Chapter

Genetics and Acquired Hearing Loss

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Abstract

Hearing loss (HL) is a worldwide disease with substantial economic costs for the public health. Around 466 million people have disabling hearing loss and the WHO estimated that by 2050 over 900 million people will suffer hearing loss. Several factors including infections, noise-exposure, ototoxic medications or genetic disorders could cause hearing impairment. Hearing devices such as cochlear implants and aids are the current therapies. Although the prevalence of hearing loss is very high, alternative treatments as pharmaceutical agents are currently insufficient. Within the past years, increased knowledge on hearing loss etiology and physiopathology opened new opportunities for future research towards hearing loss treatment. Here we aim to review current bibliography on genetics factors involved in hearing loss.

Keywords: hearing loss, genetics, syndromic, non-syndromic, age-related

1. Introduction

The World Health Organization (WHO) defines hearing loss (HL) as the inability to perceive the sounds with different grades of impairment, from slight to profound including deafness [1].

Sound waves move from outer (or external) to middle and then to the inner ear, three anatomically distinct structures of the ear which transmit the sound to a signal into the brain. The sound waves travel down the cannel of the outer and middle ear until hitting the tympanic membrane. Vibrations from the middle ear create movement of the fluid in the inner ear. This movement of the fluid is transmitted through the tectorial membrane to the hair cells in the organ of Corti, then the stimulus is transmitted by electric signals up to the auditory nerve to the brain. The brain interprets the electrical signals as sound. **Figure 1** shows the different compartment of the ear as described above.

Depending on the compartment affected, hearing loss could be classified as *conductive* or *sensorineural*. Conductive hearing loss is when the outer and middle ear are affected, and it results in the inability to transmit sound waves to the inner ear [3]. On the other hand, impairments in the inner ear are known as sensorineural [4]. Conductive hearing loss could be treated by medication, surgery cochlear implants or hearing aids, meanwhile sensorineural is mostly irreversible because of the complexity of the structure, the limited regeneration and access to the sensory structures in the cochlea [5].

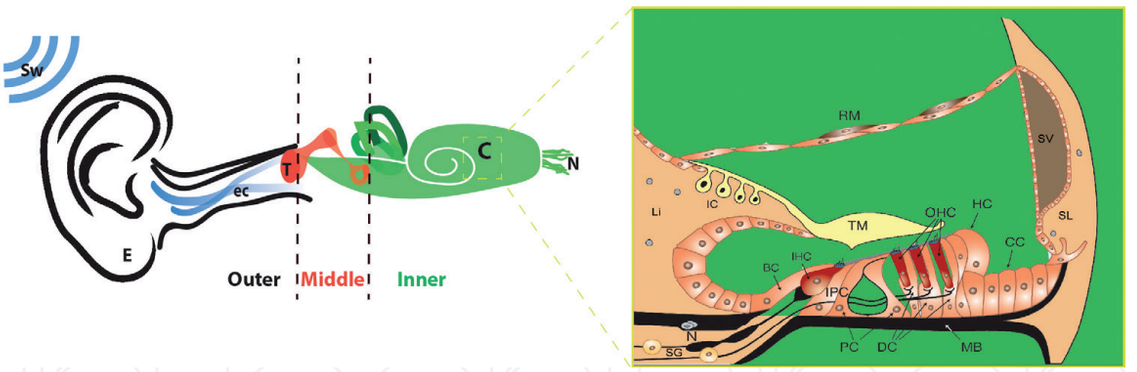

Figure 1.
Scheme of hearing system from external ear to inner ear. Path of the sound waves (in blue) through outer, middle and inner ear is represented where Sw, sound waves; E, external ear; ec, ear canal; T, tympanic membrane; C, cochlea; N, auditory nerve. Magnification of the cochlea structures (adapted from Sanchez-Calderon et al. [2]) is shown framed in yellow where BC, border cells; CC, Claudius's cells; DC, Deiter's cells; HC, Hensen's cells; IC, intermediate cells; IHC, inner hair cells; IPC, inner phalangeal cells; Li, spiral limbus; N, cochlear neurons; MB, Basilar Membrane; OHC, outer hair cells; PC, pillar cells; RM, Reisner's membrane; SG, spiral ganglion; SL, spiral ligament; SV, stria vascularis and TM, tectorial membrane.

2. Hearing loss etiology

There are several causes of hearing loss affecting over 500 million people worldwide [6]. Approximately 50% of the hearing impairment has a genetic etiology, the remaining cases are attributed to external factor such as noise or injury (acquired/spontaneous). In addition, the contribution of both (genetic predisposition and environment) is very common as found in age-related hearing loss [7, 8].

Inherited hearing loss can be autosomal recessive or dominant, X-linked or mitochondrial-related. The autosomal recessive hearing loss is caused by pathogenic variant in both alleles (the child inherits them from both parents). Autosomal dominant inheritance occurs when variants in one single allele are able to cause hearing loss. Independent of the inheritance pattern, genetics of hearing loss are classified as syndromic when they are associated with pathologies in other organs or malformations of the external ear and non-syndromic [6]. Approximately 30% of hearing loss are syndromic whereas the 70% remaining are non-syndromic [9]. Each type of hearing loss (syndromic and non-syndromic) is further classified according to the mode of inheritance into autosomal recessive, autosomal dominant, X-linked and mitochondrial hearing loss.

2.1 Syndromic hearing loss

Syndromic hearing loss (SHL) is a form of hearing impairments in which it is associated with other diseases or symptoms. Most commonly SHL is associated with diseases that affect eyes, nervous system and skin. SHL accounts for 30% of hereditary hearing loss and can be inherited in an autosomal recessive, dominant and X-linked patterns. Moreover, several genes described in SHL are also causing non-syndromic hearing loss (NSHL) such as mutations in CDH23 gene causing either Usher syndrome type 1D and autosomal recessive NSHL (DFNB12) (OMIM: 605516) [10].

2.1.1 Autosomal dominant SHL

Waardenburg syndrome (WS) is first described in 1951 by Waardenburg. It is one of the most common congenital, sensorineural SHL [11]. Clinical symptoms include lateral displacement of the inner canthus of the eye (dystopia canthorum),

pigmentations of the hair, eye and skin. It is estimated that WS is accounting for 2–5% of congenital hearing loss cases. According to the presence or absence of the clinical symptoms, Waardenburg syndrome is divided into four subtypes: WS1, WS2, WS3 and WS4. Patients with WS1, usually has dystopia canthorum, while patient with WS2 are not. WS3 also called Klein-Waardenburg syndrome characterized by dystopia canthorum and upper limb abnormalities. The last type WS4 also called Waardenburg-Shah syndrome is associated with Hirschsprung disease. Patients with WS4 are suffering from blockage of the large intestine and neurological defects. According to the hereditary hearing loss homepage, six genes are associated with WS (**Table 1**) [12]. These genes are essential for the development of melanocytes and have a major role in the function of the inner ear.

Branchio-Oto-Renal Syndrome (BOR) is the second common autosomal dominant congenital SHL. It is characterized by malformations in the ears and is associated with different types of hearing loss: conductive, sensorineural and mixed hearing loss. Moreover, BOR syndrome is affecting kidneys structure and functions which results in renal abnormalities [13]. The frequency of BOR syndrome is estimated to be 1 in 40,000 individuals. Mutations in Eyes Absent homolog 1 (*EYA1*), Sine Oculis Homebox 5 (*SIX5*) and Sine Oculis Homebox 1 (*SIX1*) genes are found to be associated with BOR syndrome (**Table 1**). These genes are required for normal embryonic development of different organs including both the kidneys and the ears.

Syndrome	Gene	OMIM entry	Inheritance
Alport syndrome	*COL4A3*	120070	AR
	COL4A4	120131	AR
	COL4A5	303630	XL
Branchio-Oto-Renal syndrome	*EYA1*	601653	AD
	SIX5	600963	AD
	SIX1	601205	AD
CHARGE syndrome	*CHD7*	608892	AD
	SEMA3E	608166	AD
Jervell and Lange-Nielsen syndrome	*KNCQ1*	607542	AR
	KCNE1	176261	AR
Norrie disease	*NDP*	300658	XL
Pendred syndrome	*SLC26A4*	605646	AR
	KCNJ10	602208	AR
	FOX11	601093	AR
Perrault syndrome	*HSD17B4*	601860	AR
	HARS2	600783	AR
	CLPP	601119	AR
	LARS2	604544	AR
	TWNK	606075	AR
	ERAL1	607435	AR
Stickler syndrome	*COL2A1*	120140	AD
	COL11A1	120280	AD
	COL11A2	120290	AD
	COL9A1	120210	AR
	COL9A2	120260	AR

Syndrome	Gene	OMIM entry	Inheritance
Treacher Collins syndrome	*TCOF1*	606847	AD
	POLR1D	613715	AD
	POLR1C	610060	AD
Usher syndrome	*MYO7A*	276903	AD
	USH1C	605242	AR
	CDH23	605516	AR
	PCDH15	605514	AR
	SANS	607696	AR
	USH2A	608400	AR
	ADGRV1	602851	AR
	WHRN	607928	AR
	CLRN1	606397	AR
	HARS	142810	AR
Waardenburg syndrome	*PAX3*	606597	AD
	MITF	156845	AD
	SNAI2	602150	AD
	SOX10	602229	AD
	PAX3	606597	AD
	EDNRB	131244	AR
	EDN3	131242	AR
	SOX10	602229	AR

Table 1.
List of syndromic hearing loss and its associated genes [12].

CHARGE syndrome is another form of autosomal dominant hearing loss syndrome that affects several organs. Patients with CHARGE syndrome are characterized by different phenotypes, from which the name of the syndrome comes from, this includes: Coloboma, Heart defects, Atresia choanae, growth Retardation, Genital abnormalities and Ear abnormalities. The degree of abnormalities varies from one patient to another. It ranges from very severe and vital cases to minor phenotypes. The prevalence of CHARGE syndrome estimated to be 1 in 8500 to 10,000 newborns worldwide. Chromodomain helicase DNA-binding protein-7 (*CHD7*) is found to be the common cause of CHARGE syndrome. *CHD7* is a transcription factor protein that regulates chromatin [14].

2.1.2 Autosomal recessive SHL

Usher syndrome is an autosomal recessive sensorineural hearing loss (SNHL) with retinitis [15]. According to the clinical phenotype, Usher syndrome is classified to three main types: Usher 1 (USH1), Usher 2 (USH2) and Usher 3 (USH3). USH1 is characterized by severe to profound SNHL, severe vestibular impairments and early onset retinitis pigmentosa. Mutations in several genes are found to be the cause of USH1 syndrome (**Table 1**). The most common genes causing USH1 are *MYO7A* and *CHD23*. Both genes are important for the development and function of inner ear hair cells. Patients with USH2 are found to suffer from moderate to severe SNHL with mid onset retinitis pigmentosa and no vestibular impairment. Usherin (*USH2A*) and Adhesion-G protein coupled receptor VI (*ADGRVI*) are found to be

mutated in patients diagnosed with USH2. The last type is USH3 that is characterized by variable phenotypes of progressive hearing loss, vestibular impairment and late onset retinitis pigmentosa. The prevalence of Usher syndrome is estimated to be 1 in 6000 to 10,000 with USH1 and USH2 being the most common types.

The second common autosomal recessive SHL is *Pendred Syndrome* which is characterized by hearing loss and thyroid enlargement [16]. The hearing loss ranges from severe to profound are usually developed at early childhood [17]. A characteristic feature of Pendred syndrome is the Mondini malformation which is a combination of enlarged vestibular aqueduct and abnormal shape of the cochlea. The prevalence of Pendred syndrome is ranged from 1 to 7.5 per 100,000 newborns. Three genes are found to be mutated in patients with Pendred syndrome: *SLC26A4* which encodes for sodium-independent transporter of chloride iodide protein called Pendrin [18], *FOXI1* [19] and *KCNJ10* [20]. Approximately 50% of Pendred syndrome patients had mutations in *SLC26A4* gene, whereas the other two genes mutated in Pendred syndrome patients account for less than 2% of the cases are).

Jervell and Lange-Nielsen Syndrome is the third common autosomal recessive syndromic hearing loss. This condition is characterized by profound hearing loss with arrhythmia and long QT interval in the electrocardiogram that may result in heart failure and sudden death [21]. The prevalence of this syndrome is estimated to affect 1.6–6 per million people worldwide [22]. Genes found to be mutated in patients with this syndrome are potassium channel voltage-gated KQT-like subfamily member 1 (*KCNQ1*) [23] and potassium channel voltage-gated ISK-related subfamily member 1 (*KCNE1*) [24] with majority of the mutations (90%) occurs in *KCNQ1*. These channels are important for the movement of the potassium ions in order to maintain the normal function of the inner ear and cardiac muscle.

2.1.3 X-linked SHL

Hearing loss conditions inherited with an X-linked pattern are rare. Only few syndromes with few patients were reported. Norrie disease and Mohr-Tranebjaerg syndrome are examples of X-Linked SHL.

Norrie disease is a rare X-linked recessive disorder characterized by progressive visual impairment. One-third of males with Norrie disease will develop progressive hearing loss and other phenotype-like intellectual disabilities. Mutation in *NDP* gene is the cause of 95% of the affected individuals. *NDP* is a gene that encodes Norrin protein which regulates vascularization of the retina [25].

Mohr-Tranebjaerg syndrome also called deafness dystonia optic atrophy syndrome is another X-linked recessive syndrome that is associated with early onset hearing loss, movement disability and visual impairment. Less than 70 cases of this syndrome were reported worldwide. *TIMM8A* is the causative gene for this syndrome which encodes the Translocase of Inner Mitochondrial Membrane 8 homolog A protein. This protein is important for the development of nervous system [26].

2.1.4 Mitochondrial-linked SHL

Maternally inherited diabetes and deafness (MIDD) is a mitochondrial disorder causing a syndromic form of diabetes accompanied by sensorineural hearing loss and some cases include renal problems, pigmentary retinopathy, ptosis, myopathy, cardiomyopathy and/or neuro-psychiatric symptoms (OMIM: 520000) [27, 28]. Mutations in MT-TL1, MT-TK or MT-TE mitochondrial genes coding for mtRNAs, which participate in the protein production in mitochondria and impair their functioning had been linked in MIDD [29].

2.2 Non-syndromic hearing loss

Hearing loss which is not associated with any other disease or symptoms is called non-syndromic hearing loss (NSHL). It accounts for more than 70% of hereditary hearing loss. According to the hereditary hearing loss homepage, there are more than 100 genes associated with NSHL and more than 6000 causative variants are identified so far which makes it extremely heterogeneous [30].

According to the mode of inheritance, NSHL can be classified as autosomal recessive (75–85%), autosomal dominant (20–25%) and X-linked or mitochondrial (1–2%). The loci responsible for NSHL are named DEN which stands for Deafness. Letter "A" is added, if the mode of inheritance is autosomal dominant (DFNA), "B" if the inheritance is recessive (DFNB) and "X" if the inheritance is X-linked (DFNX). The numbers indicate the chronological order of gene discovery.

2.2.1 Autosomal dominant NSHL genes (DFNA)

Autosomal dominant forms account for 20–25% of NSHL and are characterized by post-lingual progressive hearing loss [31]. More than 40 genes are associated with autosomal dominant NSHL. *DIAPH1* gene which is located in the DFNA1 locus is one of the first loci described for autosomal dominant NSHL. It encodes protein that is important for polymerization with actin which plays major role in cytoskeletal of hair cells in the inner ear. Mutations in *DIAPH1* are associated with early onset progressive hearing loss and some patients may have mild thrombocytopenia without bleeding tendencies [32].

WFS1 encodes for Wolframin protein which plays role in regulating cellular Ca_2^+ homeostasis and is involved in the process of sensory perception of sound. Mutations in *WFS1* are found to be associated with DFNA6, DFNA14 and DFNA38 in which they are characterized by hearing loss in low frequency [33, 34]. Some missense mutations in this gene are also associated with congenital profound hearing loss, progressive optic atrophy and diabetes. The above-mentioned phenotypes are a form of autosomal recessive hearing loss condition known as Wolfram syndrome [35].

The *TECTA* gene that encodes the tectorin-alpha protein forms the tectorial membrane in the cochlea and the otolithic membrane in the vestibular system. Mutations in *TECTA* are found in families with DFNA8/12 in which hearing loss could be pre- or post-lingual [36]. The severity of hearing loss varies depending on the domain where the mutation occurs. Some mutations in *TECTA* are also associated with DFNB21 hearing loss in which hearing loss is prelingual with severe to profound phenotype [37].

Deafness autosomal dominant 5 (*DFNA5*) gene that encodes for the Gasdermin-E protein is another gene associated with autosomal dominant non-syndromic hearing loss [38]. Gasdermin-E plays essential role in cellular response to DNA damage by regulating TP53.

Other genes associated with autosomal dominant hearing loss are listed in **Table 2**.

2.2.2 Autosomal recessive NSHL

Autosomal recessive hearing loss account for majority (75–85%) forms of non-syndromic hearing loss in which the hearing loss is prelingual and severe to profound. The most common gene causing autosomal recessive NSHL is *GJB2* accounts for 50% of the cases. The other 50% of the autosomal recessive NSHL resulted from mutations in 70 genes (**Table 2**).

Gene	Locus	OMIM entry	Inheritance
ACTG1	DFNA20/26	102560	AD
ADCY1	DFNB44	103072	AR
AIFM1	DFNX5	300169	XL
BDP1	DFNB49	607012	AR
BSND	DFNB73	606412	AR
CABP2	DFNB93	607314	AR
CCDC50	DFNA44	611051	AD
CD164	DFNA66	603356	AD
CDC14A	DFNB32/105	601728	AR
CDH23	DFNB12	605516	AR
CEACAM16	DFNA4B	614591	AD
CIB2	DFNB48	605564	AR
CLDN14	DFNB29	605608	AR
CLIC5	DFNB103	607293	AR
COCH	DFNA9	603196	AD
COL11A1	DFNA37	120280	AD
COL11A2	DFNB53, DFNA13	120290	AR, AD
COL4A6	DFNX6	303631	XL
CRYM	DFNA40	123740	AD
DCDC2	DFNB66	605755	AR
DIAPH1	DFNA1	602121	AD
DMXL2		612186	AD
ELMOD3	DFNB88	615427	AR
EPS8	DFNB102	600206	AR
EPS8L2	DFNB106	614988	AR
ESPN	DFNB36	606351	AR
ESRP1		609245	AR
ESRRB	DFNB35	602167	AR
EYA4	DFNA10	603550	AD
FAM65B	DFNB104	611410	AR
GIPC3	DFNB15/72/95	608792	AR
GJB2	DFNB1A, DFNA3A	121011	AR, AD
GJB3	DFNA2B	603324	AD
GJB6	DFNB1B, DFNA3B	604418	AR, AD
GPSM2	DFNB82	609245	AR
GRHL2	DFNA28	608576	AD
GRXCR1	DFNB25	613283	AR
GRXCR2	DFNB101	615762	AR
GSDME/DFNA5	DFNA5	608798	AD
HGF	DFNB39	142409	AR
HOMER2	DFNA68	604799	AD
IFNLR1	DFNA2C	607404	AD
ILDR1	DFNB42	609739	AR

Gene	Locus	OMIM entry	Inheritance
KARS	DFNB89	601421	AR
KCNQ4	DFNA2A	603537	AD
KITLG	DFNA69	184745	AD
LHFPL5	DFNB66/67	609427	AR
LMX1A	DFNA7	600298	AD
LOXHD1	DFNB77	613072	AR
LRTOMT/COMT2	DFNB63	612414	AR
MARVELD2	DFNB49	610572	AR
MCM2	DFNA70	116945	AD
MET	DFNB97	164860	AR
MIRN96	DFNA50	611606	AD
MPZL2		604873	AR
MSRB3	DFNB74	613719	AR
MTRNR1		561000	MIT
MTTS1		590080	MIT
MYH14	DFNA4A	608568	AD
MYH9	DFNA17	160775	AD
MYO15A	DFNB3	602666	AR
MYO3A	DFNB30	606808	AR, AD
MYO6	DFNB37, DFNA22	600970	AR, AD
MYO7A	DFNB2, DFNA11	276903	AR, AD
NARS2	DFNB94	612803	AR
NLRP3	DFNA34	606416	AD
OSBPL2	DFNA67	606731	AD
OTOA	DFNB22	607038	AR
OTOF	DFNB9	603681	AR
OTOG	DFNB18B	604487	AR
OTOGL	DFNB84	614925	AR
P2RX2	DFNA41	600844	AD
PCDH15	DFNB23	605514	AR
PDE1C		602987	AD
PDZD7	DFNB57	612971	AR
PJVK	DFNB59	610219	AR
PNPT1	DFNB70	610316	AR
POU3F4	DFNX2	300039	XL
POU4F3	DFNA15	602460	AD
PPIP5K2	DFNB100	611648	AR
PRPS1	DFNX1	311850	XL
PTPRQ	DFNB84, DFNA73	603317	AR, AD
RDX	DFNB24	179410	AR
REST	DFNA27	600571	AD
ROR1	DFNB108	612959	AR
S1PR2	DFNB68	609427	AR
SERPINB6	DFNB91	173321	AR

Gene	Locus	OMIM entry	Inheritance
SIX1	DFNA23	601205	AD
SLC17A8	DFNA25	607557	AD
SLC22A4	DFNB60	604943	AR
SLC26A4	DFNB4	605646	AR
SLC26A5	DFNB61	604943	AR
SMAC/DIABLO	DFNA64	605219	AD
SMPX	DFNX4	300226	XL
STRC	DFNB16	606440	AR
SYNE4	DFNB76	615535	AR
TBC1D24	DFNB86, DFNA65	613577	AR, AD
TECTA	DFNB21, DFNA8/12	602574	AR, AD
TJP2	DFNA51	607709	AD
TMC1	DFNB7/11, DFNA36	606706	AR, AD
TMEM132E	DFNB99	616178	AR
TMIE	DFNB6	607237	AR
TMPRSS3	DFNB8/10	605511	AR
TNC	DFNA56	187380	AD
TPRN	DFNB79	613354	AR
TRIOBP	DFNB28	609761	AR
TSPEAR	DFNB98	612920	AR
Unknown	DFNY1	400043	YL
USH1C	DFNB18	605242	AR
WBP2		606962	AR
WFS1	DFNA6/14/38	606201	AD
WHRN	DFNB31	607928	AR

Table 2.
List of genes associated with autosomal dominant (AD), autosomal recessive (AR), X-linked (XL) and mitochondrial (MIT) non-syndromic hearing loss (NSHL) [12].

GJB2 gene is one of the gap junction proteins that are expressed in the inner ear, which encodes connexin 26. This protein allows the exchange of potassium ions between the cells in the inner ear. More than 100 mutations identified in *GJB2* were found to cause DFNB1 and DFNA3 [39].

Other gene related to *GJB2* is *GJB6* that encodes for connexin 30 protein. Studies show that both genes can be inherited together and 8% of patients with *GJB2* mutation also carry mutation in *GJB6* [40].

OTOF gene encodes otoferlin protein that is responsible for the neural transmission at the synaptic cleft of the inner hair cell. Mutations in this gene cause prelingual, profound autosomal recessive hearing loss (DFNB9) and will result in damage of the neural receptors of the inner ear that will result on interruption of the nerve pathways to the brain [41].

Conventional and unconventional myosins are group of genes that are functioning as actin-binding proteins. Conventional myosins regulate contractility of actin filaments, while unconventional myosins are essential for vesicle trafficking and endocytosis [42]. Mutations in some unconventional myosins are associated with NSHL. *MYO6* is an example of unconventional myosins that is expressed in the

inner hair cell of the cochlea. Mutation in *MYO6* causes DFNB37, a form of non-syndromic deafness characterized by prelingual severe to profound hearing loss [43]. Other genes are listed in **Table 2**.

2.2.3 X-linked NSHL

This form of hearing loss is very rare and only few genes are associated with non-syndromic hearing loss (**Table 2**). This form of hearing loss is characterized by progressive, conductive and sensorineural hearing loss. Mutations in *POU3F4* gene which cause DFNX2, account for 50% of the cases [44]. *POU3F4* gene encode for POU domain class 3 transcription factor 4 protein, which regulates the proliferation of neural cells in middle and inner ear early during development. Because this form of hearing loss is X-linked, the severity of hearing loss differs from male to female. In males, hearing loss is prelingual and range from severe to profound while in females hearing loss is post-lingual and less severe.

2.2.4 Mitochondrial-linked NSHL

Despite the crucial role of mitochondria producing the energy for the cell, there are mtDNA mutations which lead to non-syndromic hearing impairment. The carriers exhibited sensorineural hearing loss with variable severity and onset [45]. These mutations have been reported in the mitochondrial genes encoding for 12S rRNA and tRNA genes [46, 47].

2.3 Age-related hearing loss

The auditory system exhibits senescent changes with the past time which could trigger to acquire sensorineural hearing loss. The most of acquired-hearing loss are characterized by a bilateral inner ear degeneration determined by genetic factors superimposed with environmental stress [48], excluding injuries and severe infections. Noise, drugs, aging and/or other systemic conditions (i.e., diabetes or hypertension [49, 50]) are numerous variables that can contribute to the final outcome of the disease [51, 52]. It is habitual among the causes of life related hearing loss that the severity progress beginning as mild loss and worsening over time.

The noise-induced hearing loss (NIHL) is one of the most common work-related diseases caused by the extreme exposure to noise. Recurrent exposure to noise causes physical damage to hair cells in the cochlea. Moreover, genetic predisposition and systemic conditions also contribute to the prevalence and severity of the phenotype making it difficult to distinguish the cause [53]. In the same line, there is a correlation between hazardous daily noise exposure and the prevalence of hearing loss among youth population [54, 55].

Ototoxic agents like certain drugs or heavy metals could contribute to the development of hearing impairment. Drugs such as cisplatin and aminoglycoside trigger hair cells apoptosis by enhancing the production of oxygen reactivity spices and has up to 50% reported incidence of irreversible hearing loss [56, 57].

The age-related hearing loss (ARHL) or presbycusis is caused by progressive atrophy of the inner ear during aging [58, 59]. The onset and prevalence of the disease vary widely as is multifactorial and many components (genetic and environmental) could play a role. Moreover, the heritability of AHRL had been stablished around 50% [60–64] and through genome-wide association studies and animal models, several age-related hearing loss genes had been identified [65–67]. The estimated prevalence of ARHL is one-third of adults above 65 years old and it doubles by each decade of life span [68, 69].

ARHL had been well-documented during the years because of its high prevalence in the population. Characterized cochlea manly by atrophy in the basal turns of the cochlea and is manifested by abrupt high-tone hearing loss [70, 71]. ARHL is commonly classified as sensory, neural and metabolic. Sensory ARHL stems from the progressive degeneration of organ of Corti [72], neural ARHL is considered when there is 50% or more of cochlear neurons loss [73] and metabolic ARHL is

Gene	Gene name	Phenotype	Study	Ref.
APOE	Apolipoprotein E	undefined	GWAS	[79]
ARHI	Age-related Hearing Loss	SN, M	GWAS	[80–82]
CDH23	Cadherin-related 23	SN, M	Model, GWAS	[83–86]
COX 3	cytochrome c oxidase subunit 3	M	Model	[87, 88]
EDN1	Endothelin-1	M	Model, GWAS	[89, 90]
GRHL2	Grainyhead-like 2	SN	GWAS	[91]
GRM7	Metabotropic glutamate receptor type 7	SN	GWAS	[92]
GST	Glutathione S-transferase	M	Model, GWAS	[93–95]
IQGAP2	IQ motif containing GTPase activating protein 2	undefined	GWAS	[96, 97]
ITGA8	Integrin, alpha 8	SN	Model	[98, 99]
KCNMA1	Potassium large conductance calcium-activated channel, subfamily M, alpha member 1	SN	Model	[100]
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	SN	GWAS	[101, 102]
KCNQ4	Potassium voltage-gated channel, KQT-like subfamily, member 4	SN, M	Model, GWAS	[103, 104]
NAT2	N-acetyltransferase 2	M	GWAS	[105–107]
P2X	Ligand-gated ion channel purinergic receptor 2	undefined	GWAS	[108]
PCDH15	Protocadherin-related 15	SN	Model, GWAS	[109, 110]
PTPRD	tyrosine phosphatase, receptor type D	undefined	GWAS	[111]
SLC26A4	Solute carrier family 26 member 4	SN	Model	[112]
SLC7A8	Solute carrier family 7 member 8	SN, M	Model, GWAS	[67]
SLC9A3R1	Regulator 1 of SLC9 transporter	SN	Model, GWAS	[113]
SPATC1L	Spermatogenesis and centriole associated 1	undefined	GWAS	[114]
SPNS2	Spinster homolog 2	M	Model	[115, 116]
TBL1Y	Transducin beta-like 1 Y-linked	SN	Model, GWAS	[117]
THRB	Thyroid hormone receptor 1	SN, M	Model, GWAS	[118]
TNF	Tumor necrosis factor	M	GWAS	[119]
UCP2	Uncoupling protein 2	SN	GWAS	[120, 121]

Inner ear phenotype classification: sensorineural (SN), metabolic (M) and both of them (SN and M). Study type: genome-wide association study and study-case (GWAS) and in vitro or in vivo model (Model).

Table 3.
ARHL-related genes.

caused by the atrophy of the stria vascularis resulting in a decrease in endolymphatic potential [74]. Also, there is a mixed type where the progressive degeneration of sensory cells is observed along loss of cochlear neurons [75–77]. Moreover, still controversial if the loss of neurons is a secondary consequence or a primary cause.

The task to distinct between genetic and environmental factors in acquired hearing loss is very challenging. In this regard, to progress the understanding of the mechanisms that lead to the damage, physiopathology of age-related hearing loss had been assessed by *in vitro* (cell lines) and *in vivo* (rodents and zebrafish) models [70]. The studies provided evidences of specific inner damage such as inflammation, oxidative stress, reduced cochlear blood flow, disrupted ion hemostasis and death of sensory and neuronal cells [78]. **Table 3** summarizes all current knowledge on ARHL-related genetic factors.

2.3.1 Consequences of suffering ARHL

Age-related hearing loss affects communication and information reception reducing the quality of live and psychosocial well-being (e.g., anxiety or depression) of elder population. Limitation in communication has an impact on social and personal relationships triggering to loss of autonomy and dependency [122, 123]. Even though the World Health Organization estimates that by 2025 approximately 500 million will suffer from age-related hearing loss; there is a lack of awareness by health care professionals as well as no educational programs on how patients could overcome obstacles caused by hearing loss.

Few studies have investigated the psychological factor and how individuals develop their lives in the presence of hearing loss. The studies reveal that maladaptive behavior (e.g., escape, avoiding social interaction and/or pretending to understand) has a negative effect on well-being of elder patients comparing to adaptive strategies (e.g., training verbal skills or self-awareness) [124, 125]. Additionally, there is a significant increase of hearing aids use by cases who attend audiology clinic with a relative than others attending alone [126]. Therefore, elder population with acquired hearing loss requires social support from family and health care professionals. Educational programs on how to use hearing aids and communication strategies as well as counseling for follow-up and feedback are needed in order to increase adherence to treatment and improve life quality [127].

3. Hearing loss treatments

Hearing loss is not a curable disease however science made some considerable progress. Current therapies based on cochlear implants (a device that provides direct electrical stimulation to the auditory nerve in the inner ear) and hearing aids (are non-surgically placed in the ear canal) which help patients to recover partly hearing.

Hearing aids could be a stigma in the society as are negatively perceived as well as expensive making that only one out of five people who could benefit from a hearing aid actually wears it (WHO, [128]). Therefore, the major barriers to improve hearing in elder population include perception that hearing loss is a normal part of aging or is not amenable to treatment.

Based on the animal research studies, several clinical trials are working to investigate the effects of a variety of drugs to prevent hearing loss including antioxidants, ROS scavengers, alpha lipoic acid, N-acetylcysteine or anti-inflammatory agents [129–134].

New generation treatments based on microRNA, short interfering RNA as well as tissue regeneration using stem cells are promising tools [135, 136]. Due to

the in-depth study of stem cell and its therapeutic potential, stem cell technology opened new approaches for hair cell and auditory nerve regeneration [137, 138]. By using two strategies of endogenous stem cell activation and exogenous stem cell transplantation, exciting results on restoring hearing function are showed. Even though the use of stem cells to repair cochlear injury is relatively new, they appear to be a very promising possibility for the treatment of hearing loss induced by noise, aging or ototoxic drugs. These three causes comprise a major part of the burden of hearing loss, so if this approach were successful could have a large public health effect of hearing impairment. Further research should be supported to solve the problems which limit stem cells application in humans.

4. Conclusion

Of the senses that humans use to interact with their environment, hearing is considered as one of the dominant after vision. The loss of hearing can occur through genetic mutations, through environmental factors or through a combination of both. ARHL is an increasingly important public health problem which reduces life's quality, isolation, dependence and frustration. Besides basic research and more effective therapies for the optimal treatment, management of the condition is still a pending task. Social support by the family and health care professionals is critical to the life quality of the older adults with hearing loss. The quality of care and well-being could be improved by active education and counseling to provide appropriate support to facilitate everyday communication.

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Conflict of interest

There is no conflict of interest.

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