

## Autosomal recessive nonsyndromic deafness genes: a review

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## 1. 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.

## 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 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 unknown. 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<sup>+</sup> 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

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**Table 1.** Summary of reported mutations in 42 genes in families with autosomal recessive nonsyndromic deafness<sup>1</sup>

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
-	<i>GJB3 (Cx31)</i>	1p34.3	813	2	4	China	-	28
DFNB1A	<i>GJB2 (Cx26)</i>	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	<i>GJB6 (Cx30)</i>	13q12.11	786	3	5	Europe, Israel, U.S., Tunisia	del(GJB6-D13S1854)- Caucasians del(GJB6-D13S1830)- Caucasians	6
DFNB2	<i>MYO7A</i>	11q13.5	6528	49	5	China, Pakistan	-	68, 69
DFNB3	<i>MYO15A</i>	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	<i>SLC26A4</i>	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	<i>TMIE</i>	3p21.31	471	4	8	Pakistan, India, Turkey	p.R84W- Turkey, India p.R81C- Pakistan	166, 168
DFNB7/DFNB11	<i>TMC1</i>	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	<i>TMPRSS3</i>	21q22.3	1365	13	16	Pakistan, Palestine, Germany, Turkey, England, Canada	c.del207C- Spain, Greece, Canada, Pakistan p.C407R- Pakistan p.P404L- Turkey, Tunisia	74, 170, 171
DFNB9	<i>OTOF</i>	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	<i>CDH23</i>	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	<i>GIPC3</i>	19p13.3	939	6	7	Pakistan, India, Netherlands	-	201
DFNB16	<i>STRC</i>	15q15.3	5328	29	3	Pakistan, Palestine	-	134
DFNB18	<i>USH1C</i>	11p15.1	2700	27	2	India, China	-	112, 117
DFNB21	<i>TECTA</i>	11q23.3	6465	23	8	Iran, Palestine, Lebanon, Pakistan	p.C1619X- Palestine	74, 129, 213, 214
DFNB22	<i>OTOA</i>	16p12.2	3420	28	3	Palestine	500kb deletion- Palestine	74, 136
DFNB23	<i>PCDH15</i>	10q21.1	5364	37	6	Pakistan, Caucasian	-	122, 126
DFNB24	<i>RDX</i>	11q22.3	1752	14	4	Pakistan, Iran	-	100
DFNB25	<i>GRXCR1</i>	4p13	873	4	4	Netherlands, Pakistan	-	187
DFNB28	<i>TRIOBP</i>	22q13.1	7098	24	9	Palestine, India, Pakistan	p.R347X- Palestine p.Q581X- Palestine p.3225_3226insC- India	96, 98
DFNB29	<i>CLDN14</i>	21q22.13	720	2	3	Pakistan, Greece	-	30

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DFNB30	<i>MYO3A</i>	10p12.1	4851	35	3	Israel	-	56
DFNB31	<i>WHRN</i>	9q32	2724	12	2	Palestine, Tunisia	-	105
DFNB35	<i>ESRRB</i>	14q24.3	1527	11	5	Pakistan, Turkey	-	47
DFNB36	<i>ESPN</i>	1p36.31	2565	13	3	Pakistan, Morocco	-	86
DFNB37	<i>MYO6</i>	6q14.1	3858	35	3	Pakistan	-	67
DFNB39	<i>HGF</i>	7q21.11	2187	18	3	Pakistan, India	c.482+1986_1988del13-Pakistan (36 families), India (2 families) c.482+1991_2000del110-Pakistan	155
DFNB42	<i>ILDR1</i>	3q21.1	1920	12	11	Pakistan, Iran	c.1032delG- Pakistan (2 families)	195, 196
DFNB49	<i>MARVELD2/ TRIC</i>	5q13.2	1677	7	5	Pakistan	IVS4+2T>C- Pakistan	34
DFNB53	<i>COL11A2</i>	6p21.32	5211	66	1	Iran	-	132
DFNB59	<i>PJVK</i>	2q31.2	1059	7	8	Iran, Turkey, Palestine, Morocco	p.R183W- Iran, Turkey	148
DFNB61	<i>PRESTIN/ SLC26A5</i>	7q22.1	2058	20	1 (possibly)	Caucasian	-	93
DFNB63	<i>LRTOMT</i>	11q13.4	756	9	5	Tunisia, Turkey, Pakistan, Iran	-	179, 180
DFNB67	<i>LHFPL5</i>	6p21.31	660	4	5	Pakistan, Turkey, Palestine	-	74, 172, 174, 175
DFNB73	<i>BSND</i>	1p32	963	4	1	Pakistan	p.112T- Pakistan	51
DFNB74	<i>MSRB3</i>	12q14.3	558	8	2	Pakistan	p. C89G- Pakistan (6 families) p.R19X- Pakistan (2 families)	192, 193
DFNB77	<i>LOXHDB1</i>	11q13.3-q13.4	6636	40	1	Iran	-	181
DFNB79	<i>TPRN (C9orf75)</i>	9q34.3	1953	4	5	Pakistan, Morocco, Netherlands	c.42_52 del - Pakistan, Morocco	182
DFNB82	<i>GPSM2</i>	1p13.3	2055	15	2	Turkey, Palestine	-	190, 191
DFNB84	<i>PTPRQ</i>	12q15	6384	42	3	Netherlands, Morocco, Palestine	-	185, 186
DFNB91	<i>SERPINB6</i>	6p25.2	1131	7	1	Turkey	-	156
-	<i>PDZD7</i>	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).

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).

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, erythrokeratoderma 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 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 ligand-binding 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 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 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 initially 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 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.

### 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 (*dfer*) and deaf circler 2 Jackson (*dfer-2J*), carry *Ush1c* mutations and show deafness and circling behaviour (111). Studies of *dfer* 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 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  $\alpha$ -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).  $\alpha$ -tectorin is believed to interact with itself and with other extracellular matrix proteins including  $\beta$ -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  $\alpha$ -chain polypeptide subunits ( $\alpha 1$ ,  $\alpha 2$  and  $\alpha 3$ ), 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 identified 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 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 Dfmb59 knock-in mice (148). The Dfmb59 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 (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).

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).

### 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

## Autosomal recessive nonsyndromic deafness

(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 identified 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).

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. *GRXCRI* (DFNB25) (MIM 613283)

The *GRXCRI* 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 *GRXCRI* 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 *GRXCRI* 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 *GRXCRI* 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)

## 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 ARNSHL families of Indian and Pakistan origin.

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**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; dfer: deaf circler; dfer-2J:

deaf circler 2 Jackson; av: Ames waltzer; Bth: Beethoven mouse; sr: spinner mouse; ENaC: (amiloride-sensitive) sodium channel; hscy: hurry-scurry

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