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 canal 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].
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 factors 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 variants 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          | 607115     | AR          |
|                                   | LARS2         | 604544     | AR          |
|                                   | TWNK          | 606075     | AR          |
|                                   | ERAL1         | 607435     | AR          |
| Stickler syndrome                 | COL2A1        | 120340     | AD          |
|                                   | COL11A1       | 120280     | AD          |
|                                   | COL11A2       | 120290     | AD          |
|                                   | COL9A1        | 120210     | AR          |
|                                   | COL9A2        | 120260     | AR          |
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

| Syndrome               | Gene    | OMIM entry | Inheritance |
|------------------------|---------|------------|-------------|
| Treacher Collins syndrome | TCOF1   | 606847     | AD          |
|                        | POLR1D  | 613715     | AD          |
|                        | POLRIC  | 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    | 606997     | 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].
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, pigmented 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          |
| BSN1      | 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    | DFNB93      | 605608     | AR          |
| CLIC5     | DFNB103     | 607293     | AR          |
| COCH      | DFNA9       | 603196     | AD          |
| COL1A1    | DFNA37      | 120280     | AD          |
| COL1A2    | 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          |
| ESPR1     |             | 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         |
| MYH4         | DFNA4A| 608568     | AD          |
| MYH9         | DFNA17| 160775     | AD          |
| MYO15A       | DFNB3 | 602666     | AR          |
| MYO3A        | DFNB30| 606808     | AR          |
| MYO6         | DFNB37, DFNA22| 600970 | AR, AD      |
| MYO7A        | DFNB2, DFNA11| 276903 | AR, AD      |
| NARS2        | DFNB94| 612803     | AR          |
| NLRL3        | 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          |
| PDE2D7       | DFNB57| 612971     | AR          |
| PJKV         | DFNB9 | 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| 603337   | AR, AD      |
| RDX          | DFNB24| 179410     | AR          |
| REST         | DFNA27| 600571     | AD          |
| ROR1         | DFNB108| 612959    | AR          |
| S1PR2        | DFNB68| 609427     | AR          |
| SERPINB6     | DFNB91| 173321     | AR          |
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

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].

| 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          |
| TMMRPS3       | DFNB8/10| 605511 | AR          |
| TNC           | DFNA56| 187380     | AD          |
| TPRN          | DFNB79| 613354     | AR          |
| TROBP         | DFNB28| 609761     | AR          |
| TSPEAR        | DFNB98| 612920     | AR          |
| Unknown       | DFNY1 | 400043     | YL          |
| USHHC         | DFNB18| 605242     | AR          |
| WBP2          |       | 606962     | AR          |
| WFS1          | DFNA6/14/38| 606201 | AD          |
| WHRN          | DFNB31| 607928     | AR          |
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 established 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 mainly 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]  |
| COX3   | 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] |
| ITG4   | 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).
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 distinguish 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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