Review Article

Genetics of Nonsyndromic Congenital Hearing Loss

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Congenital hearing impairment affects nearly 1 in every 1000 live births and is the most frequent birth defect in developed societies. Hereditary types of hearing loss account for more than 50% of all congenital sensorineural hearing loss cases and are caused by genetic mutations. HL can be either nonsyndromic, which is restricted to the inner ear, or syndromic, a part of multiple anomalies affecting the body. Nonsyndromic HL can be categorised by mode of inheritance, such as autosomal dominant (called DFNA), autosomal recessive (DFNB), mitochondrial, and X-linked (DFN). To date, 125 deafness loci have been reported in the literature: 58 DFNA loci, 63 DFNB loci, and 4 X-linked loci (http://hereditaryhearingloss.org/) [6].

Many genes are involved in inner-ear function, and the ear is very sensitive to mutations in genetic loci. This is because the physiology and structure of the inner ear are unique and unlike other anatomical locations. Mutations in genes that control the adhesion of hair cells, intracellular transport, neurotransmitter release, ionic homeostasis, and cytoskeleton of hair cells can lead to malfunctions of the cochlea and inner ear.

1. Introduction

Hearing loss (HL) is a common disorder, and congenital hearing impairment affects nearly 1 in every 1000 live births; it is one of the most distressing disorders and the most frequent birth defect in developed societies [1]. Hearing impairment affects speech development, language acquisition, and education in children and, as a result, often leads to decreased opportunities in work life as those with hearing loss move to isolating themselves from society. In the US, it is estimated that the social costs of untreated hearing loss over the course of a lifetime can reach up to $11 million for every untreated person [2]. These costs could be decreased by 75 percent with early intervention and treatment [3].

Hereditary hearing loss accounts for almost 50% of all congenital sensorineural hearing loss cases, and it is caused by genetic mutations [4]. Deafness can be the result of a mutation in a single gene or a combination of mutations of different genes; it can also be a result of environmental causes such as trauma, medications, medical problems, and environmental exposure or the result of an association between environmental factors and genetics [5].

HL can be either nonsyndromic, which is restricted to the inner ear, or syndromic, a part of multiple anomalies affecting the body. Nonsyndromic HL can further be categorised by its mode of inheritance. Approximately 20% of nonsyndromic sensorineural hearing loss (NSSHHL) is inherited as autosomal dominant, which is also referred to as DFNA; this type of hearing loss is usually delayed onset. Eighty percent of inherited HL is autosomal recessive (DFNB), in which hearing loss is generally congenital, but some forms may emerge later in life. The inheritance of the remaining types of HL is either mitochondrial or X-linked (DFN) (less than 1 percent) [2]. To date, 125 deafness loci have been reported in the literature: 58 DFNA loci, 63 DFNB loci, and 4 X-linked loci (http://hereditaryhearingloss.org/) [6].
In recent years, with the increase in studies of genes involved in congenital hearing loss, genetic counselling and treatment options have emerged and increased in availability. In diagnostic tests, genes that are common causes of hearing loss, such as GJB2, GJB6, SLCO26A4, and OTOF, are frequently involved [7]. The results of these tests can be used when counselling parents about the prognosis of a child’s hearing loss, predicting recurrence in the future offspring and taking into consideration therapeutic options like cochlear implantation [2]. In recent studies, some viral vectors were delivered into the inner ear to replace the normal copy of the gene with the defective gene causing hearing loss. In an animal study, an adenovirus-delivered SLC17A8 (VGLUT-3; vesicular glutamate transporter 3) was found to restore hearing in the mice. In another study, hair cell development and regeneration were induced by delivering the ATOH1 gene [8, 9].

This minireview has presented an overview and described the currently known genes associated with nonsyndromic congenital hearing loss and mutations that cause dysfunctional proteins in the inner ear (Table 1).

2. Genes and Proteins Related to Nonsyndromic Hearing Loss

2.1. Adhesion Proteins. The stereocilia of hair cells in the cochlea are linked and interconnected to the tectorial membrane by different adhesion proteins. Hair bundles are stabilized by a set of temporary links such as transient lateral links and ankle links. These links also induce growth and maturation with signalling complexes [10]. In mature hair cells, stereocilia are connected by tectorial attachment crowns, horizontal top connectors, and tip links [2]. To date, several genes related to the linking apparatus have been reported. These are DFNA4 (CEACAM16 (carcinogenic antigen-related cell adhesion molecule 16)) [11], DFNB12 (CDH23 (cadherin 23)) [12], DFNB16 (STRC (stereocilin)) [13], DFNB18 (USH2C (harmonin)) [14, 15], DFNB22 (OTOA (otoacorin)) [16], DFNB23 (PCDH15 (protocadherin 15)) [17], DFNB31 (WHRN (whirlin)) [18], DFNB66/67 (TMHS (tetraspan membrane protein)) [19], and DFNB84 (PTPRQ (tyrosine phosphate receptor Q)) [20].

The PTPRQ and TMHS genes, as well as cadherin 23 and protocadherin 15, are parts of the transient lateral link. During development, they prevent the fusion of each stereocilium themselves [2]. In mature hair cells, they become the main parts of the tip link and act as a gate, channeling mechanotransduction and providing stability, taking a central role in auditory function [21].

Whirlin and harmonin regulate the link complexes and serve as scaffolding proteins. Mutations in these proteins cause autosomal recessive type hearing loss, but Sans, which is a third scaffolding protein, is related to a complex syndromic hearing loss, Usher syndrome. The other genes, USH2α and VLGR1b, are also associated with Usher syndrome, and they are part of the stereociliary ankle link [22].

Stereocilin is an extracellular matrix protein that attaches the tallest stereocilia of the outer hair cells to the tectorial membrane [13]. The attachment site of this tectorial membrane is generally formed by CEACAM16. In a similar way, otoancrin also attaches nonsensory cells to the tectorial membrane [16].

2.2. Transport Proteins. In the inner ear, all parts of the myosin family can be used for the transportation of different proteins. When using ATP, these myosin proteins bind to the actin cytoskeleton and move forward. Binding sites for carried proteins are on the carboxyl-terminal tails of the transport proteins [23]. The myosins related to hereditary hearing loss are myosin la (DFNA48) [24], myosin IIa (DFNB30) [25], myosin VI (DFNA22/DFNB37) [26, 27], myosin VIIa (DFNA11/DFNB2) [28, 29], nonmuscle myosin heavy chain IX (DFNA17) [30], nonmuscle myosin heavy chain XIV (DFNA4) [31], and myosin XV (DFNB3) [32]. They all have their own unique functions in the inner-ear hair cells [2].

2.3. Proteins of Synapses. VGLUT3, which is a vesicular glutamate receptor, plays a role in the inner hair cells’ synapses. It is encoded by SLC17A8 in the DFNA25 locus and related to autosomal recessive hearing loss [33]. This protein regulates both the exocytosis and the endocytosis of glutamate. Otoferlin (encoded by OTOF) is a protein that works with myosin VI at the synaptic cleft of the inner hair cell and plays a role in the calcium-dependent fusion of vesicles to the plasma membrane. As a result, glutamate is released and the afferent neuron is excited [34]. In an animal study with OTOF and SLC17A8 knockout mice, there was a reduction in the number of postsynaptic ganglion cells, and it was concluded that these proteins are very important for the preservation and development of normal hearing [35].

2.4. Electromotility. The cochlea is sensitive and selective to sounds delivered by the outer hair cells. This is introduced with a process called electromotility, and a protein called Prestin is thought to be responsible for this [2]. It changes the membrane’s potential and enables the outer hair cell length to be altered. When this occurs, the outer hair cell becomes longer upon hyperpolarization and shorter upon depolarization, so it amplifies its sensitivity to the sound [36]. This protein is encoded as SLC26A5 and was first described by Zheng et al. in 2000 [37]. Mutations in SLC26A5 are the cause of DFNB61 hearing loss [38].

2.5. Cytoskeleton. Mutations in some genes associated with the organisation of the cytoskeleton can cause NSSHL; these are ESPN (espin), RDX (radixin), TROBP (trio-binding protein), ACTG1 (diaphanous), and SMPX (small muscle protein, X-linked).

The protein espin provides stability to the stereocilial cytoskeleton. A mutation in ESPN can cause DFNB36 and autosomal dominant hearing loss [39]. More stereocilia stability can be achieved with radixin. It links actin filaments to the plasma membrane and presents along the stereocilia. Mutations in RDX can cause DFNB24 and autosomal recessive deafness [40]. γ-actin acts as a building block for the stereocilia of hair cells. These stereocilia are constantly undergoing depolymerisation at the base and
Table 1: Genes related with nonsyndromic hearing loss.

| Locus       | Gene     | Chromosomal localization | Type of inheritance | Protein                          | Function                                                      | Reference |
|-------------|----------|--------------------------|---------------------|----------------------------------|---------------------------------------------------------------|-----------|
| DFNA1       | DIAPH1   | 5q31                     | AD                  | Diaphanous 1                     | Actin polymerisation (cytoskeleton)                           | [44]      |
| DFNA2A      | RCNQ4    | 1p34                     | AD                  | KCNQ4                            | Voltage-gated K+ channel (ion haemostasis)                    | [51]      |
| DFNA2B      | GJB3 (Cx31) | 1p34               | AD                  | Connexin 31                      | Gap junction (ion haemostasis)                                | [57]      |
| DFNA3A      | GJB2 (Cx26) | 13q12            | AD                  | Connexin 26                      | Gap junction (ion haemostasis)                                | [54]      |
| DFNA3B      | GJB6 (Cx30) | 13q12            | AD                  | Connexin 30                      | Gap junction (ion haemostasis)                                | [55]      |
| DFNA4       | MYH14    | 19q13                   | AD                  | Nonmuscle myosin heavy chain XIV | Transport                                                      | [31]      |
| DFNA4       | CAECAM16 | 19q13                   | AD                  | Carcinogenic antigen-related cell adhesion molecule 16 | TM attachment crown (adhesion)                              | [11]      |
| DFNA8/12    | TECTA    | 11q22-24                | AD                  | A-tectorin                       | Stability and structure of TM (ECM)                          | [28]      |
| DFNA9       | COCH     | 14q12-q13               | AD                  | Cochlin                          | Structure of spiral limbus                                    | [30]      |
| DFNA10      | EYA4     | 6q22-q23                | AD                  | Eyes absent 4                    | Regulation of transcription (transcription factor)            | [42]      |
| DFNA11      | MYO7A    | 11q12.3-q12             | AD                  | Myosin VII                       | Transport                                                      | [43]      |
| DFNA13      | COLHIA2  | 6p21                     | AD                  | Type I collagen α2               | Stability and structure of TM (ECM)                          | [36]      |
| DFNA15      | POU3F4   | 5q31                     | AD                  | Class 3 POU                      | Regulation of transcription (transcription factor)            | [35]      |
| DFNA17      | MYH9     | 22q                      | AD                  | Nonmuscle myosin heavy chain IX   | Transport                                                      | [24]      |
| DFNA20/26   | ACTG1    | 17q25                    | AD                  | y-actin                          | Building cytoskeleton (cytoskeleton)                          | [50,56]  |
| DFNA22      | MYO6     | 6q13                     | AD                  | Myosin VI                        | Regulation of exocytosis, anchoring stereocilia (cytoskeleton) | [29]      |
| DFNA25      | SLC17A8  | 12q21-24                | AD                  | VGLUT-3                          | Regulation of exocytosis and endocytosis of glutamate (transport) | [32]      |
| DFNA28      | TPC2L3   | 8q22                     | AD                  | Transcription factor CP2-like 3  | Regulation of transcription (transcription factor)            | [52]      |
| DFNA48      | MYO1A    | 12q13-q14               | AD                  | Myosin la                        | Transport                                                      | [34]      |
| DFNA50      | MIR96    | 7q32                     | AD                  | MicroRNA96                       | Regulation of transcription (transcription factor)            | [12]      |
| DFNA51      | TJP2     | 9q31.3-3q4.3            | AD                  | Tight junction protein 2         | Cell cycle signaling, binding tight junctions to membrane     | [13]      |
| DFNA56      | TNC      | 9q31.3-3q4.3            | AD                  | Tenascin-C                        | Stability and structure of TM (ECM)                          | [14]      |
| DFNA64      | SMAC/DIABLO | 12q24.31-12q24.32      | AD                  | Activator of Caspase/Direct Inhibitor of Apoptosis protein Binding protein with a low pI | Cell cycle signaling | [15] |
| DFNA65      | TBCID24  | 16p13.3                  | AD                  | Tbc1 domain family, member 24    | Encoding a GTPase-activating protein expressed in the cochlea | [16,17]  |
| DFNA67      | OSBPL2   | 20q13.2-2q13.33         | AD                  | Oxyysterol-binding Protein-like Protein 2 | Intracellular transport of lipids, particularly oxyysterol (transport) | [40,45]  |
| DFNB1A      | GJB2 (Cx26) | 13q11-q12          | AR                  | Connexin 26                      | Gap junction (ion haemostasis)                                | [13]      |
| DFNB1B      | GJB6 (Cx30) | 13q12            | AR                  | Connexin 30                      | Gap junction (ion haemostasis)                                | [49]      |
| Locus    | Gene  | Chromosomal localization | Type of inheritance | Protein                          | Function                                      | Reference |
|----------|-------|--------------------------|---------------------|----------------------------------|-----------------------------------------------|-----------|
| DFN62    | MYO7A | 11q                      | AR                  | Myosin VIIa                      | Transport                                     | [25, 43]  |
| DFN63    | MYO15A| 17p12.2                  | AR                  | Myosin Xv                        | Transport                                     | [18]      |
| DFN64    | SLC26A4| 7q31                     | AR                  | Pendrin                          | Acid-base balance of endolymph (ion haemostasis) | [39]      |
| DFN69    | OTOF  | 2p23-p22                 | AR                  | Otoferlin                        | Fusion of synaptic vesicles with Ca\(^{2+}\) (transport) | [38]      |
| DFN62    | CDH23 | 10q21-q22                | AR                  | Cadherin 23                      | Lateral and tip link (adhesion)                | [19]      |
| Modifier of DFN62 | ATP2b2/PMCA2 | 1p32.3                  | AR                  | ATP2b2                           | ATP dependent Ca\(^{2+}\) pump                | [53]      |
| DFN16    | STRC  | 15q15                    | AR                  | Sterocilin                       | TM attachment links (adhesion)                | [20]      |
| DFN18    | USHIC | 11p5.1                   | AR                  | Harmonin                         | Scaffolding protein (adhesion)                 | [48, 58]  |
| DFN21    | TECTA | 11q22-q24                | AR                  | α-tectorin                       | Stability and structure of TM (ECM)           | [10]      |
| DFN22    | OTOA  | 16p12.2                  | AR                  | Otonocorin                       | TM attachment to nonsensory cells (adhesion)   | [21]      |
| DFN23    | PCDH15| 10q21-q22                | AR                  | Protocadherin 15                 | Lateral and tip link (adhesion)                | [22]      |
| DFN24    | RDX   | 11q23                    | AR                  | Radixin                          | Actin binding to plasma membrane (cytoskeleton) | [23]      |
| DFN28    | TRIOBP| 2q13.1                   | AR                  | Trio-binding protein             | Actin binding and organisation (cytoskeleton) | [27, 35]  |
| DFN29    | CLDNH | 2q22.3                   | AR                  | Claudin 14                       | Tight junction (ion haemostasis)               | [36]      |
| DFN30    | MYO3A | 10p11.1                  | AR                  | Myosin IIIa                      | Transport                                      | [37]      |
| DFN31    | WHRN  | 9q32-q34                 | AR                  | Whirlin                          | Scaffolding protein (adhesion)                 | [44]      |
| DFN35    | ESRRB | 14q21.1-q24.3            | AR                  | Oestrogen-related receptor β      | Regulation of transcription (transcription factor) | [47]      |
| DFN36    | ESPN  | 1p36.3-p36.1             | AR                  | Espin                            | Actin crosslinking and bundling (cytoskeleton) | [59]      |
| DFN37    | MYO6  | 6q13                     | AR                  | Myosin VI                        | Regulation of exocytosis, stereocilia anchoring (transport) | [60]      |
| DFN49    | TRIC  | 5q23.3-q41.1             | AR                  | Tricellulin                      | Tight junction (ion haemostasis)               | [53]      |
| DFN53    | COLIIA2 | 6p21.3                    | AR                  | Type XI collagen α2               | Stability and structure of TM (ECM)           | [61]      |
| DFN61    | SLC26A5| 6p21.3                    | AR                  | Prestin                          | Electromotility                                 | [62]      |
| DFN67    | TMHS  | 6p21.3                   | AR                  | Tetraspan membrane protein       | Transient link (adhesion)                      | [63]      |
| DFN73    | RSN D | 9q34.3                   | AR                  | Barttin                          | K\(^{+}\) channel maturation and trafficking (ion haemostasis) | [64]      |
| DFN79    | TPRN  | 9q34.3                   | AR                  | Taperin                          | Actin regulation (cytoskeleton)                | [65]      |
| DFN84    | PTPRO | 12q21.31-q21.2            | AR                  | Protein tyrosine phosphate receptor Q | Transient link (adhesion)                      | [66]      |
| DFN91    | QR3   | 6p25                     | AR                  | Connexin 3l                       | Gap junction (ion haemostasis)                 | [67]      |
| DFN93    | C4BP2 | 1q31.2                   | AR                  | Calcium-binding protein 2        | (ion haemostasis)                               | [68]      |
| DFN94    | NARS2 | 1q14.1                   | AR                  | Asparaginyl-t-RNA synthetase 2   | (transport)                                    | [69]      |
| DFN97    | MET   | 7q11.2                   | AR                  | MET protooncogene                | Cell-surface receptor for hepatocyte growth factor (adhesion) | [70]      |
| DFN98    | TSPEAR| 2q22.3                   | AR                  | Thrombospondin-type lamin g domain and ear repeats | Cell permeabilization (transport) | [71]      |
| DFN99    | TEMEM32E | 17q12                  | AR                  | Transmembrane protein 132e       | Extracellular receptor                         | [72]      |
| DFN101   | CRXCR2| 5q32                     | AR                  | Glutaredoxin, cysteine-rich 2    | Organisation of stereocilia (adhesion)         | [73]      |
| DFN102   | EPS8  | 12p12.3                  | AR                  | Epidermal growth factor receptor pathway substrate 8 | Regulating Rac-specific GEF activity (transcription factor) | [74]      |
| Locus      | Gene       | Chromosomal localization | Type of inheritance | Protein                                              | Function                                      | Reference |
|-----------|------------|--------------------------|---------------------|------------------------------------------------------|-----------------------------------------------|-----------|
| DFNB103   | CLIC5      | 6p21.1                   | AR                  | Chloride intracellular channel 5                     | (ion haemostasis)                            | [75]      |
|           | FAM65B     | 6p22.3                   | AR                  | Family with sequence similarity 65, member b         | (Cytoskeleton)                                | [76]      |
| Usher syndrome | SANS/USH1G | 17q24.25                 | AR                  | SANS                                                | Scaffolding protein (adhesion)               | [77]      |
| Usher syndrome | USH2A    | 1q41                      | AR                  | Usherin                                             | Ankle link (adhesion)                        | [78]      |
| Usher syndrome | VLGR1B    | AR                        |                     | Very large G protein-coupled receptor 1             | Ankle link (adhesion)                        | [79]      |
| DFN2      | PRPS1      | Xq22.3                   | X-linked            | Phosphoribosylpyrophosphate synthetase 1            | Purine and pyrimidine biosynthesis           | [80]      |
| DFN3      | POU3F4     | Xq21                      | X-linked            | Class 3 POU                                         | Regulation of transcription (transcription factor) | [81]      |
| DFN6      | SMPX       | Xp21.2                    | X-linked            | Small muscle protein X-linked                       | Stereocilial development and maintenance (cytoskeleton) | [82]      |
| DFNX6     | COL4A6     | Xq22.3                    | X-linked            | Collagen, type IV, alpha-6                          | Stability and structure of TM (ECM)          | [83]      |

DFN = nonsyndromic deafness, autosomal dominant; DFNB = nonsyndromic deafness, autosomal recessive; AD = autosomal dominant; AR = autosomal recessive; TM = tectorial membrane; ECM = extracellular matrix; $\text{Ca}^{2+}$ = calcium ion; $\text{K}^+$ = potassium ion.
actin polymerisation at the tip [41]. Mutations in ACTG1 can cause DFNA20/26 and autosomal dominant hearing loss [42, 43]. Via a constant remodelling process, other proteins are also important for continuity. Diaphanous 1 regulates the reorganisation and polymerisation of actin monomers into polymers. It is encoded as DIAPH1, and mutations in this gene can cause DFNA1 and autosomal dominant hearing loss [44]. The binding and organisation of γ-actin at the base of stereocilia are provided by two isoforms of the TRIOBP gene. Mutations in isoforms that are TRIOBP4 and TRIOBP5 can cause DFNB28 and autosomal recessive type hearing loss [45, 46]. Another protein, taperin, is localised in the base of the stereocilia and associated with DFNB79 [47]. Small muscle protein X-linked, encoded as SMPX (DFN4), has a function in stereocilial development and maintenance in response to the mechanical stress to which stereocilia are subjected [48].

2.6. Ion Homeostasis and Gap Junctions. The cochlea has two types of fluids: perilymph, which is high in sodium and low in potassium, and endolymph, which is high in potassium and low in sodium; this condition makes a highly positive potential (+80 mV) called endocochlear potential. Potassium influx into the hair cells causes depolarisation and, after that, the hair cell depolarises and moves cations back into the endolymph. This ion homeostasis involves tight junction protein 2 (TJP2), tricellulin (MARVELD2/TRIC), claudin 14 (CLDN14), KCNQ4 (KCNQ4), Barttin (BSND), ATP2b2 (ATP2b2/PMCA2), some connexins (GJBs), and pendrin (SLC26A4), and they are all related to hereditary hearing loss [2].

In a mutation of CLDN14 in DFNB29, claudin 14 protein will be absent or dysfunctional, and the space of Nuel that surrounds the basolateral surface of outer hair cells is affected and might change its electrical potential [49]. Similarly, tricellulin, which is encoded as MARVELD2/TRIC, causes DFNB49 when mutated, and it is functioning as tight junction that connects the cells together [45]. Tight junction protein 2, encoded as the TJP2 gene, binds tight junctions to the actin cytoskeleton, and mutations cause DFNA5 and autosomal dominant type hearing loss [50].

KCNQ4 encodes a protein forming a voltage-gated potassium channel. It is expressed in outer hair cells and, if mutated, causes an autosomal dominant type HL, DFNA2a [51]. It aids in the repolarisation of outer hair cells and regulates the sensitivity to sound.

Barttin and pendrin, encoded as BSND and SLC26A4, respectively, are involved in both nonsyndromic and syndromic HL. Pendrin is an anion exchanger and plays a crucial role in the acid-base balance. Both syndromic (Pendred’s syndrome, associated with goiter) and nonsyndromic HL (DFNB4) are related to the extent of the mutation in SLC26A4 [52]. Barttin protein is one of the subunits of the chloride channel. Mostly, mutations in BSND can cause Bartter syndrome, associated with hearing loss and renal abnormalities, but DFNB73 has also been attributed to a mutation in BSND and causing nonsyndromic deafness [53].

A gap junction is a channel extending over two adjacent membranes that enables the exchange of various molecules and ions in the cochlea. These junctions are made up of proteins called connexins. These junctions also play a role in the recycling of potassium ions needed for normal hearing. It is the most common cause of nonsyndromic HL and was the first identified gene is GJB2; it is encoded as connexin 26 (DFNA3a/DFNB1a) [54]. Other connexins related to nonsyndromic HL are connexin 30 (GJB6, DFNA3b/DFNB1b) [55, 56] and connexin 31 (GJB3, DFNA2b/DFNB91) [57, 58].

2.7. Others. There are also extracellular matrix proteins, that is, TECTA (α-tectorin), COL11A2 (type XI collagen α2), and COCH (cochlin), and transcription factors, such as POU4f3 (class 4 POU), POU4f4 (class 3 POU), MIR96 (microRNA 96), GRHL2 (grainy-head-like 2), ESRRB (oestrogen-related receptor β), and EYA4 (eyes absent 4) involved in hereditary HL.

3. Conclusion

This review presents an overview and description of the currently known genes related to hereditary NSHL. The functions of these genes will be better understood with time, and more genes leading to hearing loss will be discovered soon. With new studies and continued examination, the function of the cochlea will be better understood, and novel molecular and gene therapies for human sensorineural HL will hopefully be developed.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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