndromic enlargement of vestibular aqueduct (DFNB4). Am J Hum Genet. 2007; 80:1055–1063. [PubMed: 17503324]
45. Yang T, Gurrola JGII, Wu H, Chiu SM, Wangemann P, Snyder PM, Smith RJH. Mutations of *KCNJ10* together with mutations of *SLC26A4* cause digenic nonsyndromic hearing loss associated with enlarged vestibular aqueduct syndrome. Am J Hum Genet. 2009; 84:651–657. [PubMed: 19426954]
46. Hilgert N, Smith RJ, Van Camp G. Function and expression pattern of nonsyndromic deafness genes. Curr Mol Med. 2009; 9:546–564. [PubMed: 19601806]
47. Collin RWJ, Kalay E, Tariq M, Peters T, van der Zwaag B, Venselaar H, Oostrik J, Lee K, Ahmed ZM, Caylan R, Li Y, Spierenburg HA, Eyupoglu E, Heister A, Riazuddin S, Bahat E, Ansar M, Arslan S, Wollnik B, Brunner HG, Cremers CW, Karaguzel A, Ahmad W, Cremers FP, Vriend G, Friedman TB, Riazuddin S, Leal SM, Kremer H. Mutations of ESRRB encoding estrogen-related

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

receptor beta cause autosomal-recessive nonsyndromic hearing impairment DFNB35. Am J Hum Genet. 2008; 82:125–138. [PubMed: 18179891]

48. Ansar M, Amin Ud, Din M, Arshad M, Sohail M, Faiyaz-Ul-Haque M, Haque S, Ahmad W, Leal SM. A novel autosomal recessive non-syndromic deafness locus (DFNB35) maps to 14q24.1-14q24.3 in large consanguineous kindred from Pakistan. Europ J Hum Genet. 2003; 11:77–80. [PubMed: 12529709]
49. Estévez R, Boettger T, Stein V, Birkenhäger R, Otto E, Hildebrandt F, Jentsch TJ. Barttin is a Cl- channel beta-subunit crucial for renal Cl- reabsorption and inner ear K+ secretion. Nature. 2001; 414:558–561. [PubMed: 11734858]
50. Birkenhäger R, Otto E, Schürmann MJ, Vollmer M, Ruf EM, Maier-Lutz I, Beekmann F, Fekete A, Omran H, Feldmann D, Milford DV, Jeck N, Konrad M, Landau D, Knoers NV, Antignac C, Sudbrak R, Kispert A, Hildebrandt F. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. Nat Genet. 2001; 29:310–314. [PubMed: 11687798]
51. Riazuddin S, Anwar S, Fischer M, Ahmed ZM, Khan SY, Janssen AG, Zafar AU, Scholl U, Husnain T, Belyantseva IA, Friedman PL, Riazuddin S, Friedman TB, Fahlke C. Molecular basis of DFNB73: mutations of BSND can cause nonsyndromic deafness or Bartter syndrome. Am J Hum Genet. 2009; 85:273–280. [PubMed: 19646679]
52. Mermall V, Post PL, Mooseker MS. Unconventional myosins in cell movement, membrane traffic, and signal transduction. Science. 1998; 279:527–533. [PubMed: 9438839]
53. Thompson RF, Langford GM. Myosin superfamily evolutionary history. Anat Rec. 2002; 268:276–289. [PubMed: 12382324]
54. Schneider ME, Dose AC, Salles FT, Chang W, Erickson FL, Burnside B, Kachar B. A new compartment at stereocilia tips defined by spatial and temporal patterns of Myosin IIIa expression. J Neurosci. 2006; 26:10243–10252. [PubMed: 17021180]
55. Ng KP, Kambara T, Matsuura M, Burke M, Ikebe M. Identification of myosin III as a protein kinase. Biochemistry. 1996; 35:9392–9399. [PubMed: 8755717]
56. Walsh T, Walsh V, Vreugde S, Hertzano R, Shahin H, Haika S, Lee MK, Kanaan M, King MC, Avraham KB. From flies' eyes to our ears: mutations in a human class III myosin cause progressive nonsyndromic hearing loss DFNB30. Proc Natl Acad Sci USA. 2002; 99:7518–7523. [PubMed: 12032315]
57. Salles FT, C. R, Merritt Manor U Jr, Dougherty GW, Sousa AD, Moore JE, Yengo CM, Dosé AC, Kachar B. Myosin IIIa boosts elongation of stereocilia by transporting espin 1 to the plus ends of actin filaments. NatCell Biol. 2009; 11:443–450.
58. Wells AL, Lin AW, Chen LQ, Safer D, Cain SM, Hasson T, Carragher BO, Milligan RA, Sweeney HL. Myosin VI is an actin-based motor that moves backwards. Nature. 1999; 401:505–508. [PubMed: 10519557]
59. Frolenkov GI, Belyantseva IA, Friedman TB, Griffith AJ. Genetic insights into the morphogenesis of inner ear hair cells. Nat Rev Genet. 2004; 5:489–498. [PubMed: 15211351]
60. Hasson T, Gillespie PG, Garcia JA, MacDonald RB, Zhao Y, Yee AG, Mooseker MS, Corey DP. Unconventional myosins in inner-ear sensory epithelia. J Cell Biol. 1997; 137:1287–1307. [PubMed: 9182663]
61. Hertzano R, Shalit E, Rzadzinska AK, Dror AA, Song L, Ron U, Tan JT, Shitrit AS, Fuchs H, Hasson T, Ben-Tal N, Sweeney HL, de Angelis MH, Steel KP, Avraham KB. A Myo6 mutation destroys coordination between the myosin heads, revealing new functions of myosin VI in the stereocilia of mammalian inner ear hair cells. PL Genet. 2008; 4:e1000207.
62. Avraham KB, Hasson T, Steel KP, Kingsley DM, Russell LB, Mooseker MS, Copeland NG, Jenkins NA. The mouse Snell's waltzer deafness gene encodes an unconventional myosin required for structural integrity of inner ear hair cells. Nat Genet. 1995; 11:369–375. [PubMed: 7493015]
63. Hilgert N, Topsakal V, van Dinther J, Offeciers E, Van de Heyning P, Van Camp G. A splicesite mutation and overexpression of MYO6 cause a similar phenotype in two families with autosomal dominant hearing loss. Eur J HumGenet. 2008; 16:593–602.
64. Mohiddin SA, Ahmed ZM, Griffith AJ, Tripodi D, Friedman TB, Fananapazir L, Morell RJ. Novel association of hypertrophic cardiomyopathy, sensorineural deafness and a mutation in unconventional myosin VI(MYO6). J Med Genet. 2004; 41:309–314. [PubMed: 15060111]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

65. Melchionda S, Ahituv N, Bisceglia L, Sobe T, Glaser F, Rabionet R, Arbones ML, Notarangelo A, Di Iorio E, Carella M, Zelante L, Estivill X, Avraham KB, Gasparini P. *MYO6*, the human homologue of the gene responsible for deafness in Snell's waltzer mice, is mutated in autosomal dominant nonsyndromic hearing loss. Am J Hum Genet. 2001; 69:635–640. [PubMed: 11468689]
66. Sanggaard KM, Kjaer KW, Eiberg H, Nurnberg G, Nurnberg P, Hoffman K, Jensen H, Sørum C, Rendtorff ND, Tranebjaerg L. A novel nonsense mutation in *MYO6* is associated with progressive nonsyndromic hearing loss in a Danish DFNA22 family. Am J Med Genet. 2008; 146A:1017–1025. [PubMed: 18348273]
67. Ahmed ZM, Morell RJ, Riazuddin S, Gropman A, Shaukat S, Ahmad MM, Mohiddin SA, Fananapazir L, Caruso RC, Husnain T, Khan SN, Riazuddin S, Griffith AJ, Friedman TB, Wilcox ER. Mutations of *MYO6* are associated with recessive deafness DFNB37. Am J Hum Genet. 2003; 72:1315–1322. [PubMed: 12687499]
68. Liu XZ, Walsh J, Mburu P, Kendrick-Jones J, Cope MJ, Steel KP, Brown SD. Mutations in the myosin VIIA gene cause non-syndromic recessive deafness. Nat Genet. 1997; 16(2):188–190. [PubMed: 9171832]
69. Weil D, Kussel P, Blanchard S, Levy G, Levi-Acobas F, Drira M, Ayadi H, Petit C. The autosomal recessive isolated deafness, DFNB2, and the Usher 1B syndrome are allelic defects of the myosin-VIIA gene. Nat Genet. 1997; 16:191–193. [PubMed: 9171833]
70. Rhodes CR, Hertzano R, Fuchs H, Bell RE, de Angelis MH, Steel KP, Avraham KB. A Myo7a mutation cosegregates with stereocilia defects and low-frequency hearing impairment. Mamm Genome. 2004; 15:686–697. [PubMed: 15389316]
71. Weil D, Levy G, Sahly I, Levi-Acobas F, Blanchard S, El-Amraoui A, Crozet F, Philippe H, Abitbol M, Petit C. Human myosin VIIA responsible for the Usher 1B syndrome: a predicted membrane-associated motor protein expressed in developing sensory epithelia. Proc Natl Acad Sci USA. 1996; 93:3232–3237. [PubMed: 8622919]
72. Liu X, Udovichenko IP, Brown SD, Steel KP, Williams DS. Myosin VIIa participates in opsin transport through the photoreceptor cilium. J Neurosci. 1999; 19:6267–6274. [PubMed: 10414956]
73. Guilford P, Ayadi H, Blanchard S, Chaib H, Le Paslier D, Weissenbach J, Drira M, Petit C. A human gene responsible for neurosensory, non-syndromic recessive deafness is a candidate homologue of the mouse sh-1 gene. Hum Mol Genet. 1994; 3:989–993. [PubMed: 7951250]
74. Shahin H, Walsh T, Rayyan AA, Lee MK, Higgins J, Dickel D, Lewis K, Thompson J, Baker C, Nord AS, Stray S, Gurwitz D, Avraham KB, King MC, Kanaan M. Five novel loci for inherited hearing loss mapped by SNP-based homozygosity profiles in Palestinian families. Eur J Hum Genet. 2010; 18:407–413. [PubMed: 19888295]
75. Hildebrand MS, Thorne NP, Bromhead CJ, Kahrizi K, Webster JA, Fattahi Z, Bataejad M, Kimberling WJ, Stephan D, Najmabadi H, Bahlo M, Smith RJ. Variable hearing impairment in a DFNB2 family with a novel *MYO7A* missense mutation. Clin Genet. 2010; 77:563–571. [PubMed: 20132242]
76. Riazuddin S, Nazli S, Ahmed ZM, Yang Y, Zulfiqar F, Shaikh RS, Zafar AU, Khan SN, Sabar F, Javid FT, Wilcox ER, Tsilou E, Boger ET, Sellers JR, Belyantseva IA, Riazuddin S, Friedman TB. Mutation of *MYO7A* and evaluation of a novel nonsyndromic deafness DFNB2 allele with residual function. Hum Mutat. 2008; 29:502–511. [PubMed: 18181211]
77. Zina ZB, Masmoudi S, Ayadi H, Chaker F, Ghorbel AM, Drira M, Petit C. From DFNB2 to Usher syndrome: variable expressivity of the same disease. Am J Med Genet. 2001; 101:181–183. [PubMed: 11391666]
78. Friedman TB, Liang Y, Weber JL, Hinnant JT, Barber TD, Winata S, Arhya IN, Asher JH Jr. A gene for congenital, recessive deafness DFNB3 maps to the pericentromeric region of chromosome 17. Nat Genet. 1995; 9:86–91. [PubMed: 7704031]
79. Liang Y, Wang A, Probst FJ, Arhya IN, Barber TD, Chen KS, Deshmukh D, Dolan DF, Hinnant JT, Carter LE, Jain PK, Lalwani AK, Li XC, Lupski JR, Moeljopawiro S, Morell R, Negrini C, Wilcox ER, Winata S, Camper SA, Friedman TB. Genetic mapping refines DFNB3 to 17p11.2, suggests multiple alleles of DFNB3, and supports homology to the mouse model shaker-2. Am J Hum Genet. 1998; 62:904–915. [PubMed: 9529344]
80. Probst FJ, Fridell RA, Raphael Y, Saunders TL, Wang A, Liang Y, Morell RJ, Touchman JW, Lyons RH, Noben-Trauth K, Friedman TB, Camper SA. Correction of deafness in shaker-2 mice

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

by an unconventional myosin in a BAC transgene. Science. 1998; 280:1444–1447. [PubMed: 9603735]

81. Anderson DW, Probst FJ, Belyantseva IA, Fridell RA, Beyer L, Martin DM, Wu D, Kachar B, Friedman TB, Raphael Y, Camper SA. The motor and tail regions of myosin XV are critical for normal structure and function of auditory and vestibular hair cells. Hum Mol Genet. 2000; 9:1729–1738. [PubMed: 10915760]
82. Wang A, Liang Y, Fridell RA, Probst FJ, Wilcox ER, Touchman JW, Morton CC, Morell RJ, Noben-Trauth K, Camper SA, Friedman TB. Association of unconventional myosin *MYO15* mutations with human non-syndromic deafness DFNB3. Science. 1998; 280:1447–1451. [PubMed: 9603736]
83. Steel KP, Bock GR. Cochlear dysfunction in the jerker mouse. Behav Neurosci. 1983; 97:381–391. [PubMed: 6871029]
84. Sekerkova G, Zheng L, Loomis PA, Mugnaini E, Bartles JR. Espins and the actin cytoskeleton of hair cell stereocilia and sensory cell microvilli. Cell Mol Life Sci. 2006; 63:2329–2341. [PubMed: 16909209]
85. Loomis PA, Zheng L, Sekerkova G, Changyaleket B, Mugnaini E, Bartles JR. Espin cross-links cause the elongation of microvillus-type parallel actin bundles *in vivo* . J Cell Biol. 2003; 163:1045–1055. [PubMed: 14657236]
86. Naz S, Griffith AJ, Riazuddin S, Hampton LL, Battey JF Jr, Khan SN, Riazuddin S, Wilcox ER, Friedman TB. Mutations of ESPN cause autosomal recessive deafness and vestibular dysfunction. J Med Genet. 2004; 41:591–595. [PubMed: 15286153]
87. Donaudy F, Zheng L, Ficarella R, Ballana E, Carella M, Melchionda S, Estivill X, Bartles JR, Gasparini P. Espin gene (ESPN) mutations associated with autosomal dominant hearing loss cause defects in microvillar elongation or organisation. J Med Gene t. 2006; 43:157–161.
88. Boulouiz R, Li Y, Soualhine H, Abidi O, Chafik A, Nurnberg G, Becker C, Nurnberg P, Kubisch C, Wollnik B, Barakat A. A novel mutation in the Espin gene causes autosomal recessive nonsyndromic hearing loss but no apparent vestibular dysfunction in a Moroccan family. Am J Med Genet. 2008; 146A:3086–3089. [PubMed: 18973245]
89. Pasqualetto E, Seydel A, Pellini A, Battistutta R. Expression purification and characterisation of the C-terminal STAS domain of the SLC26 anio tra sporter prestin. Protein Expr Purif. 2008; 58:249–256. [PubMed: 18226918]
90. Mount DB, Romero MF. The SLC26 gene family of multifunctional anion exchangers. Pflugers Arch. 2004; 447:710–721. [PubMed: 12759755]
91. Zheng J, Long KB, Matsuda KB, Madison LD, Ryan AD, Dallos PD. Genomic characterization and expression of mouse prestin, the motor protein of outer hair cells. Mamm Genome. 2003; 14:87–96. [PubMed: 12584604]
92. Liberman MC, Gao J, He DZ, Wu X, Jia S, Zuo J. Prestin is required for electromotility of the outer hair cell and for the cochlear amplifier. Nature. 2002; 419:300–304. [PubMed: 12239568]
93. Liu XZ, Ouyang XM, Xia XJ, Zheng J, Pandya A, Li F, Du LL, Welch KO, Petit C, Smith RJ, Webb BT, Yan D, Arnos KS, Corey D, Dallos P, Nance WE, Chen ZY. Prestin, a cochlear motor protein, is defective in non-syndromic hearing loss. Hum Mol Genet. 2003; 12:1155–1162. [PubMed: 12719379]
94. Tang HY, Xia A, Oghalai JS, Pereira FA, Alford RL. High frequency of the IVS2-2A.G DNA sequence variation in *SLC26A5*, encoding the cochlear motor protein prestin, precludes its involvement in hereditary hearing loss. BMC Med Genet. 2005; 6:30. [PubMed: 16086836]
95. Toth T, Deak L, Fazakas F, Zheng J, Muszbek L, Sziklai I. A new mutation in the human pres gene and its effect on prestin function. Int J Mol Med. 2007; 20:545–550. [PubMed: 17786286]
96. Shahin H, Walsh T, Sobe T, Sa'ed JA, Rayan AA, Lynch D, Lee EMK, Avraham KB, King MC, Kanan M. Mutations in a novel isoform of *TRIOBP* that encodes a filamentous-acting binding protein are responsible for DFNB28 recessive nonsyndromic hearing loss. Am J Hum Genet. 2006; 78:144–152. [PubMed: 16385458]
97. Kitajiri S, Sakamoto T, Belyantseva IA, Goodyear RJ, Stepanyan R, Fujiwara I, Bird JE, Riazuddin S, Riazuddin S, Ahmed ZM, Hinshaw JE, Sellers J, Bartles JR 3rd, Hammer JA, Richardson GP, Griffith AJ, Frolenkov GI, Friedman TB. Actin-bundling protein TRIOBP forms

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

resilient rootlets of hair cell stereocilia essential for hearing. Cell. 2010; 141:786–798. [PubMed: 20510926]

98. Riazuddin S, Khan SN, Ahmed ZM, Ghosh M, Caution K, Nazli S, Kabra M, Zafar AU, Chen K, Naz S, Antonellis A, Pavan WJ, Green ED, Wilcox ER, Friedman PL, Morell RJ, Riazuddin S, Friedman TB. Mutations in *TRIOBP*, which encodes a putative cytoskeletal-organizing protein, are associated with nonsyndromic recessive deafness. Am J Hum Genet. 2006; 78:137–142. [PubMed: 16385457]
99. Kitajiri S, Fukumoto K, Hata M, Sasaki H, Katsuno T, Nakagawa T, Ito J, Tsukita S, Tsukita S. Radixin deficiency causes deafness associated with progressive degeneration of cochlear stereocilia. J Cell Biol. 2004; 166:559–570. [PubMed: 15314067]
100. Khan SY, Ahmed ZM, Shabbir MI, Kitajiri S, Kalsoom S, Tasneem S, Shayiq S, Ramesh A, Srisailpathy S, Khan SN, Smith RJH, Riazuddin S, Friedman TB, Riazuddin S. Mutations of the RDX gene cause nonsyndromic hearing loss at the DFNB24 locus. Hum Mutat. 2007; 28:417–423. [PubMed: 17226784]
101. Shearer AE, Hildebrand MS, Bromhead CJ, Kahrizi K, Webster JA, Azadeh B, Kimberling WJ, Anousheh A, Nazeri A, Stephan D, Najmabadi H, Smith RJH, Bahlo M. A novel splice site mutation in the RDX gene causes DFNB24 hearing loss in an Iranian family. AmJ Med Genet. 2009; 149A:555–558. [PubMed: 19215054]
102. Mustapha M, Chouery E, Chardenoux S, Naboulsi M, Paronnaud J, Lemainque A, Mégarbané A, Loiselet J, Weil D, Lathrop M, Petit C. DFNB31, a recessive form of sensorineural hearing loss, maps to chromosome 9q32-34. Eur J Hum Genet. 2002; 10:210–212. [PubMed: 11973626]
103. Kikkawa Y, Mburu P, Morse S, Kominami R, Townsend S, Brown. Mutant analysis reveals whirlin as a dynamic organizer in the growing hair cell stereocilium. Hum Molec Genet. 2005; 14:391–400. [PubMed: 15590699]
104. Holme RH, Kiernan BW, Brown SD, Steel KP. Elongation of hair cell stereocilia is defective in the mouse mutant whirler. J Comp Neurol. 2002; 450:94–102. [PubMed: 12124769]
105. Mburu P, Mustapha M, Varela A, Weil D, El-Amraoui A, Holme RH, Rump A, Hardisty RE, Blanchard S, Coimbra RS, Perfettini I, Parkinson N, Mallon AM, Glenister P, Rogers MJ, Paige AJ, Moir L, Clay J, Rosenthal A, Liu XZ, Blanco G, Steel KP, Petit C, Brown SD. Defects in whirlin, a PDZ domain molecule involved in stereocilia elongation, cause deafness in the whirler mouse and families with DFNB31. Nat Genet. 2003; 34:421–428. [PubMed: 12833159]
106. Jain PK, Lalwani AK, Li XC, Singleton TL, Smith TN, Chen A, Deshmukh D, Verma IC, Smith RJ, Wilcox ER. A gene for recessive nonsyndromic sensorineural deafness (DFNB18) maps to the chromosomal region 11p14-p15.1 containing the Usher syndrome type 1C gene. Genomics. 1998; 50:290–292. [PubMed: 9653658]
107. Smith RJH, Lee EC, Kimberling WJ, Daiger SP, Pelias MZ, Keats BJ, Jay M, Bird A, Reardon W, Guest M, Ayyagari R, Fielding Hejtmancik J. Localization of two genes for Usher syndrome type I to chromosome 11. Genomics. 1992; 14:995–1002. [PubMed: 1478678]
108. Scanlan MJ, Williamson B, Jungbluth A, Stockert E, Arden KC, Viars CS, Gure AO, Gordan JD, Chen YT, Old LJ. Isoforms of the human PDZ-73 protein exhibit differential tissue expression. Biochim Biophsy Acta. 1999; 1445:39–52.
109. Boeda B, El-Amraoui A, Bahloul A, Goodyear R, Daviet L, Blanchard S, Perfettini I, Fath KR, Shorte S, Reiners J, Houdusse A, Legrain P, Wolfrum U, Richardson G, Petit C. Myosin VIIa, harmonin and cadherin 23, three Usher I gene products that cooperate to shape the sensory hair cell bundle. EMBOJ. 2002; 21:6689–6699.
110. Siemens J, Kazmierczak P, Reynolds A, Sticker M, Littlewood-Evans A, Muller U. The Usher syndrome proteins cadherin 23 and harmonin form a complex by means of PDZ-domain interactions. Proc Natl Acad Sci USA. 2002; 99:14946–14951. [PubMed: 12407180]
111. Johnson KR, Gagnon LH, Webb LS, Peters LL, Hawes NL, Chang B, Zheng QY. Mouse models of USH1C and DFNB18: phenotypic and molecular analyses of two new spontaneous mutations of the Ush1c gene. Hum Mol Genet. 2003; 12:3075–3086. [PubMed: 14519688]
112. Ouyang XM, Xia XJ, Verpy E, Du LL, Pandya A, Petit C, Balkany T, Nance WE, Liu XZ. Mutations in the alternatively spliced exons of USH1C cause non-syndromic recessive deafness. Hum Genet. 2002; 111:26–30. [PubMed: 12136232]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

113. Bolz H, von Brederlow B, Ramirez A, Bryda EC, Kutsche K, Nothwang HG, Seeliger M, del C-Salcedó Cabrera M, Vila MC, Molina OP, Gal A, Kubisch C. Mutation of *CDH23*, encoding a new member of the cadherin gene family, causes Usher syndrome type 1D. Nat Genet. 2001; 27:108–112. [PubMed: 11138009]
114. Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, Ness SL, Polomeno R, Ramesh A, Schloss M, Srisailpathy CR, Wayne S, Bellman S, Desmukh D, Ahmed Z, Khan SN, Kaloustian VM, Li XC, Lalwani A, Riazuddin S, Bitner-Glindzicz M, Nance WE, Liu XZ, Wistow G, Smith RJ, Griffith AJ, Wilcox ER, Friedman TB, Morell RJ. Usher Syndrome 1D and Nonsyndromic Autosomal Recessive Deafness DFNB12 are caused by allelic mutations of the novel Cadherin-like gene *CDH23* . Am J Hum Genet. 2001; 68:26–37. [PubMed: 11090341]
115. Chaib H, Place C, Salem N, Dode C, Chardenoux S, Weissenbach J, el Zir E, Loiselet J, Petit C. Mapping of DFNB12, a gene for a non-syndromal autosomal recessive deafness, to chromosome 10q21-22. Hum Mol Genet. 1996; 5:1061–1064. [PubMed: 8817348]
116. Kazmierczak P, Sakaguchi H, Tokita J, Wilson-Kubalek EM, Milligan RA, Muller U, Kachar B. Cadherin 23 and protocadherin 15 interact to form tip-link filaments in sensory hair cells. Nature. 2007; 449:87–91. [PubMed: 17805295]
117. Ahmed ZM, Smith TN, Riazuddin S, Makishima T, Ghosh M, Bokhari S, Menon PS, Deshmukh D, Griffith AJ, Riazuddin S, Friedman TB, Wilcox ER. Nonsyndromic recessive deafness DFNB18 and Usher syndrome type 1C are allelic mutations of *USH1C* . Hum Genet. 2002; 110:527–531. [PubMed: 12107438]
118. Bitner-Glindzicz M, Lindley KJ, Rutland P, Blaydon D, Smith VV, Milla PJ, Hussain K, Furth-Lavi J, Cosgrove KE, Shepherd RM, Barnes PD, O' Brien RE, Farndon PA, Sowden J, Liu XZ, Scanlan MJ, Malcolm S, Dunne MJ, Aynsley-Green A, Glaser B. A recessive contiguous gene deletion causing infantile hyperinsulinism, enteropathy and deafness identifies the Usher type 1C gene. Nat Genet. 2000; 26:56–60. [PubMed: 10973248]
119. Verpy E, Leibovici M, Zwaenepoel I, Liu XZ, Gal A, Salem N, Mansour A, Blanchard S, Kobayashi I, Keats BJ, Slim R, Petit C. A defect in harmonin, a PDZ domain-containing protein expressed in the inner ear sensory hair cells, underlies Usher syndrome type 1C. Nat Genet. 2000; 26:51–55. [PubMed: 10973247]
120. Schultz JM, Yang Y, Caride AJ, Filoteo AG, Penheiter AR, Lagziel A, Morell RJ, Mohiddin SA, Fananapazir L, Madeo AC, Penniston JT, Griffith AJ. Modification of human hearing loss by plasma-membrane calcium pump PMCA2. N Engl J Med. 2005; 352:1557–1564. [PubMed: 15829536]
121. Wagatsuma M, Kitoh R, Suzuki H, Fukuoka H, Takumi Y, Usami S. Distribution and frequencies of CDH23 mutations in Japanese patients with non-syndromic hearing loss. Clin Genet. 2007; 72:339–344. [PubMed: 17850630]
122. Ahmed ZM, Riazuddin S, Ahmad J, Bernstein SL, Guo Y, Sabar MF, Sieving P, Riazuddin S, Griffith AJ, Friedman TB, Belyantseva IA, Wilcox ER. PCDH15 is expressed in the neurosensory epithelium of the eye and ear and mutant alleles are responsible for both USH1F and DFNB23. Hum Mol Genet. 2003; 12:3215–3223. [PubMed: 14570705]
123. Senften M, Schwander M, Kazmierczak P, Lillo CJB, Shin Hasson T, Geleoc GS, Gillespie PG, Williams D, Holt JR, Muller U. Physical and functional interaction between protocadherin 15 and myosin VIIa in mechanosensory hair cells. J Neurosci. 2006; 26:2060–2071. [PubMed: 16481439]
124. Alagramam KN, Murcia CL, Kwon HY, Pawlowski KS, Wright CG, Woychik RP. The mouse Ames waltzer hearing-loss mutant is caused by mutation of Pcdh15, a novel protocadherin gene. Nature Genet. 2001; 27:99–102. [PubMed: 11138007]
125. Kazmierczak P, Sakaguchi H, Tokita J, Wilson-Kubalek EM, Milligan RA, Muller U, Kachar B. Cadherin 23 and protocadherin 15 interact to form tip-link filaments in sensory hair cells. Nature. 2007; 449:87–91. [PubMed: 17805295]
126. Doucette L, Merner ND, Cooke S, Ives E, Galutira D, Walsh V, Walsh T, MacLaren L, Cater T, Fernandez B, Green JS, Wilcox ER, Shotland LI, Li XC, Lee M, King MC, Young TL. Profound prelingual nonsyndromic deafness maps to chromosome 10q21 and is caused by a novel missense mutation in the Usher syndrome type IF gene PCDH15. Eur J Hum Genet. 2009; 17:554–564. [PubMed: 19107147]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

127. Goodyear RJ, Richardson GP. Extracellular matrices associated with the apical surfaces of sensory epithelia in the inner ear: molecular and structural diversity. J Neurobiol. 2002; 53:212–227. [PubMed: 12382277]

128. Legan PK, Rau A, Keen JN, Richardson GP. The mouse tectorins. Modular matrix proteins of the inner ear homologous to components of the spermegg adhesion system. J Biol Chem. 1997; 272:8791–8801. [PubMed: 9079715]

129. Naz S, Alasti F, Mowjoodi A, Riazuddin S, Sanati MH, Friedman TB, Griffith AJ, Wilcox ER, Riazuddin S. Distinctive audiometric profile associated with DFNB21 alleles of *TECTA* . J Med Genet. 2003; 40:360–363. [PubMed: 12746400]

130. Pfister M, Thiele H, Van Camp G, Fransen E, Apaydin F, Aydin O, Leistenschneider P, Devoto M, Zenner HP, Blin N, Nürnberg P, Ozkarakas H, Kupka S. A genotypephenotype correlation with gender-effect for hearing impairment caused by *TECTA* mutations. Cell Physiol Biochem. 2004; 14:369–376. [PubMed: 15319541]

131. Legan PK, Lukashkina VA, Goodyear RJ, Kossi M, Russell IJ, Richardson GP. A targeted deletion in alpha-tectorin reveals that the tectorial membrane is required for the gain and timing of cochlear feedback. Neuron. 2000; 28:273–285. [PubMed: 11087000]

132. Chen W, Kahrizi K, Meyer NC, Riazalhosseini Y, Van Camp G, Najmabadi H, Smith RJ. Mutation of *COL11A2* causes autosomal recessive non-syndromic hearing loss at the DFNB53 locus. J Med Genet. 2005; 42:e61. [PubMed: 16033917]

133. McGuirt WT, Prasad SD, Griffith AJ, Kunst HP, Green GE, Shpargel KB, Runge C, Huybrechts C, Mueller RF, Lynch E, King MC, Brunner HG, Cremers CW, Takanosu M, Li SW, Arita M, Mayne R, Prockop DJ, Van Camp G, Smith RJ. Mutations in COL11A2 cause non-syndromic hearing loss (DFNA13). Nat Genet. 1999; 23:413–419. [PubMed: 10581026]

134. Verpy E, Masmoudi S, Zwaenepoel I, Leibovici M, Hutchin TP, Del Castillo I, Nouaille S, Blanchard S, Laine S, Popot JL, Moreno F, Mueller RF, Petit C. Mutations in a new gene encoding a protein of the hair bundle cause non-syndromic deafness at the DFNB16 locus. Nature Genet. 2001; 29:345–349. [PubMed: 11687802]

135. Jovine L, Park J, Wassarman PM. Sequence similarity between stereocilin and otoancorin points to a unified mechanism for mechanotransduction in the mammalian inner ear. BMC Cell Biol. 2002; 3:28. [PubMed: 12445334]

136. Zwaenepoel I, Mustapha M, Leibovici M, Verpy E, Goodyear R, Liu XZ, Nouaille S, Nance WE, Kanaan M, Avraham KB, Tekaia F, Loiselet J, Lathrop M, Richardson G, Petit C. Otoancorin an inner ear protein restricted to the interface between the apical surface of sensory epithelia and their overlying acellular gels, is defective in autosomal recessive deafness DFNB22. Proc. Natl. Acad. Sci. USA. 2002; 99:6240–6245. [PubMed: 11972037]

137. Walsh T, Abu Rayan A, Abu Sa'ed J, Shahin H, Shepshelovich J, Lee MK, Hirschberg K, Tekin M, Salhab W, Avraham KB, King MC, Kanaan M. Genomic analysis of a heterogeneous Mendelian phenotype: multiple novel alleles for inherited hearing loss in the Palestinian population. Hum Genomics. 2006; 2:203–211. [PubMed: 16460646]

138. Chaïb H, Place C, Salem N, Chardenoux S, Vincent C, Weissenbach J, El-Zir E, Loiselet J, Petit C. A gene responsible for a sensorineural nonsyndromic recessive deafness maps to chromosome 2p22-23. Hum Mol Genet. 1996; 5:155–158. [PubMed: 8789454]

139. Roux I, Safieddine S, Nouvian R, Grati M, Simmler MC, Bahloul A, Perfettini I, Le Gall M, Rostaing P, Hamard G, Triller A, Avan P, Moser T, Petit C. Otoferlin defective in a human deafness form, is essential for exocytosis at the auditory ribbon synapse. Cell. 2006; 127:277–289. [PubMed: 17055430]

140. Yasunaga S, Grati M, Chardenoux S, Smith TN, Friedman TB, Lalwani AK, Wilcox ER, Petit C. OTOF encodes multiple long and short isoforms: genetic evidence that the long ones underlie recessive deafness DFNB9. Am J Hum Genet. 2000; 67:591–600. [PubMed: 10903124]

141. Yasunaga S, Grati M, Cohen-Salmon M, El-Amraoui A, Mustapha M, Salem N, El-Zir E, Loiselet J, Petit C. A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. Nat Genet. 1999; 21:363–369. [PubMed: 10192385]

142. Rodriguez-Ballesteros M, Reynoso R, Olarte M, Villamar M, Morera C, Santarelli R, Arslan E, Meda C, Curet C, Volter C, Sainz-Quevedo M, Castorina P, Ambrosetti U, Berrettini S, Frei K, Tedin S, Smith J, Cruz Tapia M, Cavalle L, Gelvez N, Primignani P, Gomez-Rosas E, Martin M,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Moreno-Pelayo MA, Tamayo M, Moreno-Barral J, Moreno F, del Castillo I. A multicenter study on the prevalence and spectrum of mutations in the otoferlin gene (OTOF) in subjects with nonsyndromic hearing impairment and auditory neuropathy. Hum Mutat. 2008; 29:823–831. [PubMed: 18381613]

143. Rodriguez-Ballesteros M, del Castillo FJ, Martin Y, Moreno-Pelayo MA, Morera C, Prieto F, Marco J, Morant A, Gallo-Teran J, Morales-Angulo C, Navas C, Trinidad G, Tapia MC, Moreno F, del Castillo I. Auditory neuropathy in patients carrying mutations in the otoferlin gene (OTOF). Hum Mutat. 2003; 22:451–456. [PubMed: 14635104]
144. Chiu YH, Wu CC, Lu YC, Chen PJ, Lee WY, Liu AY, Hsu CJ. Mutations in the OTOF Gene in Taiwanese Patients with Auditory Neuropathy. Audiol Neurootol. 2010; 15:364–374. [PubMed: 20224275]
145. Varga R, Avenarius MR, Kelley PM, Keats BJ, Berlin CI, Hood LJ, Morlet TG, Brashears SM, Starr A, Cohn ES, Smith RJH, Kimberling WJ. OTOF mutations revealed by genetic analysis of hearing loss families including a potential temperature sensitive auditory neuropathy allele. J Med Genet. 2006; 43:576–581. [PubMed: 16371502]
146. Marlin S, Feldmann D, Nguyen Y, Rouillon I, Loundon N, Jonard L, Bonnet C, Couderc R, Garabedian EN, Petit C, Denoyelle F. Temperature-sensitive auditory neuropathy associated with an otoferlin mutation: Deafening fever! Biochem Biophys Res Commun. 2010; 394:737–742. [PubMed: 20230791]
147. Mirghomizadeh F, Pfister M, Apaydin F, Petit C, Kupka S, Pusch CM, Zenner HP, Blin N. Substitutions in the conserved C2C domain of otoferlin cause DFNB9, a form of nonsyndromic autosomal recessive deafness. Neurobiol Dis. 2002; 10:157–164. [PubMed: 12127154]
148. Delmaghani S, del Castillo FJ, Michel V, Leibovici M, Aghaie A, Ron U, Van Laer L, Ben-Tal N, Van Camp G, Weil D, Langa F, Lathrop M, Avan P, Petit C. Mutations in the gene encoding pejvakin, a newly identified protein of the afferent auditory pathway, cause DFNB59 auditory neuropathy. Nat Genet. 2006; 38:770–778. [PubMed: 16804542]
149. Schwander M, Sczaniecka A, Grillet N, Bailey JS, Avenarius M, Najmabadi H, Steffy BM, Federe GC, Lagler EA, Banan R, Hice R, Grabowski-Boase L, Keithley EM, Ryan AF, Housley GD, Wiltshire T, Smith RJH, Tarantino LM, Muller U. A forward genetics screen in mice identifies recessive deafness traits and reveals that pejvakin is essential for outer hair cell function. J Neurosci. 2007; 27:2163–2175. [PubMed: 17329413]
150. Chaleshtori MH, Simpson MA, Farrokhi E, Dolati M, Rad LH, Geshnigani SA, Crosby AH. Novel mutations in the pejvakin gene are associated with autosomal recessive non-syndromic hearing loss in Iranian families. Clin Genet. 2007; 72:261–263. [PubMed: 17718865]
151. Collin RWJ, Kalay E, Oostrik J, Caylan R, Wollnik B, Arslan S, den Hollander AI, Birinci Y, Lichtner P, Strom TM, Toraman B, Hoefsloot LH, Cremers CWRJ, Brunner HG, Cremers FPM, Karaguzel A, Kremer H. Involvement of DFNB59 mutations in autosomal recessive nonsyndromic hearing impairment. Hum Mutat. 2007; 28:718–723. [PubMed: 17373699]
152. Ebermann I, Walger M, Scholl HPN, Issa PC, Luke C, Nurnberg G, Lang-Roth R, Becker C, Nurnberg P, Bolz HJ. Truncating mutation of the DFNB59 gene causes cochlear hearing impairment and central vestibular dysfunction. Hum Mutat. 2007; 28:571–577. [PubMed: 17301963]
153. Weidner KM, Arakaki N, Hartmann G, Vandekerckhove J, Weingart S, Rieder H, Fonatsch C, Tsubouchi H, Hishida T, Daikuhara Y, Birchmeier W. Evidence for the identity of human scatter factor and human hepatocyte growth factor. Proc Nat Acad Sci. 1991; 88:7001–7005. [PubMed: 1831266]
154. Kilby MD, Afford S, Li XF, Strain AJ, Ahmed A, Whittle MJ. Localisation of hepatocyte growth factor and its receptor (c-met) protein and mRNA in human term placenta. Growth Factors. 1996; 13:133–139. [PubMed: 8804995]
155. Schultz JM, Khan SN, Ahmed ZM, Riazuddin S, Waryah AM, Chhatre D, Starost MF, Ploplis B, Buckley S, Velasquez D, Kabra M, Lee K, Hassan MJ, Ali G, Ansar M, Ghosh M, Wilcox ER, Ahmad W, Merlino G, Leal SM, Riazuddin S, Friedman TB, Morell RJ. Noncoding mutations of HGF are associated with nonsyndromic hearing loss DFNB39. Am J Hum Genet. 2009; 85:25–39. [PubMed: 19576567]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

156. Sirmaci A, Erbek S, Price J, Huang M, Duman D, Cengiz FB, Bademci G, Tokgöz-Yilmaz S, Hi mi B, Ozda H, Oztürk B, Kulaksizo lu S, Yildirim E, Kokotas H, Grigoriadou M, Petersen MB, Shahin H, Kanaan M, King MC, Chen ZY, Blanton SH, Liu XZ, Zuchner S, Akar N, Tekin M. A truncating mutation in *SERPINB6* is associated with autosomal-recessive nonsyndromic sensorineural hearing loss. Am J Hum Genet. 2010; 86:797–804. [PubMed: 20451170]

157. Jain PK, Fukushima K, Deshmukh D, Ramesh A, Thomas E, Lalwani AK, Kumar S, Plopis B, Skarka H, Srisailapathy CR, Wayne S, Zbar RIS, Verma IC, Smith RJH, Wilcox ER. A human recessive neurosensory non-syndromic hearing impairment locus is a potential homologue of the murine deafness (dn) locus. Hum Mol Genet. 1995; 4:2391–2394. [PubMed: 8634715]

158. Kurima K, Peters LM, Yang Y, Riazuddin S, Ahmed ZM, Naz S, Arnaud D, Drury S, Mo J, Makishima T, Ghosh M, Menon PS, Deshmukh D, Oddoux C, Ostrer H, Khan S, Riazuddin S, Deininger PL, Hampton LL, Sullivan SL, Battey JF Jr, Keats BJ, Wilcox ER, Friedman TB, Griffith AJ. Dominant and recessive deafness caused by mutations of a novel gene *TMC1* required for cochlear hair-cell function. Nat Genet. 2002; 30:277–284. [PubMed: 11850618]

159. Vreugde S, Erven A, Kros CJ, Marcotti W, Fuchs H, Kurima K, Wilcox ER, Friedman TB, Griffith AJ, Balling R, Hrabé De, Angelis M, Avraham KB, Steel KP. Beethoven, a mouse model for dominant, progressive hearing loss DFNA36. Nat Genet. 2002; 30:257–258. [PubMed: 11850623]

160. Kitajiri S, Makishima T, Friedman TB, Griffith AJ. A novel mutation at the DFNA36 hearing loss locus reveals a critical function and potential genotype-phenotype correlation for amino acid-572 of TMC1. Clin Genet. 2007; 71:148–152. [PubMed: 17250663]

161. Kalay E, Karaguzel A, Caylan R, Heister A, Cremers FP, Cremers CW, Brunner HG, de Brouwer AP, Kremer H. Four novel *TMC1* (DFNB7/DFNB11) mutations in Turkish patients with congenital autosomal recessive nonsyndromic hearing loss. Hum Mutat. 2005; 26:591. [PubMed: 16287143]

162. Sirmaci A, Duman D, Oztürkmen-Akay H, Erbek S, Incesulu A, Oztürk-Hi mi B, Arici ZS, Yüksel-Konuk EB, Ta ir-Yilmaz S, Tokgöz-Yilmaz S, Cengiz FB, Aslan I, Yildirim M, Hasanefendio lu-Bayrak A, Ayçiçek A, Yilmaz I, Fitoz S, Altin F, Ozda H, Tekin M. Mutations in *TMC1* contribute significantly to nonsyndromic autosomal recessive sensorineural hearing loss a report of five novel mutations. Int J PediatrOtorhinolaryngol. 2009; 73:699–705.

163. Hilgert N, Alasti F, Dieltjens N, Pawlik B, Wollnik B, Uyguner O, Delmaghani S, Weil D, Petit C, Danis E, Yang T, Pandelia E, Petersen M, Goossens D, Favero J, Sanati M, Smith R, Van Camp G. Mutation analysis of *TMC*1 identifies four new mutations and suggests an additional deafness gene at loci DFNA36 and DFNB7/ 11. Clin Genet. 2008; 74:223–232. [PubMed: 18616530]

164. Saïd MB, Hmani-Aifa M, Amar I, Baig SM, Mustapha M, Delmaghani S, Tlili A, Ghorbel A, Ayadi H, Van Camp G, Smith RJ, Tekin M, Masmoudi S. High Frequency of the p.R34X Mutation in the *TMC1* Gene Associated with Nonsyndromic Hearing Loss Is Due to Founder Effects. Genet Test Mol Biomarkers. 2010; 14:307–311. [PubMed: 20373850]

165. Mitchem KL, Hibbard E, Beyer LA, Bosom K, Dootz GA, Dolan DF, Johnson KR, Raphael Y. Mutation of the novel gene Tmie results in sensory cell defects in the inner ear of spinner, a mouse model of human hearing loss DFNB6. Hum Mol Genet. 2002; 11:1887–1898. [PubMed: 12140191]

166. Naz S, Giguere CM, Kohrman DC, Mitchem KL, Riazuddin S, Morell RJ, Ramesh A, Srisailpathy S, Deshmukh D, Riazuddin S, Griffith AJ, Friedman TB, Smith RJ, Wilcox ER. Mutations in a novel gene, *TMIE*, are associated with hearing loss linked to the DFNB6 locus. Am J Hum Genet. 2002; 71:632–636. [PubMed: 12145746]

167. Santos RL, El-Shanti H, Sikandar S, Lee K, Bhatti A, Yan K, Chahrour MH, McArthur N, Pham TL, Mahasneh AA, Ahmad W, Leal SM. Novel sequencevariants in the *TMIE* gene in families with autosomal recessive nonsyndromic hearing impairment. J Mol Med. 2006; 84:226–231. [PubMed: 16389551]

168. Sirmaci A, Oztürkmen-Akay H, Erbek S, Incesulu A, Duman D, Ta ir-Yilmaz S, Ozda H, Tekin M. A founder *TMIE* mutation is a frequent cause of hearing loss in southeastern Anatolia. Clin Genet. 2009; 75:562–567. [PubMed: 19438934]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

169. Guipponi M, Vuagniaux G, Wattenhofer M, Shibuya K, Vazquez M, Dougherty L, Scamuffa N, Guida E, Okui M, Rossier C, Hancock M, Buchet K, Reymond A, Hummler E, Marzella PL, Kudoh J, Shimizu N, Scott HS, Antonarakis SE, Rossier BC. The transmembrane serine protease (TMPRSS3) mutated in deafness DFNB8/10 activates the epithelial sodium channel (ENaC) *in vitro* . Hum Mol Genet. 2002; 11(23):2829–2836. [PubMed: 12393794]

170. Scott HS, Kudoh J, Wattenhofer M, Shibuya K, Berry A, Chrast R, Guipponi M, Wang J, Kawasaki K, Asakawa S, Minoshima S, Younus F, Mehdi SQ, Radhakrishna U, Papasavvas MP, Gehrig C, Rossier C, Korostishevsky M, Gal A, Shimizu N, Bonne-Tamir B, Antonarakis SE. Insertion of beta-satellite repeats identifies a transmembrane protease causing both congenital and childhood onset autosomal recessive deafness. Nat Genet. 2001; 27(1):59–63. [PubMed: 11137999]

171. Guipponi M, Antonarakis SE, Scott HS. TMPRSS3, a type II transmembrane serine protease mutated in non-syndromic autosomal recessive deafness. Front Biosci. 2008; 13:1557–1567. [PubMed: 17981648]

172. Shabbir MI, Ahmed ZM, Khan SY, Riazuddin S, Waryah AM, Khan SN, Camps RD, Ghosh M, Kabra M, Belyantseva IA, Friedman TB, Riazuddin S. Mutations of human *TMHS* cause recessively inherited nonsyndromic hearing loss. J Med Genet. 2006; 43:634–640. [PubMed: 16459341]

173. Longo-Guess CM, Gagnon LH, Cook SA, Wu J, Zheng QY, Johnson KR. A missense mutation in the previously undescribed gene Tmhs underlies deafness in hurry-scurry (hscy) mice. Proc Nat Acad Sci. 2005; 102:7894–7899. [PubMed: 15905332]

174. Kalay E, Li Y, Uzumcu A, Uyguner O, Collin RW, Caylan R, Ulubil-Emiroglu M, Kersten FF, Hafiz G, van Wijk E, Kayserili H, Rohmann E, Wagenstaller J, Hoefsloot LH, Strom TM, Nürnberg G, Baserer N, den Hollander AI, Cremers FP, Cremers CW, Becker C, Brunner HG, Nürnberg P, Karaguzel A, Basaran S, Kubisch C, Kremer H, Wollnik B. Mutations in the lipoma HMGIC fusion partner-like 5 (LHFPL5) gene cause autosomal recessive nonsyndromic hearing loss. Hum Mutat. 2006; 27:633–639. [PubMed: 16752389]

175. Tlili A, Männikkö M, Charfedine I, Lahmar I, Benzina Z, Ben Amor M, Driss N, Ala-Kokko L, Drira M, Masmoudi S, Ayadi H. A novel autosomal recessive non-syndromic deafness locus, DFNB66, maps to chromosome 6p21.2–22.3 in a large Tunisian consanguineous family. Hum Hered. 2005; 60(3):123–128. [PubMed: 16244493]

176. Khan SY, Riazuddin S, Tariq M, Anwar S, Shabbir MI, Riazuddin SA, Khan SN, Husnain T, Ahmed ZM, Friedman TB, Riazuddin S. Autosomal recessive nonsyndromic deafness locus DFNB63 at chromosome 11q13.2-q13.3. Hum Genet. 2007; 120:789–793. [PubMed: 17066295]

177. Tlili A, Masmoudi S, Dhouib H, Bouaziz S, Rebeh IB, Chouchen J, Turki K, Benzina Z, Charfedine I, Drira M, Ayadi H. Localization of a novel autosomal recessive non-syndromic hearing impairment locus DFNB63 to chromosome 11q13.3-q13.4. Ann Hum Genet. 2007; 71:271–275. [PubMed: 17166180]

178. Kalay E, Caylan R, Kiroglu AF, Yasar T, Collin RW, Heister JG, Oostrik J, Cremers CW, Brunner HG, Karaguzel A, Kremer H. A novel locus for autosomal recessive nonsyndromic hearing impairment, DFNB63, maps to chromosome 11q13.2-q13.4. J Mol Med. 2007; 85:397–404. [PubMed: 17211611]

179. Ahmed ZM, Masmoudi S, Kalay E, Belyantseva IA, Mosrati MA, Collin RWJ, Riazuddin S, Hmani-Aifa M, Venselaar H, Kawar MN, Tlili A, van der Zwaa B, Khan SY, Ayadi L, Riazuddin SA, Morell RJ, Griffith AJ, Charfedine I, Caylan R, Oostrik J, Karaguzel A, Ghorbel A, Riazuddin S, Friedman TB, Ayadi H, Kremer H. Mutations of *LRTOMT*, a fusion gene with alternative reading frames, cause nonsyndromic deafness in humans. Nature Genet. 2008; 40:1335–1340. [PubMed: 18953341]

180. Du X, Schwander M, Moresco EMY, Viviani P, Haller C, Hildebrand MS, Pak K, Tarantino L, Roberts A, Richardson H, Koob G, Najmabadi H, Ryan AF, Smith RJH, Muller U, Beutler B. A catechol-O-methyltransferase that is essential for auditory function in mice and humans. Proc Nat Acad Sci. 2008; 105:14609–14614. [PubMed: 18794526]

181. Grillet N, Schwander M, Hildebrand MS, Sczaniecka A, Kolatkar A, Velasco J, Webster JA, Kahrizi K, Najmabadi H, Kimberling WJ, Stephan D, Bahlo M, Wiltshire T, Tarantino LM, Kuhn P, Smith RJH, Muller U. Mutations in LOXHD1, an evolutionarily conserved stereociliary

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

protein, disrupt hair cell function in mice and cause progressive hearing loss in humans. Am JHum Genet. 2009; 85:328–337. [PubMed: 19732867]

182. Rehman AU, Morell RJ, Belyantseva IA, Khan SY, Boger ET, Shahzad M, Ahmed ZM, Riazuddin S, Khan SN, Riazuddin S, Friedman TB. Targeted capture and next-generation sequencing identifies C9orf75, encoding taperin, as the mutated gene in nonsyndromic deafness DFNB79. Am J Hum Genet. 2010; 86:378–388. [PubMed: 20170899]
183. Li Y, Pohl E, Boulouiz R, Schraders M, Nurnberg G, Charif M, Admiraal RJC, von Ameln S, Baessmann I, Kandil M, Veltman JA, Nurnberg P, Kubisch C, Barakat A, Kremer H, Wollnik B. Mutations in TPRN cause a progressive form of autosomal recessive nonsyndromic hearing loss. Am J Hum Genet. 2010; 86:479–484. [PubMed: 20170898]
184. Seifert RA, Coats SA, Oganesian A, Wright MB, Dishmon M, Booth CJ, Johnson RJ, Alpers CE, Bowen-Pope DF. PTPRQ is a novel phosphatidylinositol phosphatase that can be expressed as a cytoplasmic protein or as a subcellularly localized receptorlike protein. Exp Cell Res. 2003; 287:374–386. [PubMed: 12837292]
185. Schraders M, Oostrik J, Huygen PLM, Strom TM, van Wijk E, Kunst HPM, Hoefsloot LH, Cremers CWRJ, Admiraal RJC, Kremer H. Mutations in *PTPRQ* are a cause of autosomal-recessive nonsyndromic hearing impairment DFNB84 and associated with vestibular dysfunction. Am J Hum Genet. 2010; 86:604–610. [PubMed: 20346435]
186. Shahin H, Rahil M, Rayan AA, Avraham KB, King MC, Kanaan M, Walsh T. Nonsense mutation of the stereociliar membrane protein gene PTPRQ in human hearing loss DFNB84. J Med Genet. 2010; 47:643–645. [PubMed: 20472657]
187. Schraders M, Lee K, Oostrik J, Huygen PLM, Ali G, Hoefsloot LH, Veltman JA, Cremers FPM, Basit S, Ansar M, Cremers CWRJ, Kunst HPM, Ahmad W, Admiraal RJC, Leal SM, Kremer H. Homozygosity mapping reveals mutations of *GRXCR1* as a cause of autosomal-recessive nonsyndromic hearing impairment. Am J Hum Genet. 2010; 86:138–147. [PubMed: 20137778]
188. Odeh H, Hagiwara N, Skynner M, Mitchem KL, Beyer LA, Allen ND, Brilliant MH, Lebart MC, Dolan DF, Raphael Y, Kohrman DC. Characterization of two transgene insertional mutations at pirouette, a mouse deafness locus. Audiol Neurootol. 2004; 9:303–314. [PubMed: 15347914]
189. Schneider E, Märker T, Daser A, Frey-Mahn G, Beyer V, Farcas R, Schneider-Rätzke B, Kohlschmidt N, Grossmann B, Bauss K, Napiontek U, Keilmann A, Bartsch O, Zechner U, Wolfrum U, Haaf T. Homozygous disruption of PDZD7 by reciprocal translocation in a consanguineous family: a new member of the Usher syndrome protein interactome causing congenital hearing impairment. Hum Mol Genet. 2009; 18:655–666. [PubMed: 19028668]
190. Walsh T, Shahin H, Elkan-Miller T, Lee MK, Thornton AM, Roeb W, Abu Rayyan A, Loulus S, Avraham KB, King M-C, Kanaan M. Whole exome sequencing and homozygosity mapping identify mutation in the cell polarity protein GPSM2 as the cause of nonsyndromic hearing loss DFNB82. Am J Hum Genet. 2010; 87:90–94. [PubMed: 20602914]
191. Yariz KO, Walsh T, Akay H, Duman D, Akkaynak AC, King MC, Tekin M. A truncating mutation in GPSM2 is associated with recessive nonsyndromic hearing loss. Clin Genet. 2011
192. Waryah AM, Rehman A, Ahmed ZM, Bashir ZH, Khan SY, Zafar AU, Riazuddin S, Friedman TB, Riazuddin S. DFNB74, a novel autosomal recessive nonsyndromic hearing impairment locus on chromosome 12q14.2-q15. Clin Genet. 7(3):270–275.
193. Ahmed ZM, Yousaf R, Lee BC, Khan SN, Lee S, Lee K, Husnain T, Rehman AU, Bonneux S, Ansar M, Ahmad W, Leal SM, Gladyshev VN, Belyantseva IA, Van Camp G, Riazuddin S, Friedman TB, Riazuddin S. Functional null mutations of MSRB3 encoding methionine sulfoxide reductase are associated with human deafness DFNB74. Am J Hum Genet. 2011; 88(1):19–29. [PubMed: 21185009]
194. Hauge H, Patzke S, Delabie J, Aasheim H-C. Characterization of a novel immunoglobulin-like domain containing receptor. Biochem Biophys Res Commun. 2004; 323:970–978. [PubMed: 15381095]
195. Aslam M, Wajid M, Chahrour MH, Ansar M, Haque S, Pham TL, Santos RP, Yan K, Ahmad W, Leal SM. A novel autosomal recessive nonsyndromic hearing impairment locus (DFNB42) maps to chromosome 3q13.31-q22.3. Am J Med Genet. 2005; 133A(1):18–22. [PubMed: 15641023]
196. Borck G, Ur Rehman A, Lee K, Pogoda HM, Kakar N, von Ameln S, Grillet N, Hildebrand MS, Ahmed ZM, Nürnberg G, Ansar M, Basit S, Javed Q, Morell RJ, Nasreen N, Shearer AE, Ahmad

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

A, Kahrizi K, Shaikh RS, Ali RA, Khan SN, Goebel I, Meyer NC, Kimberling WJ, Webster JA, Stephan DA, Schiller MR, Bahlo M, Najmabadi H, Gillespie PG, Nürnberg P, Wollnik B, Riazuddin S, Smith RJ, Ahmad W, Müller U, Hammerschmidt M, Friedman TB, Riazuddin S, Leal SM, Ahmad J, Kubisch C. Loss-of-function mutations of ILDR1 cause autosomal-recessive hearing impairment DFNB42. Am J Hum Genet. 2011; 88(2):127–137. [PubMed: 21255762]

197. Chen A, Wayne S, Bell A, Ramesh A, Srisailapathy CR, Scott DA, Sheffield VC, Van Hauwe P, Zbar RI, Ashley J, Lovett M, Van Camp G, Smith RJ. New gene for autosomal recessive non-syndromic hearing loss maps to either chromosome 3q or 19p. Am J Med Genet. 1997; 71:467–471. [PubMed: 9286457]
198. Van Camp G, Willems PJ, Smith RJH. Nonsyndromic hearing impairment: unparalleled heterogeneity. Am J Hum Genet. 1997; 60:758–764. [PubMed: 9106521]
199. Ain Q, Nazli S, Riazuddin S, Jaleel A, Riazuddin SA, Zafar AU, Khan SN, Husnain T, Griffith AJ, Ahmed ZM, Friedman TB, Riazuddin S. The autosomal recessive nonsyndromic deafness locus DFNB72 is located on chromosome 19p13.3. Hum Genet. 2007; 122:445–450. [PubMed: 17690910]
200. Rehman AU, Gul K, Morell RJ, Lee K, Ahmed ZM, Riazuddin S, Ali RA, Shahzad M, Jaleel AU, Andrade PB, Khan SN, Khan S, Brewer CC, Ahmad W, Leal SM, Riazuddin S, Friedman TB. Mutations of GIPC3 cause nonsyndromic hearing loss DFNB72 but not DFNB81 that also maps to chromosome p19p. Hum Genet. 2011 Jun.
201. Charizopoulou N, Lelli A, Schraders M, Ray K, Hildebrand MS, Ramesh A, Srisailapathy CR, Oostrik J, Admiraal RJ, Neely HR, Latoche JR, Smith RJ, Northup JK, Kremer H, Holt JR, Noben-Trauth K. Gipc3 mutations associated with audiogenic seizures and sensorineural hearing loss in mouse and human. Nat Commun. 2011 Feb 2.:201. [PubMed: 21326233]
202. Saitoh T, Mine T, Katoh M. Molecular cloning and characterization of human GIPC3, a novel gene homologous to human GIPC1 and GIPC2. Int J Oncol. 2002; 20:577–582. [PubMed: 11836571]
203. Tsukada K, Nishio S, Usami S. the Deafness Gene Study Consortium: A large cohort study of GJB2 mutations in Japanese hearing loss patients. Clin Genet. 2010; 78:464–470. [PubMed: 20497192]
204. Dai P, Yu F, Han B, Yuan Y, Li Q, Wang G, Liu X, He J, Huang D, Kang D, Zhang X, Yuan H, Schmitt E, Han D, Wong LJ. The prevalence of the 235delC *GJB2* mutation in a Chinese deaf population. Genet Med. 2007; 9:283–289. [PubMed: 17505205]
205. Brobby GW, Müller-Myhsok B, Horstmann RD. Connexin 26 R143W mutation associated with recessive nonsyndromic sensorineural deafness in Africa. N Engl J Med. 1998; 338:548–550. [PubMed: 9471561]
206. Nal N, Ahmed ZM, Erkal E, Alper OM, Lüleci G, Dinç O, Waryah AM, Ain Q, Tasneem S, Husnain T, Chattaraj P, Riazuddin S, Boger E, Ghosh M, Kabra M, Riazuddin S, Morell RJ, Friedman TB. Mutational spectrum of *MYO15A*: the large N-terminal extension of myosin XVA is required for hearing. Hum Mutat. 2007; 28:1014–1019. [PubMed: 17546645]
207. Belguith H, Aifa-Hmani M, Dhouib H, Said MB, Mosrati MA, Lahmar I, Moalla J, Charfeddine I, Driss N, Arab SB, Ghorbel A, Ayadi H, Masmoudi S. Screening of the DFNB3 locus: identification of three novel mutations of *MYO15A* associated with hearing loss and further suggestion for two distinctive genes on this locus. Genet Test Mol Biomarkers. 2009; 13:147–151. [PubMed: 19309289]
208. Lezirovitz K, Pardono E, de Mello Auricchio MT, de Carvalho FL, Silva E, Lopes JJ, Abreu-Silva RS, Romanos J, Batissoco AC, Mingroni-Netto RC. Unexpected genetic heterogeneity in a large consanguineous Brazilian pedigree presenting deafness. Eur J Hum Genet. 2008; 16:89–96. [PubMed: 17851452]
209. Wang QJ, Zhao YL, Rao SQ, Guo YF, Yuan H, Zong L, Guan J, Xu BC, Wang DY, Han MK, Lan L, Zhai SQ, Shen Y. A distinct spectrum of *SLC26A4* mutations in patients with enlarged vestibular aqueduct in China. Clin Genet. 2007; 72:245–254. [PubMed: 17718863]
210. Albert S, Blons H, Jonard L, Feldmann D, Chauvin P, Loundon N, Sergent-Allaoui A, Houang M, Joannard A, Schmerber S, Delobel B, Leman J, Journel H, Catros H, Dollfus H, Eliot MM, David A, Calais C, Drouin-Garraud V, Obstoy MF, Tran Ba Huy P, Lacombe D, Duriez F, Francannet C, Bitoun P, Petit C, Garabédian EN, Couderc R, Marlin S, Denoyelle F. *SLC26A4*

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

gene is frequently involved in nonsyndromic hearing impairment with enlarged vestibular aqueduct in Caucasian populations. Eur J Hum Genet. 2006; 14:773–779. [PubMed: 16570074]

211. Anwar S, Riazuddin S, Ahmed ZM, Tasneem S, Ateeq-ul-Jaleel, Khan SY, Griffith AJ, Friedman TB, Riazuddin S. *SLC26A4* mutation spectrum associated with DFNB4 deafness and Pendred's syndrome in Pakistanis. J Hum Genet. 2009; 54:266–270. [PubMed: 19287372]

212. Astuto LM, Bork JM, Weston MD, Askew JW, Fields RR, Orten DJ, Ohliger SJ, Riazuddin S, Morell RJ, Khan S, Riazuddin S, Kremer H, van Hauwe P, Moller CG, Cremers CW, Ayuso C, Heckenlively JR, Rohrschneider K, Spandau U, Greenberg J, Ramesar R, Reardon W, Bitoun P, Millan J, Legge R, Friedman TB, Kimberling WJ. CDH23 mutation and phenotype heterogeneity: a profile of 107 diverse families with Usher syndrome and nonsyndromic deafness. Am J Hum Genet. 2002; 71:262–275. [PubMed: 12075507]

213. Mustapha M, Weil D, Chardenoux S, Elias S, El-Zir E, Beckmann JS, Loiselet J, Petit C. An alpha-tectorin gene defect causes a newly identified autosomal recessive form of sensorineural pre-lingual non-syndromic deafness DFNB21. Hum Mol Genet. 1999; 8:409–412. [PubMed: 9949200]

214. Meyer NC, Alasti F, Nishimura CJ, Imanirad P, Kahrizi K, Riazalhosseini Y, Malekpour M, Kochakian N, Jamali P, Van Camp G, Smith RJ, Najmabadi H. Identification of three novel *TECTA* mutations in Iranian families with autosomal recessive nonsyndromic hearing impairment at the DFNB21 locus. Am J Med Genet. 2007; 143A:1623–1629. [PubMed: 17431902]

215. Cengiz FB, Duman D, Sirmaci A, Tokgoz-Yilmaz S, Erbek S, Ozturkmen-Akay H, Incesulu A, Edwards YJK, Ozdag H, Liu XZ, Tekin M. Recurrent and Private MYO15A Mutations are Associated with Deafness in the Turkish population. Genet Test Mol Biomarkers. 2010; 14:543–550. [PubMed: 20642360]

Abbreviations

ARNSHL	autosomal recessive nonsyndromic hearing loss
ADNSHL	autosomal dominant nonsyndromic hearing loss
EVA	enlargement of the vestibular aqueduct
sh1	shaker-1 mouse
Hdb	Headbanger mouse
sv	Snell's waltzer mouse
wi	recessive mouse mutant whirler
dfcr	deaf circler
dfcr-2J	deaf circler 2 Jacksonav
av	Ames waltzer
Bth	Beethoven mouse
sr	spinner mouse
ENaC	(amiloride-sensitive) sodium channel
hscy	hurry-scurry

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Summary of reported mutations in 42 genes in families with autosomal recessive nonsyndromic deafness[1]

Locus Name	Gene Name	Chr. Locus	Size of Open Reading Frame (bp)	Number of Exons	Number of Mutations in ARNSHL	Country of Origin	Recurrent Mutations	References
-	*GJB3 (Cx31)*	1p34.3	813	2	4	China	-	28
DFNB1A	*GJB2 (Cx26)*	13q12.11	681	2	~200	Many populations; high frequency in Caucasians	Common mutations: c.35delG- Caucasians c.235delC- East Asia p.W24X- India, European Gypsies p.R143W- Ghana IVS1+1G>A- Mongolia	4, 9, 19, 203, 204, 205
DFNB1B	*GJB6 (Cx30)*	13q12.11	786	3	5	Europe, Israel, U.S., Tunisia	del(GJB6-D13S1854)-Caucasians del(GJB6-D13S1830)-Caucasians	6
DFNB2	*MYO7A*	11q13.5	6528	49	5	China, Pakistan	-	68, 69
DFNB3	*MYO15A*	17p11.2	10593	65	32	Bali, Pakistan, India, Turkey, Tunisia, Brazil	p.I892F- Bengkala village, Bali p.D2720H- Pakistan p.V2266M- Pakistan, Turkey c.5807_5813del7- Turkey c.9996_10002dup7- Turkey	82, 206, 207 208, 215
DFNB4	*SLC26A4*	7q22.3	2343	21	262 (including Pendred syndrome)	Many populations	Common mutations: p.H723R- East Asia IVS7-2A>G- China p.L236P-Caucasians IVS8+1G>A-Caucasians p.T416P-Caucasians p.V239D- Pakistan, Turkey, Palestine p.S90L- Pakistan	36, 209, 210, 211
DFNB6	*TMIE*	3p21.31	471	4	8	Pakistan, India, Turkey	p.R84W- Turkey, India p.R81C- Pakistan	166, 168
DFNB7/ DFNB11	*TMC1*	9q21.13	2283	24	30	Pakistan, India, Tunisia, Turkey, Iran, Iraq, Lebanon, Algeria	p.R34X- Tunisia, Iran, Iraq, Turkey, Pakistan, Lebanon, Algeria	158, 164
DFNB8/ DFNB10	*TMPRSS3*	21q22.3	1365	13	16	Pakistan, Palestine, Germany, Turkey, England, Canada	c.del207C- Spain, Greece, Canada, Pakistan p.C407R-Pakistan	74, 170, 171

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Locus Name	Gene Name	Chr. Locus	Size of Open Reading Frame (bp)	Number of Exons	Number of Mutations in ARNSHL	Country of Origin	Recurrent Mutations	References
							p.P404L- Turkey, Tunisia	
DFNB9	*OTOF*	2p23.3	5994	47	62	Caucasians, East Asians, Near East, South America	Common mutation: p.Q829X- Spain Some other recurrent mutations: c.1601delC- Austria, Argentina c.2905_2923del19ins11- Argentina c.4227+1G>T- Argentina p.E1700Q- Taiwan	141, 142, 144
DFNB12	*CDH23*	10q22.1	10056	69	25	Caucasians, Pakistan, India, Palestine	p.D2148N- Caucasians p.A1586P- Pakistan p.P240L- Japan p.R2029W- Japan	74, 111, 121, 212
DFNB15/72/95	*GIPC3*	19p13.3	939	6	7	Pakistan, India, Netherlands	-	201
DFNB16	*STRC*	15q15.3	5328	29	3	Pakistan, Palestine	-	134
DFNB18	*USH1C*	11p15.1	2700	27	2	India, China	-	112, 117
DFNB21	*TECTA*	11q23.3	6465	23	8	Iran, Palestine, Lebanon, Pakistan	p.C1619X- Palestine	74, 129, 213, 214
DFNB22	*OTOA*	16p12.2	3420	28	3	Palestine	500kb deletion- Palestine	74, 136
DFNB23	*PCDH15*	10q21.1	5364	37	6	Pakistan, Caucasian	-	122, 126
DFNB24	*RDX*	11q22.3	1752	14	4	Pakistan, Iran	-	100
DFNB25	*GRXCR1*	4p13	873	4	4	Netherlands, Pakistan	-	187
DFNB28	*TRIOBP*	22q13.1	7098	24	9	Palestine, India, Pakistan	p.R347X- Palestine p.Q581X- Palestine p.3225_3226insC- India	96, 98
DFNB29	*CLDN14*	21q22.13	720	2	3	Pakistan, Greece	-	30
DFNB30	*MYO3A*	10p12.1	4851	35	3	Israel	-	56
DFNB31	*WHRN*	9q32	2724	12	2	Palestine, Tunisia	-	105
DFNB35	*ESRRB*	14q24.3	1527	11	5	Pakistan, Turkey	-	47

Locus Name	Gene Name	Chr. Locus	Size of Open Reading Frame (bp)	Number of Exons	Number of Mutations in ARNSHL	Country of Origin	Recurrent Mutations	References
DFNB36	*ESPN*	1p36.31	2565	13	3	Pakistan, Morocco	-	86
DFNB37	*MYO6*	6q14.1	3858	35	3	Pakistan	-	67
DFNB39	*HGF*	7q21.11	2187	18	3	Pakistan, India	c.482+1986_1988del3- Pakistan (36 families), India (2 families) c.482+1991_2000del10- Pakistan	155
DFNB42	*ILDR1*	3q21.1	1920	12	11	Pakistan, Iran	c.1032delG- Pakistan (2 families)	195, 196
DFNB49	*MARVELD2/ TRIC*	5q13.2	1677	7	5	Pakistan	IVS4+2T>C- Pakistan	34
DFNB53	*COL11A2*	6p21.32	5211	66	1	Iran	-	132
DFNB59	*PJVK*	2q31.2	1059	7	8	Iran, Turkey, Palestine, Morocco	p.R183W- Iran, Turkey	148
DFNB61	*PRESTIN/ SLC26A5*	7q22.1	2058	20	1 (possibly)	Caucasian	-	93
DFNB63	*LRTOMT*	11q13.4	756	9	5	Tunisia, Turkey, Pakistan, Iran	-	179, 180
DFNB67	*LHFPL5*	6p21.31	660	4	5	Pakistan, Turkey, Palestine	-	74, 172, 174, 175
DFNB73	*BSND*	1p32	963	4	1	Pakistan	p.I12T- Pakistan	51
DFNB74	*MSRB3*	12q14.3	558	8	2	Pakistan	p. C89G- Pakistan (6 families) p.R19X- Pakistan (2 families)	192, 193
DFNB77	*LOXHDB1*	11q13.3-q13.4	6636	40	1	Iran	-	181
DFNB79	*TPRN (C9orf75)*	9q34.3	1953	4	5	Pakistan, Morocco, Netherlands	c.42_52 del - Pakistan, Morocco	182
DFNB82	*GPSM2*	1p13.3	2055	15	2	Turkey, Palestine	-	190, 191
DFNB84	*PTPRQ*	12q15	6384	42	3	Netherlands, Morocco, Palestine	-	185, 186

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Locus Name	Gene Name	Chr. Locus	Size of Open Reading Frame (bp)	Number of Exons	Number of Mutations in ARNSHL	Country of Origin	Recurrent Mutations	References
DFNB91	*SERPINB6*	6p25.2	1131	7	1	Turkey	-	156
-	*PDZD7*	10q24.31	1554	10	1	NA	-	189

The numbers of mutations were obtained from Human Gene Mutation Database Professional Edition accessed in June 2010 and from the original publications; The numbers of exons and ORF sizes are from the University of California Santa Cruz Genome Browser (http://genome.cse.ucsc.edu/) accessed in June 2010 (hg19).