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REVIEW

Research progress in pathogenic genes of hereditary non-syndromic mid-frequency deafness

Wenjun Xia[1], Fei Liu[2], Duan Ma (✉)[1,2]

[1]*Institute of Biomedical Sciences, Fudan University, Shanghai 200023, China;* [2]*Key Laboratory of Metabolism and Molecular Medicine, Ministry of Education, Department of Biochemistry and Molecular Biology, Institute of Biomedical Sciences, School of Basic Medical Sciences, Fudan University, Shanghai 200023, China*

Abstract **Hearing impairment is considered as the most prevalent impairment worldwide. Almost 600 million people in the world suffer from mild or moderate hearing impairment, an estimated 10% of the human population. Genetic factors play an important role in the pathogenesis of this disorder. Hereditary hearing loss is divided into syndromic hearing loss (associated with other anomalies) and non-syndromic hearing loss (not associated with other anomalies). Approximately 80% of genetic deafness is non-syndromic. On the basis of the frequency of hearing loss, hereditary non-syndromic hearing loss can be divided into high-, mid-, low-, and total-frequency hearing loss. An audiometric finding of mid-frequency sensorineural hearing loss, or a "bowl-shaped" audiogram, is uncommon. Up to now, merely 7 loci have been linked to mid-frequency hearing loss. Only four genetic mid-frequency deafness genes, namely, DFNA10 (*EYA4*), DFNA8/12 (*TECTA*), DFNA13 (*COL11A2*), DFNA44 (*CCDC50*), have been reported to date. This review summarizes the research progress of the four genes to draw attention to mid-frequency deafness genes.**

Keywords hereditary non-syndromic hearing loss; mid-frequency hearing loss; deafness genes

Introduction

With a prevalence of 0.1%, hearing loss is the most common sensory impairment affecting several million people worldwide [1]. In China, the prevalence of hearing loss ranges from 1‰–3‰ [2]. The Second National Sample Survey on Disability indicates that people with hearing disability account for 27% of all persons with disabilities [3]. Numerous factors, such as genetic and environmental factors, can cause deafness; in particular, genetic factors account for over half of all deafness cases.

Approximately 70% of hereditary hearing loss is non-syndromic hearing loss (NSHL), in which hearing impairment is not associated with any additional clinical phenotypes [4]. Monogenic hearing loss can be inherited in various ways. Autosomal recessive non-syndromic hearing loss (ARNSHL) occurs in 80% of cases and is typically pre-lingual, whereas autosomal dominant non-syndromic hearing loss (ADNSHL) accounts for approximately 20% of cases and is often post-lingual [5]. A previous study showed that syndromic deafness is frequently associated with chromosome micro-imbalances [6], and chromosomal alterations in non-syndromic patients tend to be both small and rare, focusing on specific genes [7]. To date, 87 genes for NSHL have been identified (http://hereditaryhearingloss.org/).

Patients were divided into low- (0.25–0.5 kHz), mid- (0.5–2 kHz), high- (2–8 kHz), and total-frequency hearing loss groups, as well as the total deafness group, on the basis of the frequency of hearing loss. Patients with mid-frequency hearing loss show a cookie-bite audiogram [8]. Over 80 deafness genes have been reported to date. However, only four genes have been identified to contribute to mid-frequency hearing loss: *TECTA*, *EYA4*, *COL11A2*, and *CCDC50*. This paper discusses the research progress on the four genes.

TECTA

TECTA is a causative gene of both autosomal recessive (DFNB 21) and autosomal dominant (DFNA8/A12)

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Correspondence: duanma@fudan.edu.cn

NSHL [9,10]. *TECTA* includes 23 exons and encodes α-tectorin, a non-collagenous glycoprotein of the tectorial membrane composed of 2156 amino acids; *TECTA* is located on chromosome 11q22–24 [11]. Moreover, *TECTA* is one of the major non-collagenous components of the tectorial membrane. The tectorial membrane is an extracellular matrix in the inner ear; this membrane covers the neuro-epithelium of the cochlea and contacts the stereocilia bundles of specialized sensory hair cells. Sound induces the movement of these hair cells relative to the tectorial membrane, deflects the stereocilia, and leads to fluctuations in hair-cell membrane potential, which transduces sound into electrical signals [11–13].

α-tectorin, a major non-collagenous component of the tectorial membrane, exhibits many functional domains: the entactin (ENT)-like domain, four von Willebrand factor-like type D (vWFD) domains in the zonadhesin (ZA) domain, and the zona pellucida (ZP) domain [14].

Several mutations related to hearing loss have been detected in humans [15,16]. All inactivating mutations in *TECTA* cause ARNSHL, whereas missense mutations in *TECTA* lead to ADNSHL [16,17]. Autosomal recessive mutations in *TECTA* cause a similar audiometric pattern of moderate-to-severe hearing loss, most significantly involving mid-frequency hearing loss [18–20], and the dominant mutations in *TECTA* are related to characteristic audiogram configurations, depending on which domain the mutations occur [13,14,21].

Mutations in *TECTA* account for 4% of all ADNSHL cases in a number of populations; thus, these mutations are regarded as one of the major causes of ADNSHL [22]. Missense mutations in *TECTA* cause dominant forms of non-syndromic deafness, and a genotype-phenotype correlation has been reported in humans, with mutations in the ZP and ZA domains related to mid- and high-frequency hearing losses, respectively [11]. Existing studies generally validate previously observed genotype-phenotype correlations in DFNA8/12, as well as introduce new correlations. Specifically, mutations in the entactin-G1-like domain in the first two vWFD repeats and the TIL2 repeats in the ZA and ZP domains are all associated with mid-frequency hearing loss, whereas mutations in the other regions of the ZA domain result in high-frequency hearing loss [16].

EYA4

The eyes absent homolog 4 (*EYA4*), a causative gene of mid-frequency hearing loss, encodes a 639-amino-acid protein serving as a transcription factor; EYA4 is also associated with the composition organ of Corti [23]. *EYA4* localizes to the ADNSHL locus DFNA10 on chromosome 6q23. The *EYA4* gene is encoded for the EYA4 protein, which acts through its phosphatase activity and plays an important role in eye development and for the continued function of the mature organ of Corti [24]. Research has indicated the associations between *EYA* gene mutations and post-lingual, progressive, and autosomal dominant hearing loss [25]. Additionally, several mutations in the *EYA4* were found to be associated with progressive hearing loss [25,26].

The EYA4 protein is composed of 639 amino acids with two critical domains, including a highly conserved 271-amino-acid C terminus called eyaHR, alternatively called the eya domain or eya homology domain and a more divergent proline-serine-threonine (PST)-rich transactivation domain at the N terminus. Mutations of this gene are known to cause post-lingual and progressive sensorineural hearing losses, either as non-syndromic (DFNA10) or syndromic hearing loss, depending on the location of the truncation of the mutant protein [27].

Studies on zebrafish demonstrated the eya4 expression in the mechanosensory epithelia of the zebrafish otic vesicle, as well as those in neuromasts, which are sensory patches related to the mammalian inner ear [28], and previous researchers hypothesized that Eya4 regulated the expression of Na^+/K^+-ATPase. Scientists examined the subunit levels in eya4 morphant zebrafish and demonstrated the selective reduction of two subunits. The re-expression of the Na^+/K^+-ATPase β2b subunit rescued eya4 deficiency in morphant zebrafish. Overall, these results indicate that Eya4 regulates Na^+/K^+-ATPase, thereby providing a mechanism by which human *EYA4* mutations cause both hearing loss and heart disease [29].

COL11A2

Mutations in *COL11A2* cause ADNSHL at the DFNA13 locus [30] and ARNHSL at the DFNB53 locus. COL11A2 spans ~28 kb and consists of 66 exons and an alternatively spliced exon in the N terminus [31,32]. This gene encodes one of the two α chains of type XI collagen, a minor fibrillar collagen. COL11A2 is located on chromosome 6, which is very close yet separate from the gene for retinoid X receptor β. Type XI collagen is a heterotrimer; however, the third α chain is a post-translationally modified α1 type II chain. The proteolytic processing of this type XI chain produces PARP, a proline/arginine-rich protein that is an N-terminal domain. The collagen family consists of 19 collagens encoded by at least 32 unique genes [33]. The common signature collagen motif is the sequential repetition of the amino acid triplet-Gly-X-Y-, where numerous X- and Y-positions are filled by the ring amino acids proline and hydroxyproline; these amino acids facilitate the intertwining of three collagen polypeptide chains into a triple helix [34]. Type XI collagen is a minor collagen accounting for $< 10\%$ of the total cartilage collagen. This type of collagen functions as a spacer in maintaining the interfibrillar distance and fibril diameter of

type II collagen [35]. The tectorial membrane (TM) of the mammalian cochlea is a gelatinous sheet-like structure anchored at the inner part to the apex of the interdental cells and lies on top of sensory hair cells where the long rows of outer hair cell stereocilia are anchored. The structural integrity of the TM is crucial for it to acquire its complex mechanical properties associated with the hearing process. The TM is composed of four types of collagens (II, V, IX, and XI), five types of non-collagenous glycoproteins (α-tectorin, β-tectorin, otogelin, otoanchorin, and otolin), glycosaminoglycans (uronic acid and keratan sulfate), and CEACAM16. Several of these protein mutations have been identified in human families and cause syndromic or non-syndromic HL [36,37].

A Dutch family (150 relatives in 5 generations; 49 were studied) with autosomal dominant non-syndromic sensorineural mid-frequency hearing impairment raised an association to the DFNA13 locus. Mutation analysis revealed a missense mutation in the *COL11A2* gene.

The gene mutations of this type are also associated with type III Stickler syndrome, otospondylomegaepiphyseal dysplasia (OSMED syndrome), and Weissenbacher-Zweymuller syndrome. Phenotype-genotype comparisons suggest that the different phenotypes are dependent on mutations. As collagen folding begins at the carboxy terminus, where the nucleation domain is located, mutations close to the carboxy terminus generate a more severe phenotype [38]. This positional effect of missense mutations is common to other diseases associated with collagen folding.

CCDC50

CCDC50 is a gene encoding a tyrosine-phosphorylated effector of EGF-mediated cell signaling known as "Ymer," which causes non-syndromic, post-lingual, and progressive sensorineural DFNA44; furthermore, this gene is expressed in the inner ear. Mutations in *CCDC50* cause mainly low- to mid-frequency hearing losses. The human gene (Hs.478682) is organized in 12 exons, and two alternative transcripts have been identified. The longer transcript (NM_178335) contains a 1449 nt ORF encoding a protein of 482 amino acids, whereas the shorter variant (NM_174908) without exon 6 encodes a protein of 305 amino acids [39].

Ymer is expressed in the inner ear during developmental and postnatal maturation and is associated with microtubule-based structures. Moreover, it may play a role in developing the adult inner ear. Thus, we can assume that the pathogenesis of DFNA44 hearing loss, a post-lingual, progressive form of deafness, results from the destabilization of the cytoskeleton in the PCs and stria vascularis of the adult cochlea [40].

This paper mainly introduces the four genes causing mid-frequency hearing loss, namely, *TECTA, EYA4, COL11A2,* and *CCDC50* (Table 1). Through the efforts of scientists, we have gathered further knowledge about these genes. However, the process in which these genes lead to hearing loss remains unknown. Furthermore, increasing deafness genes will be derived with the progress of sequencing and bioinformatics, and the mechanism involved will be investigated.

The genetic causes of hearing loss can be detected through sequence analysis, which helps clinicians and patients to delineate the characteristics of a disease. In addition, hearing loss occurring in early childhood can affect linguistic development; as such, strategies should be developed to determine the genetic alterations among patients for further clinical care of hearing loss.

Table 1 Summary of functions and mutations in *TECTA, EYA4, COL11A2,* and *CCDC50*

Gene	Location	Length	Protein location in Corti	Function	Nucleotide mutation	Phenotype	References
TECTA	11q22–24	90 321 bp	Tectorial membrane	Components of the tectorial membrane	c.950T>A, c.2657A>G, c.3169T>A, c.3293C>T, c.3406G>C, c.3743C>T, c.3995G>T, c.4525T>G, c.4549T>C, c.4856G>C, c.5383 + 5delGTGA, c.6026T>C	High frequency hearing loss	[13,14,16,21,22,41]
					c.1084A>T, c.1124delT, c.1395T>G, c.1685C>T, c.2444C>T, c.3107G>A, c.5331G>A, c.5372C>G, c.5383 + 2T>G, c.5458C>T, c.5471G>A, c.5509T>G, c.5509T>C, c.5597C>T, c.5600A>G, c.5609A>G, c.5618C>T, c.5668C>T, c.5692T>C, c.5839C>T, c.6062G>A	Mid frequency hearing loss	[11,14,16,18,42–45]

(*Continued*)

Gene	Location	Length	Protein location in Corti	Function	Nucleotide mutation	Phenotype	References
EYA4	6q23	291 523 bp	Unknown	Associated with composition of Corti	c.1759C>T, c.1114_1117dupTTTG, c.1048_1049dupAA, c.T1301A, c.724_8047dupAA	DFNA10 hearing loss plus dilated cardiomyopathy	[46–48]
					C.1026_1027dupAA, c.511G>C	DFNA10 hearing loss	[49]
COL11A2	6p21.32	29 819 bp	Tectorial membrane	Maintaining the interfibrillar spacing and fibril diameter of type II collagen	732delC, 2492C>A, 2406_2409del, 2405_2410ins9bp, 3991C>T, 4821_4843del, 1636C>T and IVS22-2A>G, 3032_3033insC and 4750G>T, 1982G>A	Oto-spondylo-megaepiphyseal dysplasia	[50–53]
					3991C>T and IVS53 + 5G>A	Non-syndromic cleft palate	[53]
					529C>CT, 2775_2801del 4135C>CT, IVS60-1G>GA	Non-ocular Stickler	[52,54,55]
					1861C>A, 2423G>GA, 3100C>CT	Non-syndromic hearing loss	[30,52]
					4322G>GA	WZS/non-ocular Stickler	[56]
CCDC50		69 594 bp	Unknown	Expressed in inner ear	c.1394_1401dup CACGGCAT	Non-syndromic hearing loss	[40]

Different mutations in *TECTA, EYA4, COL11A2,* and *CCDC50* contribute to various phenotypes.

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Compliance with ethics guidelines

Wenjun Xia, Fei Liu, and Duan Ma declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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