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REVIEW ARTICLE

Genetics of hearing loss: where are we standing now?

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Abstract Hearing loss (HL) is the most common sensory impairment and is caused by a broad range of inherited to environmental causes. Inherited HL consists 50–60% of all HL cases. The inherited form of HL is further classified to different categories. More than 300 syndromes and 40 genes have been identified to result in different levels of HL. Although several diagnostic or screening tests have been developed, yet there are controversies around their use.

Keywords Syndromic hearing loss · Non-syndromic hearing loss · Genetic screening · Functional genes

Introduction

Hearing impairment (HI) is the most common sensory defect and its etiology consists of a broad range of inherited (monogenic, polygenic) to environmental (infections, drugs, noise, etc.) causes [1].

Inheritance of various impaired hearing conditions was discovered long before our understanding of genetics. Since the first description of hereditary hearing impairment (HHI) in the second half of the nineteenth century, numerous HHIs have been introduced either associated with other pathophysiological conditions (referred as syndromic HI) or isolated (referred as non-syndromic HI) [2–4].

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Until recent decades, our knowledge of audiologic pathways' mechanism of development, molecular basis and corresponding genes was limited. Recent advances in genetics and genomics have led us to identification of over 300 syndromic HIs and more than 100 chromosomal loci and more than 40 genes responsible for non-syndromic HIs [5, 6].

Better understanding of impaired genes and their structure and function will open a new window for screening as well as genetic approach to treatment of HI. In the following review, we discuss the definition, classifications, epidemiology, examples of syndromes, genes and diagnostic and screening methods of HI.

Classification of hearing impairment

Hearing impairment is referred to the condition in which the ability of hearing is below the normal threshold levels and is used interchangeably with the term hearing loss (HL). HL is classified in several ways due to its attributes; based on etiology (genetic, environmental, both), onset (congenital, prelingual or postlingual), course (progressive or stable), side (bilateral or unilateral), type (conductive [CHL], sensorineural [SNHL], mixed), frequency (low <500 Hz, middle 501–2,000 Hz, >2,000 Hz) or severity (mild 21–40 dB, moderate 41–55 dB, moderately severe 56–70 dB, severe 71–90 dB, profound >90 dB). The commonly used term, deafness, usually refers to severe to profound HL [7].

Epidemiology

Estimations of HL prevalence vary depending on the considered hearing threshold, society and age. Many studies that have considered a HL of more than 35 dB HL have reported

its prevalence to be 1–2 per 1,000 live birth and increasing with age. Approximately 50–60% of prelingual HL is contributed to inherited or genetic factors (monogenic or polygenic) while the rest is acquired or caused by environmental factors such as drugs, trauma, noise and infections, specially TORCH syndrome (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) [8–10]. Since the rubella pandemic in the middle of twentieth century, the relative incidence of inherited form of HL versus environmental has changed. This increase in compare with past decades is a result of improvements in neonatal care, immunization and drug monitoring [11, 12].

Between 60 and 70% of all inherited HL cases present as single trait and are not associated with other abnormalities (non-syndromic HL) and this number is increasing as a result of ongoing discovery of new loci and genes. Almost all modes of inheritance are present within both categories of inherited HL. There are several estimations of the frequency of each mode depending on the studied population. Most common mode of inheritance is autosomal recessive (AR) with 75–80% followed by autosomal dominant (AD) 10–20%, sex-linked 1–5% and mitochondrial 0–2% [11–13].

Syndromic hearing loss

Only in a small number of over 300 known syndromes, HL is a constant or probably most significant clinical element. In many other forms, HL is mild or even absent in some patients [14]. Identification of contributing genes in syndromic HL and their mutations started with localization of *PAX3* in Waardenburg's syndrome [15] and subsequently different genes and different mutations even within a single gene have been discovered for several syndrome. A summary of the most famous syndromes and their attributes are shown in Table 1 (more information is available at http://hereditaryhearingloss.org). Some of the common syndromes within each pattern of inheritance are discussed below.

Autosomal dominant

Waardenburg's syndrome is the most common AD syndromic HL and is supposed to be responsible for 1–4% of severe to profound HL in the population. It has been categorized into four clinical types. The most common subtype is type 1 and is characterized by the presence of bilateral or unilateral SNHL (15–20% of cases) and defects in the tissues of neural crest origin. This latter includes dystopia canthorum (lateral displacement of the medial canthi), broad nose root and hypopigmentations in skin (white forelock) and eye (heterochromia iridis). Type 2 is less common and shares all clinical features of type 1 except for dystopia canthorum. Type 3 or Klein–Waardenburg's syndrome (addition of upper limb skeletal abnormalities and mental retardation to type 1) and type 4 or Shah–Waardenburg's syndrome (addition of Hirschprung's disease to type 2) are the rare subtypes [9, 15, 16].

Branchio-oto-renal (BOR) syndrome is the second most common disorder in this category with approximately 2% prevalence among severe to profound HL population. It is characterized by association of branchial (branchial clefts, fistulas, and cysts) otologic (HL, pinna malformation, preauricular pit, and external auditory canal stenosis) and renal abnormalities (dysplasia or agenesia, polycystic kidneys, malformations of the calyces). HL is the major feature of this syndrome and is found in 70–100% of cases. The HL can be conductive, sensorineural or mixed, manifest at any time from early childhood to young adulthood, and is variable even within members of a family [1, 17, 18].

Some of the other major but less common forms of AD syndromic HL are shown in Table 1.

Autosomal recessive

Pendred syndrome is the most frequent syndromic HL. This disorder accounts for approximately 4–8% of individuals with severe to profound HL and is inherited in an AR fashion. Clinical features include SNHL, goiter (euthyroid or hypothyroid) and structural defects of the temporal bone and inner ear. SNHL is present in almost all patients (in majority of patients it is bilateral, profound and prelingual; however, in some individuals it may develop later in childhood and then progress) and is accompanied with various abnormalities of inner ear such as Mondini dysplasia (incomplete cochlea with less than normal 2.5 turns), dilated vestibular aqueduct and vestibular malfunction [19–21]. Goiter usually develops in early puberty and ranges from no enlargement of the thyroid to the development of large goiters [19]. Mutation in *PDS* gene that encodes pendrin (an iodide-chloride pump) is the underlying genetic etiology. Mutations in *PDS* gene can also generate a non-syndromic HL (DFNB4) [14].

Usher syndrome is the association of SNHL with retinitis pigmentosa (RP). It is one of the most common forms of AR syndromic HL with prevalence of 3–6% in severe to profound HL population and accounts for 50% of the deafblind individuals in United States. It is divided into three different types. Type 1 (about 60% of all cases) is defined by congenital severe to profound HL with vestibular dysfunction (results in ineffectiveness of hearing aids and altered motor development) and RP onset in first decade. Type 2 (about 30% of all cases) patients show moderate to severe SNHL, normal vestibular function and RP onset later in life (first to second decade). In type 3, SNHL and vestibular dysfunction are progressive and onset of RP is variable [20, 22, 23].

Table 1 Summary of syndromic causes of hearing loss, their mode of inheritance, mutated genes and produced proteins/functions

Inheritance	Syndrome	Associated features	Loci	Gene/locus	Function(s)
Autosomal dominant	Waardenburg		9		
		Type 1: bilateral or unilateral SNHL, dystopia canthorum, patchy hypopigmentations in skin, white forelock, heterochromia iridis)	1	*PAX3*/2q35	Transcription and regulatory factors for migration of neural crest cells
		Type 2: same as type 1; without dystopia canthorum	4	*MITF*/3p14.1-p12.3	
				Unknown/1p21-p13.3	
				Unknown/8p23	
				SNAI2/8q11	
		Type 3: same as type 1 plus upper limb skeletal abnormalities and mental retardation	1	*PAX3*/2q35	
		Type 4: same as type 2 plus Hirschprung's disease	3	*EDNRB*/13q22	
				EDN3/20q13.2-q13.3	
				SOX10/22q13	
	Branchio-oto-renal (BOR)	Branchial (branchial clefts, fistulas, and cysts) otologic (HL, pinna malformation, preauricular pit, external auditory canal stenosis), renal abnormalities (dysplasia or agenesia, polycystic kidneys, malformations of the calyces)	4	*EYA1*/8q13.3	Transcription and regulatory factors in development of inner ear and kidney
				SIX1/14q21.3-q24.3	
				SIX5/19q13.3	
				Unknown/1q31	
	Treacher Collins	CHL, high-frequency SNHL, hypoplastic zygomas, microtia, micrognathia, coloboma of eyelid	1	*TCOF1*/5q32-q33.1	Encodes TREACLE protein; nucleolar-cytoplasmic transport
	Stickler		4		
		Type 1: SNHL, cleft palate, spondyloepiphyseal dysplasia, hypermobility in early adulthood, degenerative arthropathy by the third or fourth decade ocular abnormalities (congenital myopia and retinal detachment)	1	*COL2A1*/12q13.11-q13.2	Encode collagen type II and XI
		Type 2: same as type 1	1	*COL11A1*/1p21	
		Type 3: same as type 1 without ocular abnormalities	2	*COL11A2*/6p21.3	
				COL9A1/6q13	
	Neurofibromatosis type 2	SNHL and tinnitus secondary to vestibular schwannoma, variety of other tumors (meningiomas, astrocytomas, ependymomas), cataract, symptoms appear during adolescence or early 20s	1	*NF2*/22q12	Encodes Merlin; tumor suppressor

Table 1 continued

Inheritance	Syndrome	Associated features	Loci	Gene/locus	Function(s)
Autosomal recessive	Usher		14		
		Type 1: severe to profound SNHL, vestibular dysfunction, RP in first decade	8	Unknown/14q32 *MYO7A*/11q13.5 *USH1C*/11p15.1 *CDH23*/10q22.1 Unknown/21q21 *PCDH15*/10q21-22 *SANS*/17q24-25 Unknown/15q22-23	Encode myosin, harmonin, organization of transmembrane and Cadherin-like proteins and adhesion molecules
		Type 2: moderate to severe SNHL, normal vestibular function, RP in first to second decade	4	*USH2A*/1q41 Unknown/3p23-24.2 *VLGR1*/5q14.3-q21.3 *WHRN*/9q32	
		Type 3: progressive SNHL, vestibular dysfunction, RP onset variable	2	*USH3A*/3q21-q25 *PDZD7*/10q23.31	
	Pendred	SNHL, goiter, Mondini dysplasia, dilated vestibular aqueduct, vestibular malfunction	2	*SLC26A4*/7q21-34 *FOXI1*/5q35.1	Pendrin; iodide-chloride pump
	Jervell and Lange-Nielsen	Severe to profound SNHL (usually at birth), prolonged QT interval, torsade de pointe arrhythmias (early childhood), syncope, seizure	2	*KCNQ1*/11p15.5 *KCNE1*/21q22.1-22.2	Encode delayed rectifier potassium channels
	Alström	Obesity, retinal dystrophy, diabetes mellitus type II, SNHL, acanthosis nigricans, cardiomyopathy (in firs decade)	1	*ALMS1*/2p13	Unknown function
	Bartter type 4	SNHL (present at birth), hypokalemic metabolic alkalosis, elevated plasma rennin and aldosterone, normal blood pressure, increased levels of urine chloride and prostaglandins	3	*BSND*/1p31 *CLCNKA*/1p36 *CLCNKB*/1p36	CLCNK; Kidney-specific chloride channel BSND; encodes Barttin, a subunit for CLCNK
	Biotinidase deficiency	Cutaneous and neurologic abnormalities; SNHL, ataxia, seizure, alopecia, ketoacidosis	1	*BTD*/3p25	Biotinidase; catalyzer of biotin-dependent carboxylase degradation
	Refsum	Progressive SNHL, retinitis pigmentosa, cerebellar ataxia, peripheral neuropathy, elevated protein levels in CSF	2	*PHYH*/10pter-p11.2 *PEX7*/6q22-q24	Defective phytanic acid metabolism
	Wolfram (also known as DIDMOAD)	Diabetes mellitus (first decade), diabetes insipidus (second decade), optic atrophy (second decade), progressive SNHL (second decade)	3	*WFS1*/4p16.1 *WFS2*/4q22-q24	Wolframin; structural protein in endoplasmic reticulum

Table 1 continued

Inheritance	Syndrome	Associated features	Loci	Gene/locus	Function(s)
X-linked recessive	Alport	Postlingual high-frequency SNHL, progressive nephropathy (from hematuria to renal failure), anterior lenticonus (pathognomonic), macular flecks	3	*COL4A5*/Xq22 *COL4A3*/2q36-q37 *COL4A4*/2q36-q37	Collagens in basement membranes of the cochlea, eye nd kidney
	Fabry	Multiple vascular lesions; anginas in abdomen or extremities, renal failure, cardiomyopathy High-frequency SNHL	1	*GLA*/Xq22	Encodes alpha-galactosidase A; lysosomal storage disease
	Mohr-Tranebjaerg	Severe to profound SNHL, dystonia, optic atrophy, fractures, and mental retardation	1	*TIMM8a*/Xq22	Organization of heterooligomeric complexes in the mitochondrial intermembrane space
	Gusher	Mixed HL, stapes fixation and vestibular abnormalities	1	*POU3F4*/Xq21.1	Transcription factor
Mitochondrial	Kearns–Sayre syndrome	Chronic progressive external ophthalmoplegia, pigmentary retinopathy, cardiomyopathy	Several	various mitochondrial deletions	Organization of electron transport chain
	MELAS	Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes	9	*MTTL1, MTTQ MTTH, MTTK MTTS1, MTND1 MTND5, MTND, MTTS2*	Mitochondrial tRNAs, electron transport chain
	MERRF	Myoclonic epilepsy, ragged red fibers	7	*MTTK, MTTL1, MTTH, MTTS1, MTTS2, MTTF, MTND5*	Mitochondrial tRNAs, electron transport chain
	MIDD	Diabetes, deafness	3	*MTTL1* *MTTE* *MTTK*	Mitochondrial tRNAs
	NARP	Neuropathy, ataxia, RP	1	*MTATP6*	Encodes subunits of mitochondrial ATPase

SNHL sensorineural hearing loss, *CHL* conductive hearing loss, *Mixed HL* mixed hearing loss, *RP* retinitis pigmentosa

Table 1 also summarizes some of the other main AR syndromes.

X-linked

X-linked dominant (XLD) and recessive (XLR) forms of syndromic HL are rare (approximately 1–2% of all HHIs) [11]. Y-linked genes have also been investigated but discovered genes give rise to isolated HL rather than associated with syndromes [24].

Alport syndrome is probably the most well-known one in this category and constitutes about 1% of individuals with severe to profound HL. Although different modes of inheritance occur, majority of cases (about 85%) show an XLR mode of inheritance (followed by AR 15% and AD 5%). The syndrome presents with SNHL (late-onset, progressive, high frequency), progressive nephropathy (starts with hematuria and leads to end stage renal disease) and ocular abnormalities (anterior lenticonus, macular flecks). The hematuria starts earlier than HL in first decade of life but is microscopic and might be missed. SNHL is present in almost 75% of patients at the age of 20 years. The onset of ocular signs is usually later in the second decade and third decade of life [24, 25].

Table 1 demonstrates summary of other syndromes in this category.

Mitochondrial

The proportion of HL caused by mutated mitochondrial DNA (mtDNA) is unknown and depending on different settings of study and populations has been reported between 0 and 2% [13, 26]. This includes both syndromic and non-syndromic HL, although most of identified mutated genes in mtDNA cause isolated HL. The reasons for such variety in estimation of prevalence are mainly because the subsequent HL usually develops at a later age (and is sometimes absent) and secondly that some of these syndromes are inherited in both mitochondrial and non-mitochondrial mode.

Systemic neuromuscular syndromes such as KSS (Kearns–Sayre syndrome), MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes), MERRF (myoclonic epilepsy and ragged red fibers), NARP (neuropathy, ataxia, and retinitis pigmentosa) and MIDD (maternally inherited diabetes and deafness) are some of the known causes of HL in this category. The HL part is mostly sensorineural and usually develops later in life and after onset of other clinical features [7, 27].

Non-syndromic hearing loss

Non-syndromic HL as aforementioned presents as a single trait and is always attributed to a single gene defect. As in syndromic HL, mutated genes could be inherited in various patterns, though AR inheritance is the most frequent mode. AD forms are generally postlingual while the AR ones usually result in prelingual HL. Most of the responsible genes encode essential proteins for the process of normal hearing and even though a mutation does not change the protein structure dramatically (either a missense mutation in an AD genes or carrier of a mutated AR gene), still it makes the person more vulnerable to develop HL in future [28, 29].

The loci and genes responsible for single trait HL have been given a standard nomenclature. DFNA stands for autosomal dominant, DFNB for autosomal recessive; DFN for X-linked and DFNM for modifiers of other genes [9].

In genetic databases, there are genes that cause both syndromic and non-syndromic HL or show both dominant and recessive inheritance pattern. The fact about these genes is that more than one identified locus and mutations in different loci will result in a HL that is inherited dominant, recessive or is associated with other clinical features [7].

Table 2 summarizes the mutated genes responsible for non-syndromic HL, their loci and function (more information is available at http://hereditaryhearingloss.org). Some of the frequent mutations within each pattern of inheritance are discussed below.

Autosomal dominant

Among AD genes, mutations in *WFS1*, *KCNQ4*, *COCH* and *GJB2* genes are more frequent [28].

WFS1 is one of the genes with multiple loci, that depending on locus or mutation type could result in different inheritance patterns or a syndromic HL (i.e. mutations in 4p16.1 causing Wolfram syndrome in contrast to mutations in 4p16.3 causing DFNA6/14/38) [30]. This gene encodes Wolframin, a trans-membrane protein, which is found in endoplasmic reticulum and is widely expressed in cochlea, brain, pancreas beta cells and heart [31]. Studies have suggested that it is active in calcium homeostasis and protein processing. Mutations that induce significant changes to Wolframin structure (nonsense or frame-shift) cause the Wolfram syndrome. More than 19 different *WFS1* mutations (insertion, deletion, polymorphism, etc.) have been identified in patients with DFNA6/14/38 globally. These patients develop a moderate to severe low-frequency SNHL in their second decade of life which is mostly bilateral and non-progressive [31].

KCNQ4 encodes a subunit of potassium channel in outer hair cells of cochlea. Its mutations have been located on locus 1p34 known as DFNA2 [32, 33]. In the same locus an allelic variant of *GJB3* gene is located which encodes connexin-31, a part of gap junctions that allow the direct cell-to-cell passage of molecules, metabolites and ions and

Table 2 Summary of non-syndromic causes of hearing loss, loci, genes, their mode of inheritance and protein/function

Inheritance	Locus	Chromosomal region	Gene	Function	Phenotype
Autosomal dominant	DFNA6/14	4p16.1	*WFS1*	Ion homeostasis; expressed in cochlea	Moderate to severe, prelingual, low-frequency hearing loss; tinnitus
	DFNA2	1p34	*KCNQ4*	Ion homeostasis/Voltage gated potassium channel	Moderate, postlingual, high-frequency hearing loss; progressive deafness; vertigo
	DFNA9	14q12-q13	*COCH*	Extracellular matrix protein	Moderate to profound, prelingual progressive high-frequency deafness; tinnitus; vertigo
	DFNA3	13q11-q12	*GJB2*	Ion homeostasis	Moderate to profound, prelingual deafness; high-frequency, progressive deafness
	DFNA48	12q13-q15	*MYO1A*	Unconventional myosin, motor protein	Moderate to severe, postlingual, progressive hearing loss
	DFNA8/12	11q22-q24	*TECTA*	Extracellular matrix protein	Severe, prelingual or postlingual U-shaped or high pitched hearing loss
	DFNA20/26	17q25.3	*ACTG1*	Forms cytoskeleton	Moderate, postlingual, progressive hearing loss; defective intracellular cytoskeletal proteins
	DFNA10	6q23	*EYA4*	Transcription factor	Moderate to severe, postlingual, progressive hearing loss
	DFNA4	19q13.33	*MYH14*	Expressed in the cochlea	Moderate to profound, fluctuating, progressive deafness
	DFNA22	6q13	*MYO6*	Unconventional myosin, motor protein	Moderate to profound, postlingual, progressive hearing loss because of hair-cell defect
	DFNA11	11q13.5	*MYO7A*	Unconventional myosin, motor protein, hair bundle	Moderate to severe, postlingual, progressive, high-frequency hearing loss
	DFNA5	7p15	*DFNA5*	Unknown function	Moderate to severe, postlingual, high-frequency hearing loss, progressive deafness
	DFNA2	1p35.1	*GJB3*	Ion homeostasis/Gap junction protein	Moderate to severe, postlingual, high-frequency hearing loss; progressive deafness; tinnitus
	DFNA15	5q31	*POU4F3*	Transcription factor	Moderate to severe, postlingual, progressive hearing loss by the fifth decade of life
	DFNA36	9q13-q21	*TMC1*	Transmembrane hair-cell protein	Moderate to profound, postlingual hearing loss; rapidly progressive deafness
	DFNA13	6p21.3	*COL11A2*	Extracellular matrix protein/collagen	Moderate to severe, postlingual, U-shaped hearing loss
	CRYM	16p13.11-p12.3	*CRYM*	Cytosolic thyroid hormone, binding protein	Moderate to severe prelingual deafness by the second decade of life
	DFNA28	8q22	*TFCP2L3*	Transcription Factor	Moderate to severe, postlingual, progressive hearing loss by the fifth decade of life
	DFNA3	13q12	*GJB6*	Ion homeostasis/Gap junction protein	Moderate to profound, prelingual hearing loss; high-frequency progressive deafness
	DFNA17	22q11.2	*MYH9*	Unconventional myosin, motor protein, hair bundles	Moderate to profound, postlingual hearing loss; progressive high-frequency deafness
	DFNA44	3q28	*CCDC50*	Cytoskeletal formation	
	DFNA1	5q31	*DIAPH1*	Actin polymerization, cytoskeletal formation	Moderate to profound, postlingual, low-frequency hearing loss; progressive deafness; hair-cell defect
Autosomal recessive	DFNB1	13q12	*GJB2*	Gap junction subunits, ion homeostasis	Profound, some moderate to severe. Prelingual, some newborns pass the screening
	DFNB4	7q31	*SLC26A4*	Ion homeostasis	Variable high-frequency hearing loss, frequently postlingual; enlarged vestibular aqueduct in 20% of postlingual hearing loss
	DFNB3	17p11.2	*MYO15A*	Unconventional myosin, motor protein	Profound, prelingual; hair-cell defect
	DFNB9	2p22-p23	*OTOF*	Expressed in: inner hair cells, spiral ganglion, and semicircular canals	Flat auditory brain-stem response; otoacoustic emissions acceptable; auditory neuropathy

Table 2 continued

Inheritance	Locus	Chromosomal region	Gene	Function	Phenotype
	DFNB12	10q21-q22	*CDH23*	Interacts with myosin 7A, hair-bundle adhesion protein	High-frequency hearing loss; profound with ATP2B2 modifier; hair-cell defect
	DFNB7/11	9q13-q21	*TMC1*	Makes protein Tmc1, expressed in inner and outer hair cells	Profound, prelingual hearing loss; hair-cell defect
	DFNB8/10	21q22	*TMPRSS3*	Expressed in: spiral ganglion, supporting cells, and stria vascularis	DFNB8: profound, prelingual expressed via stria vascularis DFNB10: moderate and progressive hearing loss, postlingual
	DFNB21	11q	*TECTA*	Extracellular membrane protein	Profound, postlingual, progressive with high U-shaped hearing loss
	DFNB28	22q13	*TRIOBP*	Actin-binding cytoskeletal formation protein, hair bundle	Profound prelingual hearing loss, hair-cell defect
	DFNB6	3p14-p21	*TMIE*	Transmembrane protein, required for maturation of hair cells	Profound, prelingual hearing loss; transmembrane protein
	DFNB59	2q31.1-q31.3	*PJVK*	Signaling of hair cells and neurons	
	DFNB36	1p36.3	*ESPN*	Actin-bundling	Profound, prelingual hearing loss; hair-cell defect and vertigo
	DFNB23	10p11.2-q21	*PCDH15*	Adhesion protein, hair bundle	Profound, prelingual hearing loss; hair-cell defect
	DFNB35	14q24.1-24.3	*ESRRB*	Transcription factor	
	DFNB2	11q13.5	*MYO7A*	Unconventional myosin, motor protein	Profound, prelingual hearing loss, with balance disorders in USH1B
	DFNB1	13q12	*GJB6*	Gap junction subunit, ion homeostasis	Profound, some moderate to severe, usually prelingual hearing loss; some pass newborn screening
	DFNB49	5q13.1	*TRIC*	Ion homeostasis	
	DFNB67	6p21.3	*TMHS*	Hair bundle, adhesion protein	
	DFNB16	15q21-q22	*STRC*	Extracellular matrix protein	Postlingual and stable, high-frequency hearing loss
	DFNB29	21q22	*CLDN14*	In tight junction at hair cells and supporting cells; ion homeostasis	Profound, prelingual hearing loss; hair-cell defect
	DFNB24	11q23	*RDX*	Hair bundle; cytoskeletal formation	
	DFNB37	6q13	*MYO6*	Unconventional myosin; motor protein	Profound, prelingual hearing loss; hair-cell defect, vertigo and possibly retinitis pigmentosum
	DFNB30	10p11.1	*MYO3A*	Unconventional myosin; motor protein	Profound, prelingual, progressive with high-frequency hearing loss; hair-cell defect
	DFNB61	7q22.1	*SLC26A5*	Motor protein of cochlear outer hair cells	
	DFNB31	9q32-q34	*WHRN*	Strengthens stereocilia tips	Prelingual hearing loss; hair-cell defect
	DFNB18	11p14-15.1	*USH1C*	Forms scaffolding proteins in cilia	Profound, prelingual hearing loss; hair-cell defect; mutation spliced out of retinal transcript
		1p35.1	*GJB3*	Gap junction; ion homeostasis	
	DFNB53	6p21.3	*COL11A2*	Extracellular matrix protein	
	DFNB22	16p12.2	*OTOA*	Extracellular matrix protein	Moderate, prelingual hearing loss; hair-cell defect
X-linked	DFN1	Xq21.3-22, AR	*DDP1*	TIMM8A protein, evolutionary conserved novel polypeptide	

Table 2 continued

Inheritance	Locus	Chromosomal region	Gene	Function	Phenotype
	DFN2	Xq21-q24, AR	Unknown	Unknown	Severe to profound hearing loss, variable onset and progression
	DFN3	Xq21.1, AR	*POU3F4*	Transcription factor	Congenital hearing loss; rapid progression
	DFN4	Xp21.2, AD	Unknown	Unknown	Severe to profound, congenital hearing loss
	DFN5	X	Unknown	Unknown	
	DFN6	Xp22, AR	Unknown	Unknown	Severe to profound hearing loss; onset during the first decade; progressive
Y-linked	DFNY1	Y	Unknown	Unknown	Mild to severe hearing loss, progressive
Mitochondrial	12S rRNA	Mitochondrial	*MT-RNR1*	RNA translation	
	tRNA	Mitochondrial	*MT-TS1*	RNA translation	

therefore mediate intercellular communication. DFNA2 patients present with postlingual, moderate to severe, high-frequency SNHL. Depending on which gene is mutated vertigo (*KCNQ4* mutations) or tinnitus (*GJB3* mutations) could be associated [28, 30].

Mutations in *TECTA* gene although it might not be as frequent as *WFS1* or *KCNQ4* (8 mapped mutations) but once mutated gives rise to a significant HL [34]. The gene encodes alpha-Tectorin, a major component of the tectorial membrane. Mutations are mostly affecting zona pellucida domain of alpha-Tectorin and result in progressive, moderate to severe, high-frequency SNHL which could present pre- or postlingually [30].

More details on AD non-syndromic HL genes are listed in Table 2.

Autosomal recessive

Although AR non-syndromic HL is more likely to be seen in societies with high rate of consanguineous marriages, nevertheless most frequent mutations causing non-syndromic HL occur in genes with AR pattern of inheritance [28].

GJB2 gene is the most frequent single gene defect leading to HL. It encodes Connexin 26, a gap junction subunit and highly expressed in cochlea (important for potassium recycling into stria vascularis during mechanosensory transduction of sound). Mutations of *GJB2*, which is responsible for DFNB1 and DFNA3, are the most frequent single cause of isolated HHL. 35delG consists more than 55% of the identified mutations. *GJB6* (encodes Connexin 30) is also located in DFNB1 and shares the same clinical presentation. These patients develop a non-progressive, severe to profound bilateral SNHL (with a down-sloping or flat audiometry) early in life (mostly prelingual) [6, 30] with intact vestibular function [35].

SLC26A4 encodes for Pendrin (a trans-membrane chloride/iodide pump) and maintains the homeostasis of endolymph. More than 40 *SLC26A4* mutations have been mapped in patients with DFNB4 and Pendred syndrome. Clinical presentation of DFNB4 include prelingual, bilateral, high-frequency SNHL and in 20% of patients an enlarged vestibular aqueduct (which makes it difficult to distinguish from Pendred syndrome) [28, 36].

Other identified AR inherited mutated genes are listed in Table 2.

X-linked and mitochondrial

Non-syndromic HL due to single X-linked or mitochondrial gene defects is rare but important because of their distinctive inheritance pattern.

In almost 50% of all pedigrees with X-linked non-syndromic HL, mutations in DFN3 locus are found. This locus contains *POU3F4* gene that encodes a transcription factor [24]. This is the same gene accountable for Gusher syndrome (Table 1). The affected males mostly present with a progressive moderate to severe mixed HL usually in their first decade of life. Furthermore, DFN3 is the only X-linked inherited HL that could be associated with different anomalies of temporal bone or cochlea (i.e. pseudo-Mondini dysplasia). Vestibular problems distinguish Gusher from DFN3 [24, 30].

Mutations of mtDNA mostly cause a broad spectrum of maternally inherited abnormalities. However, some of the mutations in mitochondrial genes manifest as a non-syndromic HL, which is generally a progressive bilateral SNHL [37]. Mutations of mitochondrial genes have also been proposed to be responsible for aminoglycoside-induced SNHL and presbyacusis. Several studies have identified higher incidence of such mutations in affected patients [38, 39].

Mutations of *MT-RNR1* and *MT-TS1* genes [encode for 12S-ribosomal RNA and tRNA(Ser), respectively] have been identified to cause maternally inherited SNHL with

unknown mechanisms. Almost all mutations of 12S-sRNA and few mutations of tRNAs increase susceptibility to aminoglycoside-induced SNHL [38–40].

More information on X-linked and mitochondrial causes of non-syndromic HL are demonstrated in Table 2.

Functional approach to hereditary hearing loss

Analysis of families and pedigrees with HL has led us to the discovery of the underlying mutated genes and their impaired functions. Our evolving knowledge of genetics during recent decades has markedly enabled us to understand the role of different proteins in process of normal hearing and their functions.

The genes involved in the process of hearing have additionally been classified based on their functions. The five major categories include hair bundle morphogenesis, ion homeostasis, extracellular matrix composition, transcription factors, and mitochondrial. However, there are still some genes with unknown functions [41]. Functions and/or products of relevant genes are stated in Tables 1 and 2.

The extent of alteration in gene function is determined by multiple factors such as type of the mutation (point mutations, insertions, deletions, etc.), location of the mutation inside the gene (exon or intron) and number of defective alleles. Interestingly, these factors could result in contrary outcomes. For instance, intronic mutations affecting splicing sites have been found to cause BOR syndrome [42], while another intronic mutation has been found to actually preserve hearing in Jervell and Lange-Nielsen syndrome by incomplete skipping of an exon in defective *KCNQ1* [43].

Simultaneous heterozygous recessive mutations have also been recognized to cause HL by partial alteration of multiple genes. It has been reported that 10–50% of cases of DFNB1 due to mutation in *GJB2* (which encodes connexin 26) have only one mutant allele. Studies have found simultaneous heterozygous mutations in *GJB6* (which encodes connexin 30) and have suggested a possible digenic AR inheritance [44]. Digenic inheritance is not always limited to genes within the same locus. An interesting example is the study that reported a pedigree where with maternal transmission of SNHL was observed with reduced penetrance and further segregation analysis revealed a two-locus mitochondrial and autosomal recessive gene model of transmission [45].

Diagnostic methods and screening

It is estimated that each year 24,000 infants are born with HL just in the United States while only 400 infants are diagnosed with PKU at birth and yet the necessity of screening tests for HHI have not been recognized universally [11].

Currently, some laboratories offer commercially available screening or diagnostic genetic tests and some provide audioprofiling tests to predict an underlying genetic basis. For instance, Laboratory for Molecular Medicine of Partners Healthcare Center for Personalized Genetic Medicine (PCPGM) offers physicians access to 33 genetic diagnostic and screening tests for hearing loss [46] or University of Iowa that have developed a software, AudioGene, to predict AD non-syndromic HL [47].

Understanding a patient's genetic basis for hearing loss not only solidifies a diagnosis but also allows the physician to tailor treatments and therapies towards a particular HL genotype for better patient outcomes. The decision for a physician to provide genetic screening, diagnostic, or preconception genetic tests for a patient is often a complicated and it is an emotional decision for the patient and their family. A physician should only offer a patient a genetic test to determine their molecular basis of HL after a thorough history, physical, and proper audiology testing has been performed. This allows the physician to order further tests (genetic, imaging, etc.) according to the patient's specific presentation and family history [12, 48]. A recent study regarding the steps in diagnosis of HL found that different modalities of diagnosis and screening might be more or less informative depending on the patient's ethnicity. For example, it was shown that Asian patients had a higher yield with genetic testing than imaging studies due to the high prevalence of *GJB2* mutation in this ethnic group [49].

Physicians can also order genetic panels for known patterns of gene deletions based on patients presenting with syndromic HL. In addition, patients who present with HL that might be attributed to certain families or ethnic-specific patterns of HL (i.e. Ashkenazi Jewish or French Canadian) could be tested with specific panels for HL based on common HL genes affecting their ethnicity [49].

A previous algorithm for genetic testing using single gene studies of patients with non-syndromic bilateral SNHL has been previously published [50]. The first test ordered in this algorithm involves the gene *GJB2* because as aforementioned it is the most common cause of non-syndromic HL, and responsible for up to half of AR non-syndromic HL. If only one mutation is found, a test looking for the *GJB6* deletion would be a logical next step. Residing directly adjacent to the GJB2 gene, the *GJB6* gene is located in a region that is known to be deleted in many patients with a single *GJB2* mutation. If these tests are negative, any other tests that are available for AR non-syndromic HL should be chosen at the physician's discretion.

Table 3 A summary of currently available genetic tests to aid in diagnosis and treating hearing loss

Class of hearing loss	Name of individual or collection of test(s)	Gene(s) tested	Analytical accuracy
Non-syndromic hearing loss	OtoChip	*DH23, CLRN1, GJB2* (excludes 35delG), *GJB6, GPR98* (exons 8, 20, 31–41 and 89), *MYO6, MYO7A, OTOF, PCDH15, SLC26A4 (PDS),TMC1, TMIE, TMPRSS3, MTTS* [tRNAser(UCN)], *USH1C, USH1G, USH2A, DFNB31* genes and genotyping of mutations 961delT, 961T>C, 961T>G, 1095T>C, 1494T>C, 1555A>G in MTRNR1 (12S rRNA)	97% sensitive for detecting substitution variants
	Connexin test	*GJB2; GJB6*	99.9% accurate in detecting mutations in the *GJB2* sequence analyzed
	Mitochondrial gene panel	Bi-directional DNA sequencing of entire *MTTS1* gene and bases 951–1611 of *MTRNR1* gene	99.9% accurate in detecting mutations in the sequence analyzed
Syndromic hearing loss	Pendred syndrome test	*SLC26A4* gene	In patients with SNHL and DFNB4, 1 or 2 mutations in *SLC26A4* are detected in 37% (26/70) of sporadic cases and 89% (16/18) of cases with a family history (i.e. two or more affected siblings)
	Usher syndrome (individual tests); also see OtoChip test	*MYO7A, USH1C, CDH23, PCDH15, USH1G, USH2A, GPR98 (VLGR1), DFNB31 (WHRN)*, and *CLRN1* genes	Mutations in *MYO7A, USH1C, CDH23, PCDH15* and *SANS* account for approximately 39–55, 6–7, 19–35, 10–20 and 7% of cases with a clinical diagnosis of Usher syndrome type I, respectively. Mutations in U*SH2A, GPR98* (*VLGR1*), and *DFNB31* (*WHRN*) account for approximately 80, 15 and 5% of cases with a clinical diagnosis of Usher syndrome type II, respectively. Only mutations in the *CLRN1* (*USH3A*) gene are known to be causative for Usher syndrome type 3
	Brachio-oto-renal syndrome (individual tests: *EYA1* gene sequencing; *EYA1* Deletion/ Duplication)	Bi-directional sequence analysis of 17 exons and their splice sites in the *EYA1* gene. Testing includes a non-coding exon, exon 01. If mutations are not identified by sequencing, MLPA analysis is available to detect large deletions of the gene.	Combined, these assays will detect ~40% of mutations in patients with BOR syndrome
Auditory neuropathy/ dys-synchrony	Auditory neuropathy panel	*OTOF; DFNB59*	This assay is greater than 99.9% accurate in detecting point mutations in the sequence analyzed. This test does not detect large deletions or mutations in non-coding regions that could potentially affect the expression of the *OTOF* or *DFNB59* genes
X-linked hearing loss	*POU3F4* gene test for X-linked non-syndromic hearing loss	*POU3F4*	99.9% accurate in detecting point mutations in the sequence analyzed
Autosomal dominant hearing loss	*COCH* gene test for progressive hearing loss	*COCH* (DFNA9 locus)	99.9% accurate in detecting point mutations in the sequence analyzed
	GJB2 (Connexin 26) gene test for autosomal dominant and syndromic hearing loss	*GJB2*	99.9% accurate in detecting mutations in the sequence analyzed

Table 3 continued

Class of hearing loss	Name of individual or collection of test(s)	Gene(s) tested	Analytical accuracy
Ethnicity associated hearing loss	Ashkenazi Jewish panel for hearing loss and Usher syndrome	*GJB2; GJB6; PCDH15; CLRN1*	99.9% accurate in detecting variants in the sequence analyzed; this assay detects a pathogenic variant in approximately 7% of individuals of Ashkenazi Jewish decent
	Acadian/French Canadian Usher Panel	216G>A in *USH1C*; 4338_4339delCT in *USH2A*	99.9% accurate in detecting mutations in the sequence analyzed
	Finnish common mutation for Usher syndrome	Tyr176X in *CLRN1*	99.9% accurate in detecting mutations in the sequence analyzed

Audioprofiling is a novel tool for detection of defective genes in small families with HL. Based on frequencies and hearing thresholds, audioprofiling enables categorizing of phenotypic data (in our case audiograms) and establishing genotypic correlations [51]. AudioGene is a commercially available machine-based audioprofiling system that analyzes audiograms of small families with ADHL to predict the most probable defective genes and loci for mutation screening. However, it is only available for AD patterns of HL [47, 52]. Although methods to predict mutated genes in AR pattern of HL have been introduced [51], they are not commercially available yet.

A summary of currently available genetic tests to aid in diagnosis and treating HL is displayed in Table 3.

Conclusion

HHI gene databases are growing and our knowledge of HHIs is still developing. Recent studies have revealed a better understanding of the involved genes in the process of normal hearing and their common mutations, functions and pathophysiological mechanisms. Future studies should focus on diagnostic and screening methods or possible gene therapies. Although several molecular and cellular therapies have been developed [53], until now they are mostly experimental and in their beginning steps. Therefore, the final goal of such studies should be to direct physicians and researchers toward effective screening and diagnostic tests and ultimately applicable molecular and cell therapies.

Conflict of interest None.

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